FIRM:ASTRA USA
TRADE NAME:NAROPIN IN
GENERIC NAME:ROPIVACAINE HCL MONOHYDRATE

?20 J2w1z14m11,90s

Summary Basis of Approval
Cover Form

Appl #: 020533
Firm: ASTRA USA
Reviewing Div: 170
Trade Name: NAROPIN (ROPIVACAINE HCL MONOHYDRATE) IN
Generic Name:
ROPIVACAINE HCL MONOHYDRATE

Approval Letter:	Y	Statistician Review:	Y
SBA Form:	Y	Bio/Dissolution Review:	Y
Final Printed Labeling:	N	Microbiologist Review:	N
Medical Officer Review:	Y	NAS/NRC Review:	N
Chemist Review:	Y	Pharmacologist Review:	Y
Federal Register Notice:	N	Completion Date:	20-MAY-97

DRAFT

Approval Letter And Related Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-533

SEP 24 1996

Astra USA, INC.
50 Otis Street
Westborough, Massachusetts 01581-4500

Attention: R. Wayne Frost, Pharm.D., J.D.
Associate Director, Regulatory Affairs

Dear Dr. Frost:

Please refer to your March 29, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Naropin (ropivacaine HCl) Injection 2.0 mg/ml, 5.0 mg/ml, 7.5 mg/ml, and 10.0 mg/ml.

We acknowledge receipt of your amendments dated August 16, 18, .24, 29; October 4; November 3, and 13, 1995; and February 9, 20, 26; March 21, 22, 29; May 7, 30; July 25; and August 12, 1996.

This new drug application provides for the production of local or regional anesthesia for surgery, for postoperative pain management and for obstetrical procedures.

We have completed the review of this application including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated July 25, 1996 with the revisions listed below. Accordingly, the application is approved effective on the date of this letter. The revisions are as follows:

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-533. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated March 29, 1996. These commitments, along with any completion dates agreed upon, are listed below.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments".

If you wish to pursue marketing of the % concentration of Naropin for cesarean section, you must conduct additional trials, which include maternal and fetal monitoring of pharmacokinetic data, to demonstrate safety in this population. We recommend that you submit a supplemental application to this approved NDA. You may refer to any data contained in this application in support of the supplement.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

David Morgan
Consumer Safety Officer
(301) 443-3741

Sincerely yours,

Paula Botstein MD 9/24/96

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-533
HFD-170/Div. files
HFD-170/CSO/D.Morgan
HFD-170/Bedford/Tyler/Palmisano/Landow
HFD-170/Ross/Goheer/Permutt/Doddapaneni/Moody
HFD-2/M.Lumpkin
HFD-103/P.Botstein
HFD-101/L.Carter (with labeling)
HFD-820/Yuan Yuan Chiu
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-80 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.
HFD-021/J.Treacy (with labeling)

drafted: DM/September 6, 1996/20533.ap
r/d Initials: CPMoody 9-6-96
final:

APPROVAL [with Phase 4 Commitments]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Morgan

Food and Drug Administration
Rockville MD 20857

NDA 20-533

JUN 28 1996

Astra USA , Inc.
50 Otis Street
Westborough, Massachusetts 01581-4500

Attention: R. Wayne Frost, Pharm. D., J.D.
Associate Director, Regulatory Affairs

Dear Dr. Frost:

Please refer to your March 29, 1995, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Naropin (ropivacaine HCl) Injection 2.0 mg/mL, 5.0 mg/mL, 7.5 mg/mL, and 10.0 mg/mL.

We acknowledge receipt of your amendments dated August 16, 18, 24, 29; October 4; November 3, and 13, 1995; and February 9, 20, 26; March 21, 22, 29, and May 7, 1996.

We have completed the review of this application as submitted with draft labeling and it is approvable. Before the application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the draft labeling submitted on May 7, 1996 with the revisions listed below. If additional information relating to the safety or effectiveness of this drug becomes available, revisions of the FPL may be required. The revisions are as follows:

LINE NUMBERS:

Replace with:

Change as follows:

Add table of adverse events for men versus women, e.g.

The storage condition statement on all labels and in the package insert should be revised

Please submit sixteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar material.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drugs. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170 and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising
and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

David Morgan
Consumer Safety Officer
(301) 443-3741

Sincerely yours,

Paula Botstein MD 6/28/96

Paula Botstein , M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-533
HFD-2/ Lumpkin
Office File
HFD-80
HFD-170/Division File
HFD-170/Bedford/Tyler/Palmisano/Moody/Morgan
HFD-170/Ross/Goheer/Permutt/Doddapaneni
HFD-40 (with draft labeling)
HFD-820/Chiu
District Office
HFD-170/Morgan/2-28-96/5-12-96/6-27-96/6-28-96
R/D init. by: Moody/2-28-96/5-13-96/6-27-96/6-28-96
F/T by: PO'Connor/6-28-96
Doc: 20533.ab

APPROVABLE

ORIGINAL

Astra USA

NDA 20-533
Naropin™ (ropivacaine HCl) Injection

(Request for Drug Product Exclusivity)

ORIG AMENDMENT
N(XR)

March 1, 1996

Robert Bedford, M.D.
Director, Division of Anaesthetic, Critical Care and Addiction Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD 170, Room 9B-45
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Bedford,

Reference is made to NDA 20-533, submitted on March 29, 1995 in accordance with Section 505 (b) of the Federal Food Drug and Cosmetic Act. Astra requests that upon approval of the application, the drug product Naropin™ be entitled to a period of 5 years exclusivity under 21 CFR §314.108 (b) (2).

To the best of our knowledge, a drug has not previously been approved under section 505 (b) of the act containing the active moiety in the drug for which we are seeking approval. This new product exclusivity would preclude anyone from submitting a 505 (b) (2) application or abbreviated new drug application under section 505 (j) of the act for a drug product that contains the same active moiety as contained in Naropin™ for a period of 5 years from the date of approval of this application.

Should you have any questions regarding this request, please contact me at (508)366-1100, extension 2111.

Sincerely,

R. Wayne Frost, Pharm.D., J.D.
Associate Director
Drug Regulatory Affairs

MAILING ADDRESS
Astra USA, Inc
P.O. Box 4500
Westborough, MA 01581-4500

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50 Otis Street
Westborough, MA

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508 366-1100

FAX
508 366-7406
TELEX
6810105-Cable/Astrapharm

[redacted]

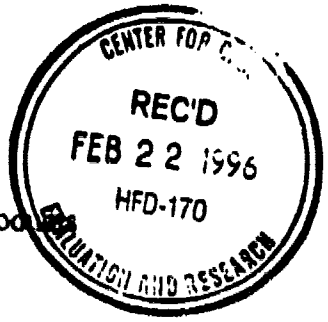
ORIGINAL

ASTRA
Astra USA

NDA 20-533
NAROPIN™ (ropivacaine HCl injection)

ORIG AMENDMENT
N(Ac)

AMENDMENT TO A PENDING NEW DRUG APPLICATION



February 20, 1996

Robert Bedford, M.D.
Director, Division of Anesthetic, Critical Care and Scheduled Drug Prod
Center for Drug Evaluation and Research
Food and Drug Administration
HFD 170, Room 9B-45
5600 Fishers Lane
Rockville, MD 20852

Dear Dr. Bedford:

Reference is made to our pending New Drug Application, submitted on March 29, 1995, for NAROPIN™ (ropivacaine hydrochloride injection), identified as NDA 20-533 and to a fax dated December 5, 1995 from Dr. Michael Theodorakis listing chemistry, manufacturing and control deficiencies.

Pursuant to 21 CFR §314.60, enclosed please find an amendment to the subject pending application which provides:

1. Responses to the chemistry, manufacturing and control deficiencies regarding the drug substance, inactive ingredients and drug product listed in the December 5, 1995 fax.

2. New and updated drug substance test methods:
   a. New method A-0839: Residual Solvents (in response to question 1)
   b. New method M-IBA-0201: Microbiological Condition replaces IBA:227 (includes use of a second media)
   c. Clarity of Solution: revised to refer to current European Pharmacopeia
   d. Updated method A-0008: IR Spectrum (new reference spectrum)
   e. Updated method A-0601: Enantiomeric Purity (includes system suitability)
   f. Updated method A-0440: Heavy Metals (revised sample preparation)
   g. Updated method A-0360: 2,6-Xylidine (revised system suitability, standard and sample preparation, includes ropivacaine sample chromatogram)

3. Withdrawal of the following dosage forms:

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[redacted]

ASTRA
Astra USA

4. Addition of the following dosage forms:

5.

This submission consists of two (2) volumes. The first volume contains the responses to the chemistry, manufacturing and control deficiencies listed in the December 5, 1995 fax, new and updated drug substance test methods, and information pertinent to the withdrawal and addition of the previously mentioned dosage forms. An archival and a review copy of this volume are provided.

The second volume contains the revised draft container and carton labeling. An archival and three review copies of this volume are provided.

Should you have any questions regarding this submission, please contact me or Paul Alessandro at (508) 366-1100.

Sincerely,

Paul Alessandro for

R. Wayne Frost
Associate Director, Drug Regulatory Affairs

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[redacted]

FIELD COPY CERTIFICATION

This document certifies that a full copy of this submission has been provided to the New England District Office located in Stoneham, Massachusetts, pursuant to 21 CFR §314.60(c).

Paul J. Alessandro
Manager, Drug Regulatory Affairs

20 Feb 96
Date

ORIGINAL

ASTRA®
Astra USA

NDA 20-533
Naropin™ (ropivacaine HCl) Injection

ORIG AMENDMENT

AMENDMENT TO A PENDING APPLICATION

N(BL)

February 9, 1996

Robert Bedford, M.D., Director
Division of Anaesthetic, Critical Care
and Addiction Drug Products
Document Control Room 9B-23
HFD-170, CDER, FDA
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Bedford,

Please refer to our pending NDA 20-533 submitted on March 29, 1995, and to the requested changes to our draft package insert in the FDA facsimile dated December 14, 1995.

Four separately bound copies of the revised draft package insert are enclosed for your review in accordance with 21 CFR 314.50(e)(ii). We have attached a brief explanation of the revisions which have been made to the package insert subsequent to the December 14 version. The documents in this submission are arranged according to the table of contents.

With regard to the "Class Labeling", which is actually a modified class labeling based on the bupivacaine package insert, we have incorporated revisions based on your suggestions and recommendations from the Anesthetic and Life Support Drugs Advisory Committee Meeting. We would also like to participate in the process of rewriting the comprehensive local anesthetic class labeling at a later date.

Should you have any questions regarding this submission, please contact me at (508)366-1100.

Sincerely,

R. Wayne Frost

R. Wayne Frost, Pharm.D., J.D.
Associate Director
Drug Regulatory Affairs

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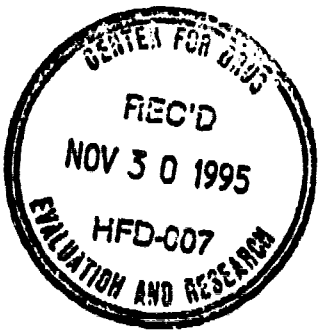
ORIGINAL

ASTRA®
Astra USA

NDA 20-533
NAROPIN™
(ropivacaine HCl monohydrate)

NEW CORRESP
C

CORRESPONDENCE



November 29, 1995

Mr. David Morgan
Consumer Safety Officer
Pilot Drug Evaluation Staff
HFD 007, Room 9B-45
5600 Fishers Lane
Rockville, MD 20852

Dear Mr. Morgan,

Please refer to our NDA 20-533 submitted on March 29, 1995 and to your phone conversation with Wayne Frost on May 12, 1995 in which you requested copies of all letters addressed to the external reviewers for this file.

As you requested in a recent telephone conversation with Wayne Frost, we are now asking that the reviewers return their copies of our file to us and we are providing you with copies of the letters addressed to each of the reviewers.

Please contact me at (508) 366-1100 extension 2111 should you have questions regarding this information.

Sincerely,

Kathleen S. Shim

R. Wayne Frost, Pharm.D., J.D.
Associate Director
Regulatory Affairs

enclosures

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[redacted]

ASTRA

Astra USA

ORIGINAL

NDA 20-533
NAROPIN™
(ropivacaine HCl monohydrate)

SAFETY UPDATE REPORT

November 6, 1995

ORIG AMENDMENT
N(SU)

Mr. David Morgan
Consumer Safety Officer
Pilot Drug Evaluation Staff
HFD 007, Room 9B-45
5600 Fishers Lane
Rockville, MD 20852

Dear Mr. Morgan,

Pusuant to 21 CFR 314.50(d)(5)(vi)(b) we are enclosing a Safety Update Report to our pending application, NDA 20-533, for Naropin™.

A review of all available information reveals no new information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. However, since the original March 29, 1995 submission, the following relevant reports have been completed and are now being provided to FDA:

- Body Temperature during Postoperative Epidural Infusion of Ropivacaine: A Retrospective Analysis
- Ropivacaine and Bupivacaine in Obstetrics: A Meta-Analysis of Neurologic Adaptive Capacity Scores of the Neonate and Delivery Variables
- 4 Week Epidural (Continuous Infusion) Tolerance Study in the Beagle Dog of Ropivacaine (LEA 103) and Bupivacaine (LEA 131)
- A Double Blind Comparison Between Epidural Ropivacaine 0.25% and Bupivacaine 0.25% given as Top-Up Doses for Pain Relief During Labour

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Should you have any questions regarding this submission, please contact me at (508)366-1100.

Sincerely,

R. Wayne Frost, Pharm.D., J.D.
Associate Director
Drug Regulatory Affairs

ORIGINAL

ASTRA
Astra USA

NDA 20-533
NAROPIN™
(ropivacaine HCl monohydrate)

November 3, 1995

ORIG AMENDMENT
N(BL)

Mr. David Morgan
Consumer Safety Officer
Pilot Drug Evaluation Staff
HFD 007, Room 9B-45
5600 Fishers Lane
Rockville, MD 20852

Dear Mr. Morgan,

Please refer to our pending NDA 20-533 submitted on March 29, 1995. Also refer to the facsimile from FDA to Astra on September 25, 1995 requesting that we modify the clinical pharmacology and pharmacokinetics section of our label.

We are now providing FDA with a modified version of our package insert in the requested format. The information is presented on a floppy disk formatted in WordPerfect 6.0. A paper copy of the document is also provided.

Should you have any questions regarding this submission, please contact me at (508)366-1100.

Sincerely,

R. Wayne Frost, Pharm.D., J.D.
Associate Director
Drug Regulatory Affairs

MAILING ADDRESS
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ORIGINAL

ASTRA®
Astra USA

NDA 20-533
NAROPIN™
(ropivacaine HCl monohydrate)

. NEW CORRESP

Response to Request for Information

September 13, 1995

Mr. David Morgan
Consumer Safety Officer
Pilot Drug Evaluation Staff
HFD 007, Room 9B-45
5600 Fishers Lane
Rockville, MD 20852

Dear Mr. Morgan,

Please refer to our NDA 20-533 submitted on March 29, 1995. Also refer to the teleconference between FDA and Astra on August 7, 1995 regarding the request for our pharmacokinetic and clinical pharmacology integrated summaries in electronic format.

We are now providing FDA with a diskette containing WordPerfect versions of those summaries. Please note that the appendix of each of the documents is the same and is therefore converted only once. Also, since the figures did not convert satisfactorily, and from the information we received at our teleconference were not needed by FDA, they do not appear in the converted version. The absence of these figures results in the page location in both document's tables of content to be incorrect. Also, because the figures are not present, the pagination incorrectly indicates that the pharmacokinetic summary has a total of 136 pages and the clinical pharmacology document has 105 pages. It is possible, however, to search in the document via chapter numbers and headings. Please let us know whether this electronic file proves to be satisfactory.

A paper copy of the documents contained on the diskette is also included.

Should you have any questions regarding this submission, please contact me at (508)366-1100.

Sincerely,

R. Wayne Frost
Associate Director
Drug Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 14 1995
HFD-007

MAILING ADDRESS
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NDA 20-533
NAROPIN™
(ropivacaine HCl monohydrate)

Response to Request for Information

ORIG AMENDMENT
N(EE)

August 29, 1995

Robert Bedford, M.D.
Director
Pilot Drug Evaluation Staff
HFD 007, Room 9B-45
5600 Fishers Lane
Rockville, Maryland 20°

Dear Dr. Bedford:

Please refer to our NDA 20-533 submitted on March 29, 1995 and to the FDA letter dated June 19, 1995 from Ahmed El-Tahtawy, R.Ph, Ph.D. requesting further information regarding the Pharmacokinetics section of our application.

At this time, a response to the first question regarding the pharmacokinetic population analysis for protein binding is provided.

This correspondence completes the responses to the issues raised in the June 19, 1995 letter from the Agency.

Please contact me at (508) 366-1100, extension 2111 should you have any additional questions regarding this information.

Sincerely,

for R. Wayne Frost, Pharm.D., J.D.
Associate Director
Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 3 1 1995
HFD-007

20533\ebf.001
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ORIGINAL

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Astra USA

NDA 20-533
NAROPIN™
(ropivacaine HCl monohydrate)

ORIG AMENDMENT
N(BB)

Response to Request for Information

August 24, 1995

Mr. David Morgan
Consumer Safety Officer
Pilot Drug Evaluation Staff
HFD 007, Room 9B-45
5600 Fishers Lane
Rockville, MD 20852

Dear Mr. Morgan,

Please refer to our NDA 20-533 submitted on March 29, 1995. Also refer to the teleconference between FDA and Astra on August 7, 1995 regarding the request for pharmacokinetic data in electronic format.

We have thus far submitted 10 of the requested 14 reports and are now supplying FDA with the remaining 4 pharmacokinetic reports:

Study	Subjects	Administration	Indication
AF8674	healthy volunteers	iv	-
91Ro43	healthy volunteers	iv	-
89Ro07	patients	epidural	elective surgery (varicose veins)
87Ro11	patients	brachial plexus (subclavian)	elective orthopedic surgery in the upper limbs

The data are stored using Excel for Windows (version 5.0). A list of the variables contained within the datasets is attached. Each dataset consists of at least two sheets. Sheet one contains demographic data and sheet two contains plasma data. In addition, studies AF8674 and 91Ro43 have a third sheet which contains urine data. Please consult the study report for supplementary information regarding patients 5 and 9 in Study 91Ro43.

In addition, we are also providing a second diskette which contains the pharmacokinetic summaries, in the FDA requested format, for all 14 studies. A paper copy of these summaries is also included.

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Please contact me at (508) 366-1100 extension 2111 should you have questions regarding this information.

Sincerely,

Kathleen S. Shim

for: R. Wayne Frost, Pharm.D., J.D.
Associate Director
Regulatory Affairs

ORIGINAL

ASTRA
Astra USA

NDA 20-533
NAROPIN™
(ropivacaine HCl monohydrate)

NEW CORRESP

Response to Request for Information

August 23, 1995

Mr. David Morgan
Consumer Safety Officer
Pilot Drug Evaluation Staff
HFD 007, Room 9B-45
5600 Fishers Lane
Rockville, MD 20852

Dear Mr. Morgan,

Please refer to our NDA 20-533 submitted on March 29, 1995. Also refer to the teleconference between FDA and Astra on August 7, 1995 regarding the request for pharmacokinetic data in electronic format.

We submitted four of the requested reports on August 18 and we are now providing FDA with two diskettes which contain an additional six sets of electronic data from the following pharmacokinetic reports:

Study	Subjects	Administration	Indication
90Ro46	healthy volunteers	epidural	-
90Ro27	healthy volunteers	iv	-
9oRo31	healthy volunteers	iv	-
92Ro61	patients	epidural	post-op
90Ro33	patients	epidural	cesarean section
91Ro42	healthy volunteers	rectal	-

The data are stored using Excel for Windows (version 5.0). A list of the variables contained within the datasets is attached. Each dataset consists of at least two sheets. Sheet one contains demographic data and sheet two contains plasma data. In addition, studies 90Ro27, 90Ro31, and 91Ro42 have a third sheet which contains urine data.

MAILING ADDRESS
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Please contact me at (508) 366-1100 extension 2111 should you have questions regarding this information

Sincerely,

R. Wayne Frost, Pharm.D., J.D.
Associate Director
Regulatory Affairs

ORIGINAL

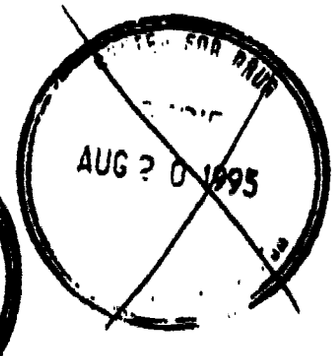
ASTRA
Astra USA

NDA 20-533
NAROPIN™
(ropivacaine HCl monohydrate)

ORIG AMEND. DT
N(BZ)

Response to Request for Information

August 18, 1995



Mr. David Morgan
Consumer Safety Officer
Pilot Drug Evaluation Staff
HFD 007, Room 9B-45
5600 Fishers Lane
Rockville, MD 20852

Dear Mr. Morgan,

Please refer to our NDA 20-533 submitted on March 29, 1995. Also refer to the teleconference between FDA and Astra on August 7, 1995 regarding providing pharmacokinetic reports in electronic format, and to the telephone request from the FDA statistical reviewer, Tom Permutt, for SAS datasets for the postoperative pain study O1 (92Ro58).

We are now providing FDA with electronic data (review copy only) from the following pharmacokinetic reports. A paper copy is also included.

Study	Subjects	Administration	Indication
90Ro14	patients	epidural	hysterectomy
90Ro19	patients	infiltration	post-op pain
91Ro45	patients	epidural	labor
91Ro52	healthy volunteers	intercostal	

The data are stored using Excel for Windows (version 5.0). A list of the variables contained within the datasets is presented with the paper copy. Each dataset consists of two sections. Section one contains demographic data and section two contains plasma data. These studies do not have any urine data. We plan to provide you with the rest of the requested electronic pharmacokinetic data within two weeks.

In addition, we are also providing FDA with a second disk which contains three files for the study on postoperative pain, Study O1 (92Ro58). The three files are README.LST, IMPORT.SAS and TRANS.XPO. In addition to the electronic file, we have enclosed a paper copy of README.LST. The first page of this file describes the entire electronic file. We have also included paper copies of the dataset contents and two version of a PROC PRINT of each dataset, one with and one without formatted variables.

MAILING ADDRESS
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Westborough, MA 01581-4500

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Westborough, MA

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508 366-1100

FAX
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TELEX
6810105-Cable/Astrapharm

The documents in this submission are arranged according to the attached table of contents. Please contact me at (508) 366-1100 extension 2111 should you have questions regarding this information.

Sincerely,

Kathleen L. Lim

for R. Wayne Frost, Pharm.D., J.D.
Associate Director
Regulatory Affairs

ORIGINAL

ASTRA
Astra USA

ORIG AMENDMENT
N(E5)

NDA 20-533
NAROPIN™
(ropivacaine HCl monohydrate)

Response to Request for Information

August 16, 1995

Mr. David Morgan
Consumer Safety Officer
Pilot Drug Evaluation Staff
HFD 007, Room 9B-45
5600 Fishers Lane
Rockville, MD 20852

Dear Mr. Morgan,

Please refer to our NDA 20-533 submitted on March 29, 1995 and to the FDA letter dated June 19, 1995 from Ahmed El-Tahtawy, R.PH, Ph.D. requesting further information regarding the pharmacokinetics section of our application.

We are now providing FDA with our responses to four of the five questions along with a new supporting report entitled, "Identification of Human Cytochrome P450 Isozymes Mediating LEA103 (ropivacaine) metabolism". Question number one regarding a more detailed report of the assumptions and procedures used in the pharmacokinetic population analysis for protein binding has not been addressed yet since the person responsible for this information is on vacation. We will provide you with a response to that question as soon as possible.

Please contact me at (508) 366-1100 extension 2111 should you have questions regarding this information.

Sincerely,

Kathleen S. Glinn

for: R. Wayne Frost, Pharm.D., J.D.
Associate Director
Regulatory Affairs

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NDA 20-533
NAROPIN™
(ropivacaine HCl monohydrate)

NEW CORRESP

C

General Correspondence

July 31, 1995

Mr. David Morgan
Consumer Safety Officer
Pilot Drug Evaluation Staff
HFD 007, Room 9B-45
5600 Fishers Lane
Rockville, MD 20852

Dear Mr. Morgan,

Please refer to our NDA 20-533 submitted on March 29, 1995 for NAROPIN™.

As you requested, I am enclosing a copy of the cover letter which we sent to Dr. Merin in response to his request for more information as he reviews the cardiotoxicity information in this application. A copy of his request is also enclosed.

If you should have any questions regarding this submission, please contact me at (508)366-1100 ext. 2111.

Sincerely,

R. Wayne Frost, Pharm.D., J.D.
Associate Director
Regulatory Affairs

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[redacted]

[redacted]

ASTRA®
Astra USA

July 17, 1995

NEW CORRESP
C

David Morgan, CSO
Pilot Drug Evaluation Staff (HFD-007)
CDER, FDA
5600 Fishers Lane
Parklawn Building
Room 9B-45
Rockville, MD 20857

Dear Mr. Morgan:

Attached please find the cover letter and shipping labels for the clinical study and cardiotoxicity reports that you requested we send to your external reviewers. Please let me know if the reviewers are missing any of the requested information.

I look forward to working with you towards the successful approval of our NAROPIN™ NDA.

Sincerely,

R. Wayne Frost, Pharm., J.D.
Associate Director, Regulatory Affairs

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[redacted]

ORIGINAL

ASTRA®
Astra USA

NDA 20-533

NAROPIN™
(ropivacaine HCl monohydrate)

NEW CORRESP
C

May 23, 1995

David Morgan, CSO
Pilot Drug Evaluation Staff
5600 Fishers Lane
Parklawn Building Room 9B-45
Rockville, MD 20857

Dear Mr. Morgan:

At your request, I have enclosed a desk copy of Volume 1.1 of the ropivacaine HCl NDA #20-533.

Please note that the annotated package insert is contained within this volume. I was wondering if this would be sufficient for the external reviewers rather that the Word Perfect version of diskette.

I look forward to discussing this with you.

Sincerely,

R. Wayne Frost, Pharm.D., J.D.
Associate Director, Regulatory Affairs

NAI
5-30-95

MAILING ADDRESS
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ASTRA®
Astra USA

April 25, 1995

NDA 20-533
Ropivacaine

ORIGINAL

C

. NEW CORRESP

David Morgan
CSO, Pilot Drug Evaluation Staff
HFD 007, Room 9B-45
5600 Fishers Lane
Rockville, MD 20857

Dear Mr. Morgan:

Would you please check on our acknowledgement letter for the receipt, by your division, of the ropivacaine HCl NDA. We have not received one from your group to date. Thank you for your assistance in this matter.

Sincerely,

R. Wayne Frost, Pharm.D., J.D.
Associate Director, Regulatory Affairs

WAL
Letter
10/24/95

CENTER FOR DRUG
REC'D
APR 26 1995
HFD-007

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ASTRA
Astra USA

NDA 20-533
Naropin™
(ropivacaine HCl monohydrate)

Drug User Fee

March 29, 1995

Food and Drug Administration
P.O. Box 7777-W745
Philadelphia, PA 19175-7745

Dear Sir/Madam:

Please refer to our NDA 20-533 submitted on March 29, 1995 for NAROPIN™.

We inadvertently did not include a copy of Form FDA 3397 with the original submission and user fee payment (User Fee I.D. Number 2657) and are now providing a copy of that form to you. We apologize for any inconvenience this oversight may have caused.

If you should have any questions regarding this submission, please contact Wayne Frost, Pharm.D., J.D., at (508)366-1100 ext. 2111.

Sincerely,

R. Wayne Frost, Pharm.D., J.D.
Associate Director
Regulatory Affairs

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ASTRA®
Astra USA

ORIGINAL

NDA 20-533
NAROPIN™
(ropivacaine HCl monohydrate)

Amendment To A Pending Application

April 5, 1995

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

. NEW CORRESP

C

Dear Sir or Madam,

Please refer to our NDA 20-533 submitted on March 29, 1995 for NAROPIN™.

We inadvertently did not include a copy of Form FDA 3397 with the original submission and user fee payment (User Fee I.D. Number 2657) and are now providing a copy of that form to you. We apologize for any inconvenience this oversight may have caused.

If you should have any questions regarding this submission, please contact Wayne Frost, Pharm.D., J.D., at (508)366-1100 ext. 2111.

Sincerely,

R. Wayne Frost, Pharm.D., J.D.
Associate Director
Regulatory Affairs

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Astra USA

NDA 20-533
Naropin™
(ropivacaine HCl Injection)

DUPLICATE

ORIG AMENDMENT
N(BL)

AMENDMENT TO A PENDING APPLICATION

March 29, 1996

Robert Bedford, M.D.
Director
Division of Anaesthetic, Critical Care
and Addiction Drug Products
Center for Drug Evaluation and Research
HFD-170
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Bedford,

Please refer to our pending NDA 20-533 submitted on March 29, 1995, to the FDA facsimile dated February 29, 1996 outlining requirements for phase IV commitments to this file, and to the FDA request for five copies of color mock-ups of representative samples of the draft labeling.

These documents are provided on the following pages according to the attached table of contents. Note that four copies of the draft labeling are located in the review copy and one copy is located in the archival copy.

Should you have any questions regarding this submission, please contact me at (508)366-1100.

Sincerely,

R. Wayne Frost, Pharm.D., J.D.
Associate Director
Drug Regulatory Affairs

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[redacted]

ASTRA®
Astra USA

NDA 20-533
Naropin™
ropivacaine HCl

Drug User Fee

March 29, 1995

Food and Drug Administration
P.O. Box 7777-W745
Philadelphia, PA 19175-7745

Dear Sir/Madam:

In accordance with the Prescription Drug User Fee Act of 1992, we are enclosing a check in the amount of for our new NDA, 20-533, for Naropin™. As required by the Act, this check represents half of the fee which is due. The remaining half will be due 30 days from the date FDA issues an invoice and an action letter for the application.

Sincerely,

R. Wayne Frost, Pharm.D., J.D.
Associate Director, Regulatory Affairs

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ASTRA
Astra USA

NDA 20-533
Naropin™ (ropivacaine HCl Injection)

ORIG AMENDMENT
N(BL)

AMENDMENT TO A PENDING APPLICATION

ORIGINAL

May 7, 1996

Robert Bedford, M.D.
Director, Division of Anaesthetic, Critical Care and Addiction Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD 170, Room 9B-45
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Bedford,

Please refer to our pending NDA 20-533 submitted on March 29, 1995, and to the revised draft package insert submitted on February 26, 1996.

We have incorporated some minor revisions to the package insert and are providing a copy for your review. The revisions that have been made have been itemized by line number on the following pages.

Should you have any questions regarding this submission, please contact me at (508)366-1100, extension 2111.

Sincerely,

R. Wayne Frost, Pharm.D., J.D.
Associate Director
Drug Regulatory Affairs

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[redacted]

1. Line 1:

2. **DESCRIPTION**

Line 5:

Line 11:

Line 35:

3. **PHARMACOKINETICS**
Clinical Trials
Epidural Administration In Post Operative Pain Management

Line 239:

4. **DOSAGE AND ADMINISTRATION**

Line 899:

5. **HOW SUPPLIED**

Line 915:

The following sentences which specify how many units are contained within each carton were deleted:

Also, the following dosage forms have been deleted as we do not plan to market them.

Summary Basis of Approval

MEMORANDUM FOR THE RECORD

Date: March 13, 1996
NDA: 20-533
Sponsor: Astra, USA

CSO: David Morgan

Summary Basis of Approval

All reviews performed by this division and external reviewers will serve as the summary basis of approval for NDA 20-533 Naropin (ropivacaine Hcl) Injection 2.0 mg/mL, 5.0 mg/mL, and 10.0 mg/mL.

Final Printed Labeling

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

Division Of Anesthetic, Critical Care, And Addiction Drug Products

Application Number: NDA 20-533
Name of Drug: Naropin (ropivacaine HCL) Injection
Sponsor: Astra USA

Dates:

Correspondence date: July 25, 1996
CDER Date: July 26, 1996
Review Date: August 28, 1996

Type of Submission: Major Labeling Revisions

Material Reviewed

Minor Draft Labeling Amendment submitted by sponsor 5-7-96.

Approvable Letter dated June 28, 1996 which contained labeling recommendations to the sponsor's Draft Label dated May 7, 1996.

Sponsor fax dated July 12, 1996 in response to approvable letter.

Agency's Fax to the Sponsor with final agreed upon recommendations dated July 17, 1996.

Major Draft Labeling Amendment (AL) submitted on July 25, 1996 which incorporated all proposed changes.

Discussion

An Approvable letter with recommended labeling changes dated June 28, 1996 was submitted to the sponsor. The sponsor was requested by the agency to provide clarification and support documentation from their NDA for the labeling changes that were in question. Negotiations between the agency and the sponsor resulted in a revised list of labeling changes that were detailed in a fax to the sponsor dated July 17, 1996.

Review

The review of this label revealed that the labeling revision requested in our June 28, 1996, Approvable letter, and fax dated July 17, 1996 were incorporated as follows:

Pharmacokinetics section:

Pharmacodynamics subsection:

"In two clinical pharmacology studies ..... no changes in cardiac output."

Epidural Admin.. In Surgery

Epidural Admin. in Labor and Delivery

CHANGES PER THE SPONSORS 'S JULY 12, 1996 SUBMISSION:

Adverse Reactions:

Incidence <1%

Table 2

Tables 3 and 4

Other Comments

As requested by the Primary Medical Officer, the sponsor was contacted to clarify the numbers of patients receiving bupivacaine in their Safety Update.

Conclusions

Review of the label revealed no other changes, other than acceptable editorial corrections.

Recommendations

I recommend that the amendment submitted July 25, 1996, be approved.

David Morgan 9-9-96
Project Manager

Concur: Corinne P. Moody
Chief
Project Management Staff

Attachments:

1. Minor Draft Labeling Amendment dated 5-7-6
2. Approvable (AE) letter dated 6-28-96
3. Sponsor's submission 7-12-96 in response to our AE letter
4. Agency's Fax 7-17-96
5. Major Draft labeling Amendment dated 7-25-96

. MEDICAL OFFICER REVIEW

IND#: 20-533 Study L-2
NAME: A dose-response study of 0.75% ropivacaine with epinephrine in epidural anesthesia in patients undergoing lower limb surgery

SPONSOR: Astra
PO Box 4500
Westborough, MA 01581-4500
Phone (508 366-1100, Fax (508) 366-7406

SUBMISSION DATE: March 29, 1995
REVIEWER: Wendell C. Stevens, MD
REVIEW DATE: August 10, 1995
SUBMISSION TYPE: Commercial IND
RECEIVED:
CSO: Vaccari

1. RESUME

BACKGROUND

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is believed to be less cardiotoxic or neurotoxic than bupivacaine and to offer as effective and longlasting sensory blockade as bupivacaine with less motor blockade. This is a dose-ranging (one concentration, varying volume) study performed in support of the sponsor's NDA.

CLINICAL STUDY

Investigator: H. Nolte, Minden, Germany

Treatment Plan: This was an open, non-randomized study in which successive groups of 15 ASA I or II patients undergoing leg varicose vein surgery were to receive 0.75% ropivacaine, 15, 20, and 25ml in the epidural space. This was preceded by morphine and scopolamine premedication. The study drug was placed at L2-L3 or L3-L4, midline, sitting position, with 3ml of the study drug as test dose and the remaining 12, 17, or 22 ml as main dose, all through the 16 gauge Crawford needle. Then the patient was placed supine.

The methods of assessment of sensory block, motor block (Bromage scale only) and safety were those noted in the Introductory Comments.

48 patients were admitted to the study but one was excluded because the operation was not varicose vein surgery. The sequence of drug amount groups was 20, 15, and 25ml, not 15, 20, then 25 ml as planned. Other protocol deviations were 1 overweight and 1

received a different narcotic than morphine or a different route of administration.

Groups were well-matched for age, weight, height, concurrent diseases and medications. More females than males received the 15 and 25 ml doses. There was adequate time between injection of the study drug and onset of surgery for assessments of blockade.

Efficacay assessment: Analgesia was achieved in all 47 evaluable patients.

1) Sensory block: Onset of lumbosacral anesthesia occurred at about 5 minutes but some patients required as long as 18 minutes. The times were longest for the higher doses. The maximum cephalad level was T3 for 15 ml, T2 for 20 ml, and C8 for 25 ml groups. But, as the dose increased, the number of patients exhibiting higher blocks increased. The duration of anesthesia at some lumbosacral dermatomes was significantly greater with higher doses. The clinical significance is probably small, however. For example, the median durations of sensory block at L5 were 4.9, 4.8, and 4.3 hours for the 15, 20 and 25 doses, respectively.

2) Motor block: Nearly all patients exhibited motor block degree 1, 50-75% showed degree 2, and only 6-20% degree 3. Once motor block occurred it lasted 3-4 hours in all groups.

3) Adequacy of anesthesia: One patient in the 15 group was the only patient to require additional medication to complete the operation.

Safety Assessments: The decline in systolic blood pressure was more rapid in the 20 ml group and certain other statistically significan. differences existed. However, my search of the raw cardiovascular data suggested all of the changes were compatible with sympathetic blockade and not treatment specific. No other unique adverse events occurred.

2. CONCLUSIONS:

The sponsor's summary analyzed the results well. All of the doses produced adequate anesthesia for leg surgery. Something which caught my attention was the duration over which the block could continue to progress. Although I estimate that the maximum cephalad spread occurred in 15-20 minutes in the average patient, additional spread continued for as long as 45 minutes in some patients. The larger volume produced more extensive blocks but were of little value in improving lumbosacral anesthesia.

3. RECOMMENDATIONS REGARDING LABELING:

This study supports the labeling indicating the speed of onset of

sensory and motor block and the durations of blockade. This study supports the use of the smaller volume range for lower extremity surgery. It supports the likely occurrence of decreased blood pressure with epidural anesthesia.

Wendell C. Stevens, MD
Consultant

MEDICAL OFFICER REVIEW

IND#: 20-533 Study I-3

NAME: An open study of 0.5% and 0.75% ropivacaine, without and with epinephrine in epidural anesthsia in patients undergoing urologic surgery

SPONSOR: Astra
PO Box 4500
Westborough, MA 01581-4500
Phone (508) 366-1100, Fax (508)366-7406

SUBMISSION DATE: March 29, 1995
REVIEWER: Wendell C. Stevens, MD
REVIEW DATE: August 9, 1995
SUBMISSION TYPE: Commercial IND
RECEIVED:
CSO: Vaccari

1. RESUME

BACKGROUND

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is believed to be less cardiotoxic or neurotoxic than bupivacaine and to offer as effective and longlasting sensory blockade as bupivacaine with less motor blockade. This is an epinephrine dose-ranging study performed in support of the sponsor's NDA.

CLINICAL STUDY

Investigator: B J Lofstrom, Linkoping, Sweden

Treatment Plan: 24 ASA I or II male patients undergoing transurethral surgery participated in this open study of 0.5% (12 pts) or 0.75% (12 pts) ropivacaine epidural anesthesia. Addition of 5 ug/ml epinephrine to the study drug was randomized so that 6 patients in each group received epinephrine. Patients were to receive oral diazepam premedication and hydration with 500 ml electrolyte solution IV. An epidural catheter was placed at the L3-L4 or L4-L5 interspace via a midline Touhy needle while the patient was in the lateral position and then the patient was placed in the supine position. A 3 ml lidocaine 1.0% with 5 ug/ml epinephrine test dose was given followed by 20 ml of study drug incrementally over 3-4 minutes. The volume of drug was constant but the concentration differed in the two groups.

The methods of assessment of sensory block, motor block (Bromage scale only) and safety were those noted in the Introductory Comments.

All 24 patients enrolled the study were evaluable. Protocol deviations included rectal rather than oral route of premedication is most patients, paramedian rather than midline approach to the epidural space in 2 patients, and use of 600-1000 ml hydrating solution rather than 500 ml in most patients.

These small groups were well matched for age, weight, height, coexisting diseases and preoperative medications.

Efficacy assessment: Lumbosacral anesthesia was achieved in all patients and it was satisfactory for surgery in all patients enrolled in the study.

1) Sensory block: Onset of analgesia below T11 occurred by 8 minutes after injection. There were no differences among the groups. Sensory blockade lasted 3-6 hours in these same dermatomes and there was no difference among the groups. Maximum height of block was either T3 or T4, and again was similar among the groups. The longest median time to achieve this level was 27.5 minutes but the block continued to rise for as long as 60 minutes in some patients. Blockade was of much longer duration at the lumbosacral than at the upper thoracic dermatomes.

2) Motor block: The groups were fairly similar in frequency of Degree 1 and 2 block (0.5% ropiv+epi somewhat less) but only the 0.75% concentration with or without epinephrine produce consistent Degree 3 block. Motor blocks lasted 2-2.5 hours in most instances.

3) Adequacy of anesthesia: Analgesia was satisfactory for surgery in all instances and there was no visceral pain.

Safety Assessments: Some decrease in blood pressure was common but the magnitude of change was usual for epidural anesthesia and was not related to the concentration of drug or presence of epinephrine. No other unique adverse events occurred.

CONCLUSIONS:

The sponsor's summary analyzed the results well. The doses of drug were satisfactory for transurethral surgery and the minimal muscle relaxation with the 0.5% concentration was not a problem. Their data suggest that the addition of 5 ug/ml epinephrine does not improve the quality or duration of sensory or motor block.

RECOMMENDATIONS REGARDING LABELING:

This study supports the labeling indicating the presence of epinephrine has no major effect on the time of onset and duration of the neuronal blocking action of ropivacaine. The study supports the use of the smaller suggested dose range for transurethral surgery.

Wendell C. Stevens, MD
Consultant

MEDICAL OFFICER REVIEW

IND#: 20-533 Study L-4
NAME: A multicenter open study of 0.5%, 0.75%, and 1.0% ropivacaine in epidural anesthesaia in patients undergoing urological surgery

SPONSOR: Astra
PO Box 4500
Westborough, MA 01581-4500
Phone (508) 366-1100, Fax (508) 366-7406

SUBMISSION DATE: March 29, 1995
REVIEWER: Wendell C. Stevens, MD
REVIEW DATE: August 10, 1995
SUBMISSION TYPE: Commercial IND
RECEIVED:
CSO: Vaccari

1. RESUME

BACKGROUND

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is believed to be less cardiotoxic or neurotoxic than bupivacaine and to offer as effective and longlasting sensory blockade as bupivacaine with less motor blockade. This is a dose-ranging study performed in support of the sponsor's NDA.

CLINICAL STUDY

Investigators: D B Scott, Edinburgh, Scotland; A P Rubin, London, England, UK; C E Pither, London, England, UK

Treatment Plan: This was an open, non-randomized, parallel, three center study in which a total of 48 ASA I or II patients having urological surgery were enrolled to receive 20 ml of 0.5%, 0.75%, or 1.0% epidural ropivacaine. At each center the first 5 patients received 0.5% ropivacaine, the next 5 0.75%, and the next 5 1.0% (total 15 patients at each center). Thus, the volume of drug was constant but the milligrams given was different among the groups. The results from the 3 centers were pooled for analysis. Patients were to receive oral diazepam as premedication. The study drug was given at L1-L2 or L2-L3 for the most part, always via an epidural catheter, sometimes while in the lateral position and but more often while supine. A test dose of 3 ml 1-2% lidocaine with 5 ug/ml epinephrine preceded the study drug.

The methods of assessment of sensory block, motor block (Bromage Scale only) and safety were those noted in the Introductory Comments.

Forty-five patients completed the study, 15 at each center. Of 48 who were enrolled, one received no study drug because the catheter was thought not to be in the epidural space and two were classified as technical failures. Protocol deviations, although several in number, were minor and consisted of 1 patient getting 0.5% ropivacaine out of sequence, mistiming of oral diazepam in 11 patients, no premedication other than electrolyte solution in 9 patients, and 1 patient receiving metoprolol + hydrochlorthiazide. Two patients received slightly smaller amounts of hyrating solution than desired.

These small groups were well-matched for age (mean of all groups was 59+11(sd) years), weight, height, coexisting diseases and medications, and gender. There were 41 males and 4 females (3 females in the 0.5% and 1 in the 0.75% group). There was adequate time between injection of the drug and onset of surgery for assessments of blockade to be done.

Efficacay assessments: Two patients were termed technical failures because no block occurred and one patient did not receive a study drug.

1)Sensory block: Median onset time for analgesia at T11 or below was similar with all doses and was 2-5 minutes at T12 or L2 to 10-20 minutes at S5. Two of the 0.5% group, 4 of the 0.75% group and 1 of the 1.0% group did not achieve analgesia at S5. Maximal cephalad levels were T1 for the 0.5% group, C5 for the 0.75% group (3 pts), and C2 for the 1.0% group (1 pt). There was a tendency for the length of blockade to be positively correlated with concentration of agent. The difference was not large in clinical terms, however, with median maximal durations of 4.5, 4.8 and 5.5 hours for the 0.5%, 0.75%, and 1.0% concentrations, respectively.

2) Motor block: There were no significant differences between the groups in frequency of different degrees of motor block. Most patients had degree one block, 73-86% had degree two block, and 25-60% had degree 3 block. It took 30-40 minutes for onset of degree 3 block and the block lasted 1-3 hours.

3) Adequacy of anesthesia: Analgesia was satisfactory for surgery in all but two 0.75% group patients. One 1.0% group patient had inadequate muscle relaxation for the operation to proceed. One 0.5% patient had visceral pain.

Safety Assessments: There were no group specific cardiovascular events or changes that seemed uncommon during epidural anesthesia. One patient in the 0.75% group experienced severe bradycardia 2 hours after injection of the study drug. No other unique adverse events occurred.

2. CONCLUSIONS:

The sponsor's summary analyzed the results well. All of the dosing regimens provided about equally satisfactory anesthesia. I was impressed that in many instances as much time was required to achieve the most caudad block (S5) as the highest block (upper thoracic or cervical dermatomes). Once the lower blocks occurred they lasted several hours whereas the regression of the uppermost blocks was relatively rapid. The largest dose, 20 ml of 1.0% ropivacaine, yielded an inordinately high block in several patients. The next lower dose, 20 ml of 0.75% ropivacaine also produced cervical dermatome anesthesia.

3. RECOMMENDATIONS REGARDING LABELING:

This study supports the labeling indicating the speed of onset of sensory and motor block and the durations of blockade. It supports the recommendation to use the smallest effective dose in that the largest dose of this study was associated with very broad sensory blockade. The frequency of occurrence of hypotension indicated in the labeling is also supported by this study.

Wendell C. Stevens

Wendell C. Stevens, MD
Consultant

MEDICAL OFFICER REVIEW

IND#: 20-533 Study L-5

NAME: A comparison of 0.75% ropivacaine and 0.75% bupivacaine, both with epinephrine, in epidural anesthesia in patients undergoing urological surgery.

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SUBMISSION DATE: March 29, 1995
REVIEWER: Wendell C. Stevens, MD
REVIEW DATE: August 10, August 12, 1995
SUBMISSION TYPE: Commercial IND
RECEIVED:
CSO: Viccari

1. RESUME

BACKGROUND

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is believed to be less cardiotoxic or neurotoxic than bupivacaine and to offer as effective and longlasting sensory blockade as bupivacaine with less motor blockade. This is a comparative study of ropivacaine and bupivacaine performed in supportof the sponsor's NDA.

Investigator: M J M Gielen, Nimegen, The Netherlands

Treatment Plan: Forty-three patients, 40 males, 3 females, ASA I or II, were enrolled in this randomized, double-blind, parallel group comparison of 0.75% ropivacaine and 0.75% bupivacaine given epidurally for urological surgery. The operations were either transurethral procedures or done on external genitalia or vaginally (cystocoele). Oral diazepam 5-15 mg and balanced electrolyte solution, 500 or more ml, were given before the block. An epidual catheter was placed via a 16-18 gauge Touhy needle at L2-3 or L3-4, midline, with the patient in the lateral position. The patient was placed in the supine position and a test dose of 3 ml of the study drug was given followed by 17 ml of the same drug incrementally over 4 minutes. This gave a total dose of 20 ml of the study drug. Surgery did not begin for at least 30 minutes after drug injection.

Assessment of sensory blockade, motor blockade (Bromage Scale only), quality of anesthesia, safety and adverse events was done as described in the Introductory Comments.

Forty-One patients were available for efficacy analysis since 2 bupivacaine patients developed no neural blockade. There were 21

patients in the ropivacaine group and 20 in the bupivaciane group. The bupivacaine patients mean age was greater than the ropivaciane patients, 53±15 vs 43±14 years. They were well-matched for weight, height, coexisting disease and other medications. Sufficient time existed between injection of the study drug and onset of surgery for evaluation of drug effects. There were several protocol deviations such as lack of planned preoperative ECG in 20 ASA I patients or non-standard timing of premedication, but none of the deviations would seem to affect the assessment procedures.

Efficacy assessments: One ropivacaine and 2 bupivacaine patients needed inhaled or intravenous anesthesia to complete the surgery. One patient in the ropivacaine group experienced pain during epididectomy and one patient in the bupivacaine group experienced pain during a second introduction of the cystoscope. The other bupivacaine patient had "visceral" pain.

1) Sensory block: Analgesia occcurred at T11 and below in all patients except at S5 in 1 ropivacaine patient and at T11 in 1 ropivacaine and 1 bupivacaine patient. The highest level reached in either group was T3. There was no difference between groups in onset time, 2-10 minutes median onset time. Onset time was shortest near the injection site and longer as one tests up and down from that site. Durations of analgesia tended to be shorter with ropivacaine but the range of median durations, 3.5-7.8 hours for ropivaciane and 4.3-7.9 hours for bupivacaine suggests the difference was of little import. Although blockades as high as T3 occurred, the median heights were T8 in the ropivacaine group and T6 in the bupivacaine group.

2) Motor block: Significantly more bupivacaine patients achieved degree 2 or 3 block--7/21 ropivacaine and 16/20 bupivacaine patients had degree 3 block. It appeared that it also took longer for motor block to occur with ropivacaine. Blocks lasted longer with bupivacaine but the statistical significance seemed more certain than the clincal significance of the difference.

3) Adequacy of anesthesia: One patient in each group needed additional anesthesia because of pain at the operative site. One patient in the bupivacaine group experienced "visceral" pain.

Safety assessment: The cardiovascular changes were similar among groups and were compatible with those occurring during epidural blockade. The events were treated and did not produce persistant complications. No other adverse events needing discussion occurred.

2. CONCLUSIONS:

Both drugs were reliable in producing anesthesia for transurethral and perineal area surgery in the volumes and concentrations used. The protocol was followed well except for some details of patient

preparation, e.g., ECG, timing of premedication. I conclude that the effects of 0.75% ropivacaine and 0.75% bupivacaine are quite similar except for greater degree of motor blockade with bupivacaine. I note again the long time which sometimes is required for anesthesia to develop at S5 with drugs given epidurally in the lumbar area.

3. RECOMMENDATIONS REGARDING LABELING:

The study supports the statements regarding greater motor blockade with bupivacaine. The dosing recommendations appear to be appropriate as do the statements regarding occurrence of adverse effects.

Wendell C. Stevens, MD
Consultant

MEDICAL OFFICER REVIEW

IND#: 20-533 Study L-6
NAME: A comparison of 0.5%, 0.75%, and 1.0% ropivacaine and 0.5% and 0.75% bupivacaine in epidural anesthesia in patients undergoing urologic, orthopedic and gynecological surgery, and surgery for varicose veins.

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SUBMISSION DATE: March 19, 1995
REVIEWER: Wendell C. Stevens, MD
REVIEW DATE; August 12 and 13, 1995
SUBMISSION TYPE: Commercial IND
RECEIVED:
CSO: Vaccari

1.RESUME

BACKGROUND

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is believed to be less cardiotoxic or neurotoxic than bupivacaine and to offer as effective and longlasting sensory blockade as bupivacaine with less motor blockade. This a dose-ranging (several concentrations, single volume) study comparing ropivacaine and bupivacaine performed in support of the sponsor's NDA.

CLINICAL STUDY

Investigator: J A W Wildsmith, Edinburgh, Scotland

Treatment Plan: 120 ASA I or II patients were enrolled in this randomized, double-blind parallel group study. Oral benzodiazepine premedication and up to 250 ml of electrolyte solution were given preblock. A 16 gauge Touhy needle was placed into the epidural space midline at L3-4 or L2-3 with the patient in the lateral position, an epidural catheter was placed and a 3 ml test dose of 1% lidocaine with 5 ug/ml epinephrine was given. Then 15 ml of the test drug was given incrementally over 2 minutes and 15 seconds. Thirty minutes were allowed for assessment of blockade before beginning surgery.

The methods of assessment of sensory block, motor block (Bromage Scale only) and safety were those noted in the Introductory Comments.

There were 110 evaluable patients from the 120 who were enrolled. Of the 10 exclusions, 1 was for inability to identify the epidural

space, 1 because of a lesion at the site of the planned epidural, and 8 patients (4 bupivacaine and 4 ropivacaine) for technical failure (catheter placement seemed satisfactory but no blockade occurred).

Protocol deviations occurred in timing of premedication, fluid administration and preoperative testing. They did not seem to be significant to the assessment of blockade.

Groups were similar with regard to age, weight, height, diseases requiring surgery, coexisting diseases which might affect outcome, concurrent medications, and time between injection of drug and onset of surgery.

Efficacy assessment: Eighteen of the 110 patients received supplementary anesthesia before surgery, proportionately about the same for ropivacaine and bupivacaine patients. In 5 instances this was due to inadequate block and in nearly all of the remainder "no comment" was given as the reason.

1) Sensory block: Onset of analgesia occurred at the same rate for ropivacaine and bupivacaine groups for the dermatomes involving surgery. Onset was slightly more rapid at upper levels with bupivacaine. Maximal spread and durations were similar with the two agents. There was a tendency for longer blocks with higher concentrations of each agent and the difference reached statistical significance in several comparisons within agent groups.

2) Motor block: The frequency of degree 3 motor block was similar with 0.75% bupivacaine and 1.0% ropivacaine. 1.0% ropivacaine gave significantly more degree 3 blockade than 0.5% ropivacaine. There was a significantly more rapid onset of motor block with 1.0% than 0.5% ropivacaine, with the difference being in the range of 60 minutes. There was a tendency for motor block to last longer the higher the concentration of agent.

3) Adequacy of anesthesia: Noted above were the 18 patients who had supplemental anesthesia before onset of surgery. Seven ropivacaine patients received additional anesthesia during surgery, about equal numbers at each concentration. Three bupivacaine patients also received supplemental anesthesia during surgery. All were given because of pain.

Safety Assessments: One ropivacaine 1.0% group patient had profound bradycardia and then asystole 29 minutes after drug injection. Recovery with treatment was complete and the operation was done. The patient's block level was T7 and the ropivacaine plasma concentration was 1.31 mg/l in a sample taken 10 minutes after the event. Other circulatory and adverse events did not appear to be unusual or related to a specific group.

CONCLUSIONS: The agents were reliable in producing analgesia. There was a tendency for longer sensory blockade and more profound and longer motor blockade the higher the concentration of either agent. Although the extent of analgesia seemed satisfactory, a fairly large number of patients received supplemental general anesthsia. Sometimes this appeared to be for "general" comfort of the patients; at other times it reflected inadequate analgesia. In any event, the additional anesthesia makes it a little hard to be sure just how adequate the anesthesia was. There did not seem to be any surprises among their data. There was a greater difference in duration of sensory and motor block with ropivacaine than bupivacaine.

3. RECOMMENDATIONS REGARDING LABELING:

The sponsor's summary analyzed the results well. The data support a concentration dependence of duration of analgesia and motor block. They support the greater sensory than motor duration of effect for ropivacaine. They support the occurrence of hypotension with epidural ropivacaine.

Wendell C. Stevens, MD
Consultant

MEDICAL OFFICER REVIEW

IND# 20-533 Study L-7
NAME: A comparison of 0.75% ropivacaine, without and with epinephrine 5 ug/ml, in epidural anesthesia in patients undergoing urologic surgery.

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SUBMISSION DATE: March 29, 1995
REVIEWER: Wendell C. Stevens, MD
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SUBMISSION TYPE: Commercial IND
RECEIVED:
CSO: Vaccari

1. RESUME

BACKGROUND

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is believed to be less cardiotoxic or neurotoxic than bupivacaine and to offer as effective and longlasting sensory blockade as bupivacaine with less motor blockade. This study was done to determine whether the combination of ropivacaine with epinephrine significantly influences ropivacaine's neural blockade and is performed in support of the sponsor's NDA.

CLINICAL STUDY

Investigator: C E Pither, London, England

Treatment Plan: Forty-five ASA I or II patients scheduled for elective urological surgery were enrolled in this randomized, double-blind, parallel group study. There were 44 evaluable patients. About one half of the procedures were shock wave lithotripsies; 4 were inguinal hernia repairs; the remainder were cystoscopic or external genitalia operations. No premedicaiton was given and patients were given 500 ml electrolyte solution preblock. Epidural anestheisa was to be done with a 16 gauge Touhy needle at L2-3 or L3-4, midline with the patient in the lateral position, an epidual catheter was placed and the patient placed supine. A test dose of 3 ml of study drug was given followed by 17 ml of the same drug incrementally over a 4 minute period. Total ropivacaine dose was 150 mgm in both groups. Surgery did not begin for at least 30 minutes, allowing time for evaluation of the block.

Assessment of sensory blockade, motor blockade (Bromage Scale only), quality of anesthesia and safety and adverse events were

done as described in the Introductory Comments.

Forty-four patients were evaluable for efficacy and safety analysis since 1 patient in the ropivacaine and epinephrine group was excluded because of technical failure (no block). Twenty-two received 0.75% ropivacaine without epinephrine and 22 received ropivacacine with epinephrine, 5 ug/ml. The groups were matched excellently for age, weight, height and gender. Coexisting diseases and concurrent medications did not appear to be significant. There were 20 protocol deviations. Most of them would not have affected the course of the neural blockade. Those that might have had an effect were L1-2 injection in 1 patient (rather than L2-3 or L3-4) and 4 ropivacaine and 3 ropivacaine with epinephrine patients in whom the study drug was injected by continuous infusion rather than in incremental boluses.

Efficacy assessment: Forty-four patients were evaluable for efficacy assessment. One patient in each group required additional local anesthetic epidurally and/or intravenous agent to complete the procedures. They were therefore not available for analysis of duration of blockade.

1) Sensory block: Lumbosacral dermatome analgesia occurred in all but one patient in the ropivacaine group. One ropivacaine patient's blockade extended to C7 and one ropivacaine with epinephrine patient had a block as high as T1. The groups had similar onset times of 5-10 minutes for segments T10 and below. Duration of blockade in segments below T10 were nearly identical for these groups, varying between 3.3 and 3.6 to 5.8 and 6.3 hours. The longest durations tended to be a the most caudad dermatomes. The median maximum spread (in contrast to the highest level attained in the group noted above) was T5 for the ropivacaine group and T4 for the ropivacaine with epinephrine group. Missed segments occurred in 1 patient in each group.

2) Motor block: Degree, onset time and duration of motor block were the same in these groups. Eight of the 22 patients in each group had degree 3 blocks and it took 45-90 minutes for the blocks to be fully manifested. Degree 3 blocks lasted 1.5-2 hours.

3) Quality of anesthesia: One patient in each group required additional epidural drug to complete surgery. One patient in each group had "visceral" pain, pain with traction on spermatic cord structures. Inadequate cremaster muscle relaxation was troublesome in 1 patient in the ropivacaine with epinephrine group.

Safety assessment: The investigators found greater increase in heart rate and decrease in diastolic and mean arterial pressure in the first 20 minutes after injection of drug in the ropivacaine with epinephrine group. As they state, this is compatible with the beta-adrenergic effect of epinephrine. A patient in the ropivacaine group had a heart rate of only 15 beats/minute 15

minutes after epidural injection. The patient responded to atropine and ephedrine and had no sequelae. The investigators report 12 ropivacaine and 8 ropivacaine with epinephrine patients experienced paresthesias during the block. Other events such as loin pain or backache were self-limited.

2. CONCLUSIONS:

0.75% ropivacaine with or without epinephrine appears to provide effective epidural anesthsaa for this type of surgery. The characteristics of the blockade are the same with or without epinephrine with the exeption of heart rate increase and greater decrease of diastolic prssure if epinephrine is added to the local anesthetic.

3. RECOMMENDATIONS REGARDING LABELING:

The study supports the lack of effect of epinephrine on the neural blockade with ropivacaine. I note again the long time before one can be sure the block will not extend to higher dermatomes, as long as 120 minutes in some patients.

Wendell C. Stevens

Wendell C. Stevens, MD
Consultant

MEDICAL OFFICER REVIEW

IND#: 20-533 Study L-8
NAME: A comparative study of 1.0% ropivacaine and 0.75% bupivacaine when used for epidural anesthesia in patients undergoing lower limb surgery

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SUBMISSION DATE: March 29, 1995
REVIEWER: Wendell C. Stevens, MD
REVIEW DATE: August 13, 1995
SUBMISSION TYPE: Commercial IND
RECEIVED:
CSO: Vaccari

1. RESUME

BACKGROUND

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is believed to be less cardiotoxic or neurotoxic than bupivacaine and to offer as effective and longlasting sensory blockade as bupivacaine with less motor blockade. This is a study comparing single concentrations of ropivacaine and bupivacaine performed in support of the sponsor's NDA.

CLINICAL STUDY

Investigator: H Nolte, Minden, Germany

Treatment Plan: 45 ASA I or II patients scheduled for varicose vein surgery were enrolled in this randomized, double-blind, parallel group comparison of 1.0% ropivacaine and 0.75% bupivacaine without epinephrine. 21 patients were randomized to receive ropivacaine and 24 bupivacaine. After morphine/scopolamine premedication and prehydration with at least 500 ml of electrolyte solution, a 19 gauge Crawford was introduced midline at L2-3 or L3-4 with the patient in the sitting position. A test dose of 3 ml of the study drug was given via the needle followed by 17 ml of the same drug (total 20 ml of study drug) incrementally over 2 minutes. Then the patient was placed supine and 30 minutes was allowed for assessment of the block before surgery began.

The methods of assessment of sensory block, motor block (Bromage Scale only) and safety were those noted in the Introductory Comments.

Protocol deviations did not appear likely to have affected outcome. They studied one more patient than planned; one bupivacaine patient was of excessive weight; the test dose was planned to be 1.0% mepivacaine with epinephrine; a bupivacaine patient recevied demerol premedication and another received atropine, 0.5 mg IV, as premedication.

The groups were similar in patient ages, weights, heights, gender, coexisting diseases and concurrent medications, and time between injection and onset of surgery.

Efficacy assessment: All patients were available for efficacy and safety assessments.

1) Sensory block: All patients had analgesia at all dermatomes below T9. The time of onset and cephalad spread were similar among groups. Ropivacaine 1.0% lasted significantly longer at the lower dermato levels than 0.75% bupivacaine.

2) Mo block: The groups were similar in the degree, time of onset and duration of motor block.

3) Adequacy of anesthesia: Analgesia for surgery was unsatisfactory in 1 ropivacaine patient and 2 bupivacainee patients.

Safety Assessments: There were no unexpected circulatory events and the groups did not differ in the magnitude of circulatory changes which occurred. Regarding other adverse events, 2 bupivacaine patients had "cannot be classified" neurologic complications after bupivacaine.

2. CONCLUSIONS:

The sponsors discussion indicates these drugs provide satisfactory epidural anesthesia "for lower limb orthopaedic surgery". However, all of the operations were varicose vein stripping procedures. No tourniquets were used. I suspect the statement is an oversight. The analgesia was nearly always satisfactory for the intended surgery. I found no surprises within their data. It appears from this study that ropivacaine and bupivacaine had nearly identical effects when used in these concentrations.

3. RECOMMENDATIONS REGARDING LABELING:

This study supports the labeling indicating speed of onset of sensory and motor block and the durations of blockade. The volume of agent used was within the recommended range. The study does not assist discrimination of effects of ropivacaine and bupivacaine. It supports the likely occurrence of decreased blood pressure with epidural anesthesia.

Wendell C. Stevens, MD
Consultant

MEDICAL OFFICER REVIEW

IND#: 20-533 Study L-9
NAME: The effect of addition of epinephrine to 0.5% and 0.75% ropivacaine when used for epidural anesthesia

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SUBMISSION DATE: March 29, 1995
REVIEWER: Wendell C. Stevens, MD
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CSO: Viccari

1. RESUME

BACKGROUND

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is believed to be less cardiotoxic or neurotoxic than bupivacaine and to offer as effective and longlasting sensory blockade as bupivacaine with less motor blockade. This study is one of several done to determine whether the combination of ropivacaine with epinephrine significantly influences ropivacaine's neural blockade and is performed in support of the sponsor's NDA.

CLINICAL STUDY

Investigator: B J Lofstrom, Linkoping, Sweden

Treatment Plan: 52 ASA I or II male patients were enrolled in this randomized, double-blind, parallel group study of epidural ropivacaine. Each of the following groups contained 14 patients: 0.5% ropivacaince; 0.5% ropivacaine with 5 ug/ml epinephrine; 0.75% ropivacaine; 0.75% ropivacaine with5 ug/ml epinephrine. A 16, 17, or 18 gauge Touhy needle was placed midline at L2-3 or L3-4 with the patient in the lateral position. After placing an epidural catheter, the patient was placed supine and test dose of 3-4 ml 1.0% lidocaine with 5 ug/ml epinephrine was given. 20 ml of the study drug was given incrementally over about 4 minutes.

The methods of assessment of sensory block, motor block (Bromage Scale only) and safety were those noted in the Introductory Comments. They also assessed for occurrence of sympathetic block with use of a skin conductance response test and measurement of skin blood flow and skin temperature at multiple sites from the hand to the foot in an effort to analyze the segmental distribution of sympathetic blockade.

Protocol deviations were numerous but of such nature that they did not appear likely to have affected outcomes. Approaches to the epidural space were often paramedian rather than midline; the drug was sometimes given in the lateral rather than the supine position and the description is such that I cannot be certain whether a catheter was placed in all instances; the time between test dose and main dose varied between 2 and 16 minutes; most premedication was given rectally rather than orally; most patients received more than the planned 500 ml of electrolyte solution preblock; skin conductance tests were measured only at 10, 20, and 30 minutes post-block, less frequently than planned.

The groups were similar in patient ages, weights, heights, coexisting diseases and concurrent medications, and times between injection and onset of surgery.

Efficacy assessment: 48 of the 52 patients were evaluable for efficacy. Two patients each in the 0.5% ropivacaine and in the 0.75% ropivacaine with epinephrine groups because no block could be demonstrated.

1) Sensory block: Lumbosacral anesthesia and analgesia to T6 occurred in all patients and slightly higher in individual patients. Onset time, spread and durations of block were similar among groups although the higher concentration tended to produce longer blockade. The median durations at T10 and below were between 3.8 and 4.4 hours for all groups.

2) Motor block: About 1/4 to 1/3 of patients in all groups had a degree 3 block. The duration of block was longer in the 0.75% ropivacaine groups than in the 0.5% groups.

3) Adequacy of anesthesia: Two patients in the 0.75% ropivacaine with epinephrine group complained of some pain during surgery but no additional agents were given. Another patient in the same group complained of visceral pain. One other patient in this latter group also was said to have inadequate muscle relaxation (transurethral operations were being done).

4) Sympathetic block: A majority of patients gave evidence of the presence of sympathetic block in the lower limb using the skin resistance response. Skin blood flow in the foot also increased. The findings were similar for all groups except that lower extremity skin flow was significantly higher in the 0.5% ropivacaine group.

Safety assessments: No untoward circulatory events occurred and changes were not notably different among the groups even though there were some statistical differences. For example, heart rate was higher in the 0.75% ropivacaine with epnephrine group than in the 0.5% ropivacaine group. Two patients has lower extremity paresthesias during the needle placement and two patients had

subarachnoid punctures.

3. CONCLUSIONS:

The sponsor's summary analyzed the results well. All doses of the drug provided adequate anesthesia for endoscopic urological surgery in these male patients. There was no advantage or detriment to addition of epinephrine to ropivacaine. There were no surprises that I detected in the data.

4. RECOMMENDATIONS REGARDING LABELING:

This study supports the labeling indicating speed of onset or sensory and motor block and the durations of blockade. The results concur with other studies suggesting no change in characteristics of the block by addition of epinephrine. The pattern of adverse events described in the labeling is supported as well.

Wendell C. Stevens, MD
Consultant

MEDICAL OFFICER REVIEW

IND#: 20-533 Study L-10
NAME: A comparison of 1.0% ropivacaine with 0.75% bupivacaine when used for epidural anesthesia in patients undergoing lower abdominal surgery in gynecology.

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SUBMISSION DATE: March 29, 1995
REVIEWER: Wendell C. Stevens, MD
REVIEW DATE: August 15 and 16, 1995
SUBMISSION TYPE: Commercial IND
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CSO: Viccari

1. RESUME

BACKGROUND

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is believed to be less cardiotoxic or neurotoxic than bupivacaine and to offer as effective and longlasting sensory blockade as bupivacaine with less motor blockade. This is a study comparing single doses of ropivacaine and bupivacaine performed in support of the sponsor's NDA.

CLINICAL STUDY

Investigator: A P Rubin, London, England

Treatment Plan: 49 ASA I or II female patients scheduled for lower abdominal gynecological surgery were enrolled in this randomized, double-blind comparison of 1.0% ropivacaine (24 patients) and 0.75% bupivacaine (25 patients) without epinephrine. After premedication with papaveretum and hyoscine, and while 500 ml of Hartmann's solution was being given, an epidural catheter was placed via a midline 16 gauge Touhy needle at L2-3 or L3-4 with the patient in the lateral position. The patient was placed supine and horizontal and 3ml of the study drug was given followed by 17 ml of the study drug as fractional doses over 4 minutes. Thirty minutes were allowed for assessment of blockade before surgery began.

The methods of assessment of sensory block, motor block and safety were those described in the Introductory Comments. In this study the motor block assessment included the RAM test--the Rectus Abdominus Muscle test to attempt to determine adequacy of abdominal muscle relaxation.

Protocol deviations did not appear likely to have affected outcomes. Four patients, 3 in the bupivacaine group and 1 in the ropivacaine group, were excluded from efficacy analysis since the lower levels of the blocks were not determined. They were replaced by new patients. There were deviations from the intended site of injection and some patients were in the lateral rather than the supine position at time of injection of the study drug.

Groups were similar in patient ages, weights, heights, coexisting diseases and concurrent medications, and times between injection and onset of surgery.

Efficacy assessment: Forty-four patients were evaluable for efficacy and 48 for safety.

1) Sensory block: Sensory block was achieved in relevant surgical dermatomes in all patients. The onset times and durations of analgesia were similar among groups. Although the median upper level of block was similar among groups, the highest block achieved was T1 in the ropivacaine group and C4 in the bupivacaine group.

2) Motor block: The incidence of various degrees of motor block determined on the Bromage Scale was similar among the groups. The time to onset of block and their durations were also similar. With regard to the RAM test results, all but one patient in each group had 60% block, that is, could only lift head and scapulae off the bed surface. Three of 22 ropivacaine and 5 of 22 bupivacaine patients had 20% block, that is, an increase in abdominal muscle tension can be felt during effort, with no other response. Thus, magnitude of block was similar among the groups.

3) Adequacy of anesthesia: Although all patients had analgesia in the dermatomes relevant for surgery, four patients in each group required general anesthesia in order for surgery to proceed. Four of 18 ropivacaine and 7 of 18 bupivacaine patients were stated have experienced visceral pain.

Safety assessments: There were no unexpected cardiovascular events and no differences among groups in the changes seen. There were no sustained adverse events nor events which seem attributable to the drugs which were use.

CONCLUSIONS:

The sponsor's discussion summarized the findings well. The drugs used at these concentrations were usually effective for lower abdominal surgery. The conditions provided by the higher concentration of ropivacaine were equivalent to a lower concentration of bupivacaine. Analgesia to pin prick does not necessarily translate into adequate conditions for surgery as shown by the need for general anesthesia in 20% of the patients. The time required for the full extent of blockade by these agents given

epidurally is impressive to me. It was certainly appropriate to make an attempt to quantify the degree of relaxation in the area relevant to surgery. The results added information to the assessment and to the comparison of agents.

RECOMMENDATIONS REGARDING LABELING:

The study supports the labeling indicating speed of onset of sensory andmotor blcikand the durations of blockade. The concentration and used in this study are compatible with labeling recommendations for this type of surgery. The labeling comments regarding safety and adverse effects are appropriate to the results of this study.

Wendell C. Stevens

Wendell C. Stevens, MD
Consultant

MEDICAL OFFICER REVIEW

IND#: 20-533 Study L-11
NAME: A comparison of 0.5% and 1.0% ropivacaine and 0.5% bupivacaine in epidural anesthesia in patients undergoing surgery for varicose veins or inguinal hernia

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SUBMISSION DATE: March 29, 1995
REVIEWER: Wendell C. Stevens, MD
REVIEW DATE: August 16, 1995
SUBMISSION TYPE: Commercial IND
RECEIVED:
CSO: Viccari

1. RESUME

BACKGROUND

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is believed to be less cardiotoxic or neurotoxic than bupivacaine and to offer as effective and longlasting sensory blockade as bupivacaine with less motor blockade. This is a study with two concentrations of ropivacaine and one concentration of bupivacaine, each delivered in a volume resulting in the same total milligram dose being administered to all patients. It is performed in support of the sponsor's NDA.

CLINICAL STUDY

Investigator: J A W Wildsmith, Edinburgh, Scotland

Treatment Plan: 91 ASA I or II patients, 38 males, 53 females, schelduled for inguinal hernia or varicose veing operations were enrolled in the randomized, double-blind comparison. Thirty patients were assigned to the 0.5% ropivacaine group, 30 to the 1.0% ropivacaine group, and 31 to the o.5% bupivacaine group. The administration of 1.0% ropivacaine was not blinded since the smaller volume of the agent to be injected was obvious to the investigator. Patients were premedicated with 10-20 mg of oral trimazepam. No prehydration with IV fluids was done. A 16 gauge Touhy needle was placed midline at the L3-4 or L2-3 interspace with the patient in the lateral position. A test dose of 5 or 2.5 ml of the study drug was give followed by 15 ml of study drug in groups getting 0.5% concentration drugs or 7.5 ml in the group getting the 1.0% concentration agent. The needle was removed and the patient was place in the supine position. Surgery did not begin for at least 30 minutes to allow assessment of the block

The methods of assessment of sensory block, motor block (Bromage Scale only) and safety were those noted in the Introductory Comments.

Protocol deviations did not appear likely to have affected outcomes. Several deviations occurred including inclusion of a patient with psychiatric disease; either no premedication or occurrence of a long period between giving premedication and doing the block; variations is the site of needle placement and patient position during performance of the block.

The groups were similar with regard to patients'ages, weights, heights, gender, operations being done, coexisting diseases and concurrent medications, time between injection and onset of surgery, and duration of surgery.

Efficacy assessment: All of the enrolled patients were evaluable for efficacy and safety.

1) Sensory block: With exceptions for scattered dermatomes, all patients had analgesia at T10 or below and the median cephalad maximal cephalad level was T7 for all groups. The onset times were also similar although for the L5 segment, onset occurred significantly faster with 0.5% than 1.0% ropivacaine. I cite this to indicate that statistical differences can be noted but the clinical importance of them may not be great. Duration of lumbosacral analgesia, even with 0.5% ropivacaine was between 4.9 and 5.8 hours. Blockade with 1.0% ropivacaine was signigicantly longer than with 0.5% ropivacaine.

2) Motor block: Only 1 of the 91 patients had a degree 3 motor block. He was in the 0.5% bupivacaine group. Bupivacaine, 0.5%, resulted in more degree 2 blocks than 0.5% ropivacaine, 11/31 vs. 4/30. Duration of motor block was significantly less with 0.5% ropivacaine than the other agents.

3) Adequacy of anesthesia: Analgesia to pin prick did not necessarily equate with adequate surgical conditions. Four, 9, and 4 patients in the 0.5% ropivacaine, 0.75% ropivacaine, and 0.5% bupivacaine groups, respectively, required supplemental anesthesia. Interestingly, more 1.0% than 0.5% ropivacaine patients were stated to have unsatisfactory muscle relaxation. Relaxation was satisfactory in all bupivacaine patients.

Safety assessment: There were no unexpected circulatory events and the difference among groups in the changes which occurred were small. An example of a significant difference among agents was a slight increase in heart rate early after injection of 0.5% ropivacaine and decrease after 0.5% bupivacaine. Occurrence of other adverse events were similar among groups and not disturbing.

2. CONCLUSIONS:

The sponsor's summary analyzed the results well. Their efforts to compare identical milligram doses required, by design, injecting unequal volumes of agents. This may have led to less adequate anesthesia with 1.0% ropivacaine compared to the other drugs with regard to some variables. The need for supplemental anesthesia was fairly frequent in all groups. Again it was impressive over how long a period the extent of the blockade continues to develop.

RECOMMENDATIONS REGARDING LABELING:

The results support the labeling regarding onset and duration of sensory and motor block. The duration of motor block tended to less with ropivacaine than bupivacaine. The study is compatible with the labeling statements about adverse effects.

Wendell C. Stevens

Wendell C. Stevens, MD
Consultant

MEDICAL OFFICER REVIEW

IND#: 20-533 Study L-12
NAME: A clinical and pharmacokinetic comparison between ropivacaine and bupivacaine in epidural anesthesia: A double-blind multi-center study in women undergoing hysterectomy using 0.5%, 0.75%, and 1.0% ropivacaine and 0.5% bupivacaine.

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SUBMISSION DATE: March 29, 1995
REVIEWER: Wendell C. Stevens, MD
REVIEW DATE: August 16, 1995
SUBMISSION TYPE: Commercial IND
RECEIVED:
CSO: Viccari

1. RESUME

BACKGROUND

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is believed to be less cardiotoxic or neurotoxic than bupivacaine and to offer as effective and longlasting sensory blockade as bupivacaine but less motor blockade. This is a multi-center dose-ranging study using multiple concentrations of ropivacaine and a single concentration of bupivacaine in epidural anesthesia for abdominal surgery. It is performed in support of the sponsor's NDA.

CLINICAL STUDY

Investigators: B T Finucane, Edmonton, Alberta, Canada; A Sandler, Toronto, Ontario, Canada; J McKenna, Ottawa, Ontario, Canada.

Treatment Plan: 125 women, ASA I or II, scheduled for abdominal hysterectomy were enrolled in this randomized, double-blind, parallel group study done at 3 institutions. The treatment groups were 0.5%, 0.75% and 1.0% ropivacaine and 0.5% bupivacaine, all without epinephrine. They were to receive oral diazepam premedication and could be given fentanyl IV "if necessary". Patients were to receive 1000 electrolyte solution preblock. The block was done with a 16 or 18 gauge Touhy needle at L2-3 or at L3-4 if necessary, midline, with the patient in the lateral position. A test dose of 3 ml 1.5% lidocaine with 5 ug/ml epinephrine was given through the needle followed by 25 ml of study drug. Surgery did not begin for at least 30 minutes after the injection or later if more time was required for analgesia to occur at T6. If no block occurred in 60 minutes alternative anesthesia would be used.

The methods of assessment of sensory block,motorblock (Bromage Scale using the 0 to 4 scale) and safety were those noted in the Introductory Comments.

Protocol deviations were few and included a patient of smaller size than criteria allowed and alterations in premedication plans.

The groups were similar with regard to patients' ages, weights, heights, race, medical histories, concurrent medications, time between injection and onset of surgey, and duration of surgery.

Efficacy assessment: 116 patients were evaluable for efficacy, 117 for safety. The decrease from 125 is accounted for by 2 not receiving any study drug, there were 6 technical failures, and 1 patient was excluded for protocol violation. Treatment was discontinued in 40 patients, largely because of inadequate anesthesia for operation. By group these discontinuations were 13/27 0.5% ropivacaine, 13/27 0.75% ropivacaine. 5/30 1.0% ropivacaine, and9/29 0.5% bupivacaine.

1) Sensory block: The groups other than the 0.5% ropivacaine group were similar in the number of patients achieving lumbosacral analgesia and the groups were all similar with regard to achieving analgesia to T6. Two patients in the 0.5% ropivacaine group had no anesthesia at lumbosacral dermatomes. Median onset times were similar among the groups. The duration of analgesia with 1.0% ropivacaine was longer than the other groups and varied between 2.9 and 6.0 hours depending on the dermatomes being examined.

2) Motor block: 0.5% ropivacaine produced significantly less motor block than the other drugs, especially the higher degrees of block. The onset time of block was shorter with 1.0% ropivacaine than the other drugs with a time shorter by 10-20 minutes. 1.0% ropivacaine also gave significant longer blocks than the other drugs, blocks lasing 5-6 hours at the hip, 4-5 hours at the knee and ankle, and 3-4 hours at the foot. Sensory block outlasted motor block by a median time of 1 hour for all ropivacaine groups 0.7 hour for bupivacaine.

3) Adequacy of anesthesia: The frequency of need for additional anesthesia was noted above. Overall ratings of satisfactory and unsatisfactory were not different among the groups.

Safety assessments: There were no unexpected circulatory events and the groups did not differ in the magnitudeof circulatory changes which occurred. Likewise, there were no persistent or remarkable adverse events.

2. CONCLUSIONS:

The sponsor's summary analyzed the results well. The study seemed to be about as carefully conducted and analyzed as could be done

multicenter approach. There was a fairly high frequency of inadequate anesthesia. The larger the dose of ropivacaine the better the analgesia, muscle relaxation and surgical conditions. The data show again that analgesia to pin prick and relaxatio of the legs does not necessarily equate to adequate surgical conditions. The larger dose of ropivacaine seemed to provide better conditions than the smaller dose of bupivacaine. This pattern with ropivacaine has occurred in other studies.

RECOMMENDATIONS REGARDING LABELING:

This study supports thelabeling indicating speed of onset of sensory and motor block and the durations of blockade. It supports an increase in degree of sensory and motor block with increased concentration of ropivacaine. It supports, but not especially strongly, the separation of sensory and motor blockade. The study supports the statistical expectations regarding adverse effects.

Wendell C. Stevens, MD
Consultant

MEDICAL OFFICER REVIEW

IND#: 20-533 Study L-13
NAME: A clinical comparison of the anesthesia provided by ropivacaine 0.75% and bupivacaine 0.75% administered epidurally in women undergoing gynecological surgery: a double-blind study.

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SUBMISSION DATE: March 29, 1995
REVIEWER: Wendell C. Stevens, MD
REVIEW DATE: August 17, 1995
SUBMISSION TYPE: Commercial IND
RECEIVED:
CSO: Vaccari

1. RESUME

BACKGROUND

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is believed to be less cardiotoxic or neurotoxic than bupivacaine and to offer as effective and longlasting sensory blockade as bupivacaine with less motor blockade. This study compares single, relevant doses of ropivacaine and bupivacaine in providing epidural anesthesia for abdominal surgery. It is performed in support of the sponsor's NDA.

CLINICL STUDY

Investigator: Philip Bridenbaugh, Cincinnati, Ohio

Treatment Plan: Sixty-nine ASA I, II, or III patients scheduled for gynecological surgery were enrolled in this randomized, double-blind, parallel group comparison of 0.75% ropivacaine (34 patients) and 0.75% bupivacaine (35 patients), both without epinephrine. Patients were premedicated with midazolam, 1-3 mg IV, and/or fentanyl, 50-100 ug IV, and received 500 ml or more of balanced electrolyte solution preblock. The epidural block was initiated with a 17 or 18 gauge Touhy needle placed at the L2-3 or L3-4 interspace with the patient in the lateral position. A 4 ml test dose of 1.5% lidocaine with 5 ug/ml epinephrine was given followed by 20ml of the study drug given incrementally over a 3 minute period. Then the patient was placed in the supine position . At least 45 minutes elapsed between the injection and onset of surgery.

The methods usedto assess sensory block, motor block (Bromage Scale and Rectus Abdominus Muscle test), adequacy of anesthesia and

safety were those described in the Introductory Comments.

Protocol deviations were few in number and not of a magnitude likely to affect outcomes.

The groups were well-matched for patients' ages, weights, heights, coexisting diseases and concurrent medications, surgical procedures, times between injection and surgery, durations of surgery, and ASA category. There was only one ASA III patient (ropivacaine group).

Efficacy assessment: Sixty-seven of the 69 enrolled patients were evaluable for efficacy. Two ropivacaine group patients were excluded, 1 because no block occurred and 1 because the patient moved and dislodged the epidural needle.

Sensory block: Sensory block was achieved at T6 or below in all but 2 patients in each group. The onset times were quite similar although usually the ropivacaine block set in more slowly. The difference inonset times was statistically significant at L3, S1, and S3. Durations of block were similar among groups. Median maximum spread was to T3 and T4 in ropivacaine and bupivacaine groups, respectively.

Motor block: Bearing in mind that motor block could not be evaluated during surgery in all patients, over 90% of tested patients in each group had degree 3 block. Thus, the data may overestimate the degree of motor block which occurred. Motor block occurred earlier with bupivacaine than ropivacine regardless of degree of block. For degree 3 block, mean onset times were 30.4 minutes and 47.9 minutes for respective bupivacaine and ropivacaine groups. Bupivacaine blocks tended to last longer. Sensory block outlasted motor block with both drugs by about 2 hours. The investigators did not report RAM test data since they could not perform the test during surgery. Neither did they report RAM test resutls for the period between injection and surgery.

Safety assessment: There were no significant differences between groups in cardiovascular changes and no untoward events attributable to study drugs. The most common adverse event was moderate nausea. This occurred in both groups. The investigators list three patients with serious adverse events. One was a surgical problem (vaginal bleeding), one was intraoperative hypotension during general anesthesia and during an extensive surgical procedure, and one was edema of the tongue occurring in the recovery room followed by edema of the epiglottis occurring after discharge from the hosptial.

2. CONCLUSIONS:

The sponsor's summary analyzes the data satisfactorily. The results with the two drugs were quite similar. Major differences between

drugs included slower sensory and motor block onsets with ropivacaine. The bupivacaine motor block tended to last longer. The investigators suggest that "absence of motor blockade is considered desirable" in patients undergoing gynecological surgery. This overstates the case, in my opinion, since relaxation may assist maintenance of the lithotomy position for longer cases and will aid in abdominal gynecological procedcures. It would have been good to have the RAM test data for the period between injection and surgery.

3. RECOMMENDATIONS REGARDING LABELING:

The study supports labeling regarding onset, extent and duration of sensory and motor block. The pattern of slower onset of sensory and motor block with ropivacaine than bupivacaine is supported. The pattern of expected adverse reactions is also supported.

Wendell C. Stevens, MD
Consultant

MEDICAL OFFICER REVIEW

IND#: 20-533 Study L-14
NAME: A double-blind comparative study of 0.5% ropivacaine and 0.5% bupivacaine when used in epidural anesthesia in women undergoing hysterectomy.

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SUBMISSION DATE: March 29, 1995
REVIEWER: Wendell C. Stevens, MD
REVIEW DATE: August 23, 1995
SUBMISSION TYPE: Commercial IND
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CSO: Vaccari

1. RESUME

BACKGROUND

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is believed to be less cardiotoxic or neurotoxic than bupivacaine and to offer as effective and longlasting sensory blockade as bupivacaine with less motor blockade. This study is one of a number of comparisons of epidural ropivacaine and bupivacaine, in this study, the drugs were delivered at identical concentrations. The study is performed in support of the sponsor's NDA.

CLINICAL STUDY

Investigator: G. Hempelmann, Giessen, Germany

Treatment Plan: 38 ASA I or II women scheduled for abdominal hysteretomy were entered in this randomized, double-blind, parallel group comparison of epidural 0,5% ropivacaine and 0.5% bupivacaine without epinephrine. Patients were to be premedicated with midazolam, oral or IM, and were to receive 500-1000 ml balanced electrolyte solution preblock. An 18 gauge Touhy needle was placed at L2-3 or L3-4 with the patient in the sitting position, an epidural catheter was placed (original plan was for injection of the drug through the needle), the patient was placed supine, and 3 ml of the study drug was injected as a test dose. This was followed by 22 ml of the study drug incrementally over 3 min. Then, 45 min later after, giving time to assess the blockade, "light" general anesthesia was to be induced and maintained with thiopentone, succinylcholine, N_2O in oxygen, mechanical ventilation, and other muscle relaxant if needed.

The methods of asssessment of sensory block, motor block (Bromage Scale only) and safety were those noted in the Introductory Comments, with the exception that many of the measurements usually done in the awake, blocked patient could not be done and had to be tested after the patient awakened. The requirements for additional anesthesia were monitored.

Twenty patients were randomized to receive ropivacaine and 18 bupivacaine. Several changes and deviations from the original plan occurred. Most significant was discontinuation of the study before the projected 60 patients were entered because the blocks combined with only "light" anesthesia appeared to be inadequate for surgery in both groups. More halothane and vecuronium were required than the investigators expected to need had the blocks been effective. Other protocol deviations included giving the major amount of study drug via epidural catheter rather than via the Touhy needle; variations in timing of premedication; change from purely balanced electrolyte IV preblock to a combination of balanced electrolyte solution plus hetastarch preblock and additional hetastarch post-block and before general anesthesia; and setting of smaller allowable decreases of blood pressure and heart rate before their treatment.

Groups were well matched for age, weight, height, diseases requiring surgery (except for one patient listed below), coexisting disease and concurent medications.

Efficacy assessment: One patient in each group was eliminated from efficacy analysis for cardiovascular reasons. In the ropivacaine group a patient had bradycardia (the timing is not precisely clear to me), probably about 30 minutes after the study drug was given. During the operation, approximately 1 1/2 hours after study drug, she developed ventricular fibrillation. It was treated successfully without acute or long term sequelae. The investigators attributed the event to hypokalemia and hypothermia. In the bupivacaine group, a patient had "bronchospasm" 1 hour after drug injection and a 1 minute period of asystole 1 1/4 hours after drug injection. The latter event coincided with doing a vaginal examination as part of the surgical procedure. Her recovery with treatment was uneventful. A ropivacaine patient was excluded from efficacy analysis because the surgical disease was more extensive than allowable by inclusion criteria.

1)Sensory block: Extent and time of onset of analgesia was similar in the groups although the blocks tended to go a segment or two lower in the bupivacaine group and higher in the ropivacaine group. Durations of blockade were also similar and were as long as 7 hours in the dermatomes relevant for surgery. Note that the average durations of surgery were over 200 minutes so that determining the end of analgesia was done after patients had awakened from anesthesia sometime after that.

2) Motor block: The investigators attempted to separate partial from comlete motor block of the various degrees of blockade. The incidence of partial block was about the same for the groups but more bupivacaine patients had complete block of each degree category. The motor blockades had median durations from 4 to 7 hours with the ropivacaine block being significantly shorter regarding ability to flex the knee. Abdominal wall relaxation, judged by the operating team, was satisfactory in less than half the patients in either group.

3) Adequacy of anesthesia: The problem with adequacy of anesthesia was referred to above. The investigators felt the requirement for general anesthesia to provide adequate operating conditions suggested that the intensity of analgesia, and especially abdominal wall relaxation was inadequate in both groups. They cite the possible impacts of long surgeries and junior surgeons needing profound relaxation to do the surgery on the results.

Safety Assessments: The two patients with profound circulatory events are described above. The other adverse events were similar among the groups.

2. CONCLUSIONS:

The sponsor's summary analyzed the results satisfactorily. The conditions expected of the agents were challenging. The ability to assess the degree of sensory and motor block was confounded by general anesthesia. The extent of blockades could be assessed since these could be determined before onset of surgery. However, the protocol made it hard to know just how much of the overall conditions for surgery were contributed by the blockades and how much my the general anesthetic. I don't believe direct effects of the local anesthetic agents accounted for the circulatory events in the two patients who were excluded from efficacy analysis.

3. RECOMMENDATIONS REGARDING LABELING:

The study will not be of much help in determining dosage guidelines or in statements comparing ropivacaine and other local anesthetics. It supports the frequency of occurrence of adverse events, although even in this instance, once general anesthesia is given, the cause of adverse events becomes less clear-cut.

Wendell C. Stevens, MD
Consultant

NDA #: 20-533 Study Q2

NAME: Pre-operative Local Infiltration with Ropivacaine for Post-operative Pain Relief after Cholecystectomy.

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SUBMISSION DATE:
REVIEWER: Ronald D. Miller, MD
REVIEW DATE:
SUBMISSION TYPE: Commercial IND
RECEIVED:
CSO: Vaccari

1. RESUME:

Background

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. The objective of this study was to investigate whether pre-operative local infiltration with ropivacaine decreases post-operative pain and the demand for analgesics after elective cholecystectomy performed under general anesthesia. Infiltration with saline served as a control.

Clinical Study

Investigators: Hans Glise, MD, PhD, Department of Surgery, Trollhättan, Sweden.

Treatment Plan: 69 patients were scheduled to undergo this randomized, double-blind, placebo-controlled study with three parallel groups undergoing cholecystectomy with a subcostal incision. Patients ranged in age: 18-75 years and weighed 50-100 kg. for males and 50-90 kg. for females. Patients were randomly assigned to receive infiltration of 70 ml of either .25% ropivacaine, 0.125% ropivacaine, or saline. The solution was infiltrated along the incision line in the subcutaneous layer (50 ml) and the deep preperitoneal layers (20 ml). Incisional pain was determined at rest and movement-associated incisional pain measured by a visual analogue scale (VAS) at 6, 25, 54 and 74 hours, and 7 days after infiltration. Maximum tolerated algometer pressure and pain (VAS) at maximum tolerated pressure at the same intervals. Time to first administration of supplementary analgesics and amount of supplementary analgesics required were determined. The patients received general anesthesia with other analgesics having been given including meperdine and dixyrazine. In addition, acetaminiphen was given post-operatively upon request. Out of the 69 patients enrolled, one patient did not receive any medication reducing the number of patients to 68 for the study. One patient had post-operative bleeding and another patient exceeded the time limit for surgery. Consequently, 66 patients, valid for efficacy, were randomized in each group. Ironically, each group consisted of 22 patients.

Efficacy Assessment: There were 22 in each of the three groups.

1) Post-operative Pain Assessed by Visual Analogue Scale and Algometer: At 6 hours the median score for pain at rest was 22 ml for 0.25% ropivacaine, 40 ml for 0.125% ropivacaine, and 30 ml for the saline group. Thereafter, median scores for spontaneous pain at rest became similar in all three groups.

2) The Median Score for Mobilization Pain from Supine to Sitting Position at 6 hours: 48 ml in the 0.25% ropivacaine, 70 ml in the 0.125% ropivacaine, and 74 ml in the saline group. (See page 36)

3) Maximum Tolerated Wound Pressure and Resulting Pain: (See page 38) The median tolerated pressure at 6 hours was 355 kPa in the .25% ropivacaine, 236 kPa in the 0.125% ropivacaine, and 126 kPa in the saline group. This constitutes a significant dose related increase of pressure exerted to reach maximum pain tolerance at 6 hours.

4) Request of Post-operative Analgesics: All patients, except 2 in the .125% ropivacaine group and 1 patient in the saline group, asked for and received analgesic drugs. The median time from infiltration to the first request was 4.4 hours in the .25% ropivacaine, 4.0 hours in the 0.125% ropivacaine, and 2.4 hours in the saline group. The immediate amount of meperdine administered in the first 36 hours was 263 mg in the 0.25% ropivacaine, 375 mg in the 0.125% ropivacaine, and 398 mg in the saline group. (See page 42)

Safety Assessment: Adverse effects were reported in 11 patients (5 patients in the 0.25% ropivacaine, 4 patients in the 0.125% ropivacaine, and 2 patients in the saline group). In 3 patients, one in each treatment group, the adverse effects were considered as serious, none were viewed to be related to the study treatment. The serious effects included mild chest pains, a prolonged hospitalization due to peritoneal abscess, and re-operation due to post-operative bleeding.

2. CONCLUSIONS:

A significant dose response relationship for movement-associated pain and for pressure exerted to reach a maximum pain tolerance was found at 6 hours control. There was a significant difference between the 0.25% ropivacaine and saline groups in movement-associated pain scores at 6 hours, both the 0.125% ropivacaine and 0.25% ropivacaine were significantly better than saline regarding pressure exerted to reach maximum pain tolerance. The conclusion is a dose-dependent analgesic effect was demonstrated 6 hours after infiltration. No long-term effect on post-operative pain with pre-incisional local infiltration with ropivacaine was found.

3. RECOMMENDATIONS REGARDING LABELING:

Both concentrations of local anesthetics were satisfactory for local infiltration. Although the differences between the 0.125% ropivacaine and 0.25% ropivacaine concentrations were not large, the stronger concentration tended to be more efficacious as indicated above.

RD Miller

Ronald D. Miller, MD
Naropin Team Member

NDA #: 20-533 Study Q5

NAME: Postoperative Local Infiltration with 0.25% Ropivacaine and 0.25% Bupivacaine for Postoperative Pain Relief After Cholecystectomy and Hysterectomy: A Double-blind Comparison.

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SUBMISSION DATE:
REVIEWER: Ronald D. Miller, MD
REVIEW DATE:
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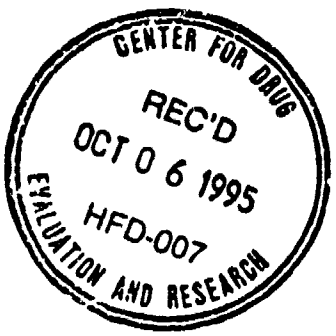

1. RESUME:

Background

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is thought to be less cardiotoxic than bupivacaine. This is one of several local infiltration studies performed in support of the sponsor's NDA.

Clinical Study

Investigators: Alan Sandler, MD, FRCPC, Anaesthetist-in-Chief, Department of Anaesthesia, Toronto General Hospital, Toronto, Ontario, Canada.

Treatment Plan: The study was randomized and double-blinded with two parallel treatment groups. Patients of either gender scheduled to undergo elective cholecystectomy and female patients scheduled for hysterectomy. ASA I - III over the age of 18 years, weighing 50 - 100 kg were to be studied. The patients were randomized in blocks of 4 with an equal probability of receiving either one of the two treatments. Two medical centers participated in the studies. They were randomized to receive local infiltration during wound closure with either 150 mg of ropivacaine or 150 mg of bupivacaine (60 ml of 0.25%). A special visual analogue scale device was used to collect pain scores. Assessment of spontaneous pain and pain during mobilization were to be performed at regular intervals during the three days postoperatively. On the day of surgery, pain assessments were performed 6 hours after the infiltration. On day 1, 2, and 3 after surgery assessments were to be performed each day at 0800, 1400, and 1700. On day 4 after surgery, spontaneous pain was assessed at 0800. Patients were thereafter to be discharged from the hospital. For safety purposes, heart rate and blood pressure were monitored postoperatively according to their standard hospital routines.

Safety Assessment: There was a total of 20 events in the ropivacaine group and 35 in the bupivacaine group were listed as adverse effects. None of these were serious and they are all itemized on the table on page 4, ranging from nausea, dizziness, and headaches.

2. CONCLUSIONS:

Due to slow recruitment of patients, the study was discontinued after nine patients had been recruited. No statistical analysis was performed. Only demographic data and safety description were collected. Because of the few number of patients and incompletion of the designed protocol, no conclusions can be drawn from this study.

RD Miller

Ronald D. Miller, MD
Naropin Team Member

NDA #: 20-533 Study Q3

NAME: Pre- or Postoperative Local Infiltration with Ropivacaine for Postoperative Pain Relief After Hysterectomy

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SUBMISSION DATE:
REVIEWER: Ronald D. Miller, MD
REVIEW DATE:
SUBMISSION TYPE: Commercial IND
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CSO: Vaccari

1. RESUME:

Background

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is thought to be less cardiotoxic than bupivacaine. This is one of several local infiltration studies performed in support of the sponsor's NDA.

Clinical Study

Investigators: Jonas Holst, MD, Department of Anaesthesiology, Karlstad Hospital, Karlstad, Sweden

Treatment Plan: The primary objective was to investigate whether the preoperative or postoperative local infiltration with ropivacaine 0.25% decreases postoperative pain and the need for analgesics after elective hysterectomy compared to not giving any local infiltration. The secondary objective was to compare the efficacy of preoperative vs. postoperative infiltration with respect to postoperative pain relief and the demand for analgesics. The study design was double-blind, randomized, controlled, with three parallel groups. 72 patients were evaluated for safety and 66 for efficacy (22 in the preoperative, 23 in the postoperative and 21 in the control group). The patients scheduled for elective hysterectomy under general anesthesia, ages 18 - 75 years, weight 50 - 90 kg, were included. The assessment methods involved incisional pain at rest and movement-associated pain by visual analogue scale (VAS) and incisional pain on pressure measured by an algometer and visual analogue scale at 6, 26, 50, 74, 122, 336 hours following surgery. Also, the time to first administration of postoperative analgesics and the amount of postoperative meperidine, Citodon tablets were recorded. Of the enrolled 76 patients, 4 refused to participate before surgery, of the 72 patients valid for study, 24 were randomized to each group. 6 patients discontinued the study, hence out of the 66 patients valid for efficacy evaluation, 22 were randomized to the preoperative infiltration group, 23 to the postoperative infiltration group, and 21 to the control group.

Efficacy Assessment: Examination of the table on page 3 summarizes the data.

1) Postoperative Algometer Pressures and Pain Tolerance: At day 14 was higher in the control group compared to the preoperative infiltration group.

2) The mean rank score for incisional pain at rest (at 50 hours) was lower in the control group compared to the preoperative infiltration group.

3) There was no difference in the time to first administration of an analgesic.

Safety Assessment: Adverse effects were experienced in 11 patients. In 4 patients, the effects were classified as serious. Including one in each treatment group had a moderately infected vaginal top hematoma which were viewed to be unlikely due to the study drug. 2 patients in the control group had a hematoma and the other had a moderate wound infection. All 4 patients recovered completely.

2. CONCLUSIONS:

The authors conclusion are correct in stating that while there were occasional significant difference, one cannot conclude that postoperative pain and the need for analgesics were any different from the control group with either the preoperative or postoperative local infiltration with ropivacaine.

3. RECOMMENDATIONS REGARDING LABELING:

This study does not support the statement on page 7 indicating that ropivacaine produced lower pain scores and a reduction in analgesic consumption when infiltrated for postoperative pain.

R D Miller

Ronald D. Miller, MD
Naropin Team Member

NDA #: 20-533 Study R2

NAME: Efficacy and Safety of 0.5% and 0.755 Ropivacaine When Used for Spinal Anesthesia in Patients Undergoing Lower Limb Surgery

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Phone 508/366-1100, Fax 508/366-7406

SUBMISSION DATE:
REVIEWER: Ronald D. Miller, MD
REVIEW DATE:
SUBMISSION TYPE: Commercial IND
RECEIVED:
CSO: Vaccari

1. RESUME:

Background

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is thought to be less cardiotoxic than bupivacaine. This is one of several studies examining its efficacy during spinal anesthesia.

Clinical Study

Investigators: JW van Kleef, University Hospital Leiden, Department of Anaesthesiology, The Netherlands

Treatment Plan: The primary objective of the study was to obtain information about the overall quality of anesthesia and safety of two concentrations of ropivacaine (0.5% and 0.75%) when used for spinal anesthesia when undergoing lower limb surgery. According to the protocol designed, this is a randomized, double-blind, parallel group study. 40 patients received 3 ml (15 and 22.5 mg) injected into the spinal canal. Onset, duration and upper and lower maximum spread of analgesia was determined by pin prick and onset, duration, and frequency of different stages of motor block using the modified Bromage scale were measured 2, 5, 10, 15, 20, 25, and 30 minutes after injection of the study drug and every 30 minutes to 5 hours, and thereafter every hour until return of normal sensation and motor function. The quality of the anesthesia, a subjective analysis assessment of analgesia and muscle relaxation were graded. Blood pressure and heart rate were measured 5, 10, 15, 20, 25, and 30 minutes after injection of the spinal anesthetic and thereafter for 30 minutes to 3 hours. Adverse effect during anesthesia and discharge and postoperatively were made between 2 - 3 weeks after surgery. 40 patients were valid for safety analysis. 1 patient in the 0.5% ropivacaine group was excluded from efficacy analysis due to a protocol deviation.

Efficacy Assessment: On page 3 the time to onset between the two drugs was virtually the same ranging from 5 minutes at the S1 level to 10 - 12 minutes for the T10 level.

Regarding duration, there was no difference at the T10 level, whereas the 0.75% ropivacaine group was longer at the T12, L5, and S1 levels. The maximum upper dermatone level was T5 and T4 in the 0.5% and 0.75% ropivacaine groups, respectively. 16 of the 19 patients in the 0.5% ropivacaine group and 17 of the 20 patients in the 0.75% ropivacaine group were viewed as satisfactory anesthesia. Regarding motor block, 16 patients in the 0.5% ropivacaine group and 10 in the 0.75% ropivacaine group were viewed as satisfactory.

Safety Assessment: No serious events were reported. The most frequent adverse effect was postoperative headache. 2 patients in the 0.5% ropivacaine group and 3 patients in the 0.75% ropivacaine group had severe headaches. 1 patient in the 0.75% ropivacaine group reported mild pain on injection site at a follow up 3 weeks after surgery. All other patients recovered completely.

2. CONCLUSIONS:

The investigators concluded that the doses used appeared to be safe and effective when used for spinal anesthesia in minor orthopedic surgery. The durations of analgesia and motor block were longer in the 0.75% ropivacaine group. The intensity of motor block was lower in the 0.5% ropivacaine group than in the 0.75% ropivacaine group.

3. RECOMMENDATIONS REGARDING LABELING:

Unless I am mistaken, there was no discussion of use of ropivacaine for spinal anesthesia.

RD Miller

Ronald D. Miller, MD
Naropin Team Member

NDA #: 20-533 Study Q7

NAME: Preoperative Local Infiltration with Ropivacaine for Postoperative Pain Relief After Hernia Repair.

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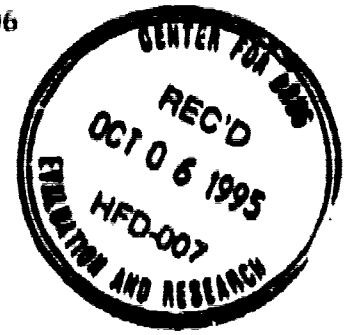
SUBMISSION DATE:
REVIEWER: Ronald D. Miller, MD
REVIEW DATE:
SUBMISSION TYPE: Commercial IND
RECEIVED:
CSO: Vaccari



1. RESUME:

Background

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is thought to be less cardiotoxic than bupivacaine. This is one of several local infiltration studies performed in support of the sponsor's NDA.

Clinical Study

Investigators: Bo Johansson, MD, Norra Älvsborgs central Hospital, Department of Surgery, Trollhättan, Sweden

Treatment Plan: The study's objective was to demonstrate a dose-response relationship in pain experienced postoperatively after hernia repair when using preoperative local infiltration with one of two doses of ropivacaine vs. saline. The secondary objective was to investigate the patient's perception of well-being and ability to function day-to-day activities for a period of 7 days after surgery. The investigators felt the study would be valid if 120 patients were included for efficacy analysis. 131 patients were enrolled. One patient randomized to 0.25% ropivacaine did not receive any study drug and was excluded from the study. 130 patients completed the study, 126 of which were valid for efficacy analysis. The patients were male, scheduled for unilateral hernia repair, had not had a previously operated hernia repair on the side in question. ASA I - II. Ages 18 - 70 years, and ≤ 100 kg in weight. The patients were to receive their hernia repair under general anesthesia and were randomized to receive preoperative local infiltration with 40 ml of 0.25% ropivacaine, 0.5% ropivacaine, or with saline. After induction of general anesthesia, 20 ml of the drug was infiltrated subcutaneous with another 12 ml below the external fascia, and 6 ml was to be injected 2 cm medial from the anterior/superior spine in the region of the ilioinguinal nerve. An additional 2 ml of the study solution was to be infiltrated around the neck of the hernial sac at the appropriate stage of surgery. Assessments of wound pain at rest and wound pain during mobilization were performed 3 hours, 6

hours, 10 hours, and 24 hours after infiltration. A final assessment was made at a follow up 7 or 8 days after surgery. Algometer pressure exerted to reach pain threshold and maximum pain tolerance and VAS score at maximum pain tolerance were recorded at the same intervals immediately after assessment of wound pain at rest and pain during mobilization. Also, first time to administration of supplementary analgesics and amount of supplementary analgesics were determined. Time to first administration of analgesic was 6.3, 6.0, and 2.5 hours in the 0.25%, 0.5% ropivacaine and saline, respectively.

Efficacy Assessment: Wound pain at rest and during mobilization were significantly lower in the ropivacaine group compared to the saline group 3 hours after infiltration. Wound pain during mobilization was significantly lower in the ropivacaine 0.5% than in the other two groups 6 hours after infiltration. (See Table on page 4). The consumption of Citodon tablets 20 hours to 7 days was significantly higher in the ropivacaine 0.25% group compared to the other two groups.

There were other subtle differences such that patients in the 0.5% ropivacaine group tolerated higher pressures than the other two groups in the first 24 hours after infiltration. However, 7 days after infiltration, the saline group tolerated higher pressures than did the other two groups.

Safety Assessment: Six patients experienced serious adverse effects were not attributed to administration of the study treatment. The most frequent adverse effect was wound hematoma which occurred more frequently in the ropivacaine groups than in the saline group. Perhaps, the use of an algometer contributed to this. Other adverse effects were equally distributed in all three groups. Wound healing was judged to be normal and over 90% of the patients in all three group.

2. CONCLUSIONS:

The investigators conclude that a dose-dependent analgesic effect was demonstrated after local infiltration with ropivacaine. They felt that the results underlined the beneficial effects of ropivacaine on pain mobilization and on the patients stated a functioning in the first 6 - 10 hours after surgery. This conclusion is clearly demonstrated 3 hours after surgery, both at rest and during mobilization. Thereafter, there was no difference at rest other than at 24 hours in which it appeared that the ropivacaine groups experienced greater pain. Regarding mobilization, once again, their 3 hour data are convincing. At 6 hours, it is questionable with possibly the 0.5% ropivacaine group being more "analgetic". Thereafter, the differences are minuscule, despite the statistical analysis.

3. RECOMMENDATIONS REGARDING LABELING:

The statement on page 7 under the section on Local Infiltration is correct. The FDA notes that once guidance on anticipated duration of effect, the data of this study suggests that the duration is somewhere between 3 - 6 hours. It is intriguing that the ropivacaine patients may have experienced more pain than the saline group 24 hours, but the data is not strong enough to make such conclusions.

RD Miller

Ronald D. Miller, MD
Naropin Team Member

NDA #: 20-533 Study R1

NAME: Safety and Efficacy of 0.5% and 0.75% Ropivacaine When Used for Spinal Anaesthesia in Patients Elective for Surgery in the Lower Part of the Body

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SUBMISSION DATE:
REVIEWER: Ronald D. Miller, MD
REVIEW DATE:
SUBMISSION TYPE: Commercial IND
RECEIVED:
CSO: Vaccari

1. RESUME:

Background

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is thought to be less cardiotoxic than bupivacaine. This is one of several studies examining its efficacy during spinal anesthesia.

Clinical Study

Investigators: Hans Nolte, Prof., MD, PhD, Department of Anaesthesiology, Klinikum Minden, Minden, Germany.

Treatment Plan: 40 patients of both genders requiring elective surgery for the lower part of the body. ASA category I - II. Ages ≥ 18 years. Weight 50 - 100 kg. The patients underwent a randomized, double-blind, parallel group study in which they received spinal anesthesia with 0.5% or 0.75% ropivacaine. As far as assessment methods are concerned, one efficacy onset duration and upper and lower maximum spread of analgesia and onset duration and frequency of different degrees of motor-block were measured at 2, 5, 10, 15, 20, 25, and 30 minutes after injection of the drug and then every 30 minutes until return of normal sensation and motor function. The quality of anesthesia and muscle relaxation was graded as satisfactory or unsatisfactory. The spread of analgesia was measured by a Fruhstrofer's wheel and degrees of motor block by a modified Bromage scale. From a safety point of view, heart rate and blood pressure before anesthesia and at 5, 10, 15, 20, 25, and 30 minutes and thereafter every 30 minutes to 3 hours were determined. Adverse effects at discharge from the recovery room and daily during hospitalization until 14 - 21 days postoperatively were measured.

Efficacy Assessment: On page 3 is a table summarizing onset and duration data. There was no evidence of a quicker onset in the 0.5% ropivacaine group. In general,

the onset at S1 was 2 minutes, at L5 was 2 minutes, at T12 was 8-12 minutes, and at T10 was 12-13 minutes. As far as duration was concerned, there was little if any difference with duration of S1, L5, T12, T10, being about 5.8, 5.8, 2.5, and 2.0 hours respectively. The duration of the 0.75% ropivacaine group was significantly longer at the T10 and T12 levels. Also, the table on page 4 describes the motor data in which the motor block was 3 ml of the study drug. 12 of 20 patients in the 0.5% ropivacaine group, and 19 of 20 patients in the 0.75% ropivacaine group stated that the motor block was satisfactory for surgery. .

Safety Assessment: The investigators state that there were no serious adverse effects. The most frequent adverse effect was bradycardia with 10 in the 0.5% and 11 in the 0.75% ropivacaine group. 7 patients in the 0.5% and 9 patients in the 0.75% ropivacaine had headaches postoperatively. The study group recovered completely. There were no significant difference between the groups with regard to blood pressure or heart rate.

2. CONCLUSIONS:

The investigators concluded that 3 ml of ropivacaine 0.5% (15 mg) and 0.75% (22.5 mg) appeared to be safe when used for spinal anesthesia and surgery of the lower part of the body. Surgery included gynecologic and urologic cases. The durations and regression times for analgesia and motor block were significantly longer in the 0.75% than in the 0.5% ropivacaine group. Intensity of the motor block was lower in the 0.5% ropivacaine group. Because there was no comparison to any other local anesthetic, a conclusion cannot be made with regard to efficacy and safety vs. using another local anesthetic.

3. RECOMMENDATIONS REGARDING LABELING:

Unless I am mistaken, there was no discussion of use of ropivacaine for spinal anesthesia.

RO Miller

Ronald D. Miller, MD
Naropin Team Member

Department of Health & Human Services Public Health Service Food & Drug Administration

PILOT DRUG EVALUATION STAFF
NDA EFFICACY REVIEW

NDA #: 20-533
NAME: Naropin
SPONSOR: Astra
SUBMISSION TYPE: Commercial NDA
CSO: D Morgan
REVIEWER: I.L. Tyler, Ph.D., M.D.

Ropivacaine *vs.* Bupivacaine: Overview of Potency Ratio

One question not directly addressed in the current ropivacaine studies under review is the relative potency of ropivacaine *versus* bupivacaine when administered epidurally. Injected intravascularly, ropivacaine is thought to be less cardiotoxic than bupivacaine — perhaps by as much as 30%.[1,2,3,4,5] But Liu has demonstrated that in dogs the other amide local anesthetics' relative cardiotoxicity is directly proportional to their anesthetic potency.[6] Does ropivacaine also follow this rule? Does its purported 30% reduction in toxicity relative to bupivacaine translate to a 30% reduction in potency as well so that clinically equipotent doses for epidural anesthesia are equally toxic?

I. Comparison *in vitro* between ropivacaine and bupivacaine.

Demonstration of an equivalent effect on the compound action potential *in vitro* studies of nerve conduction is one direct way to answer this question. Only one *in vitro* study — on frog sciatic nerve — was carried out. The results are presented in Table 1

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[1] Akerman B et al: Primary evaluation of local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). Acta Anaesth Scand 32:571,1988.
[2] Feldman HS et al: Comparative systemic toxicity of convulsant and supraconvulsant doses of intravenous ropivacaine, bupivacaine, and lidocaine in the conscious dog. Anesth Analg 69:794, 1989.
[3] Reiz S et al: Cardiotoxicity of ropivacaine — a new amide local anaesthetic agent. Acta Anaesthiol Scand 33:93, 1989.
[4] Arlock P: Actions of three local anaesthetics: Lidocaine, bupivacaine, and ropivacaine on guinea pig papillary muscle sodium channels (V max). Pharmacol Toxicol 63: 96, 1988.
[5] Moller R, Covino BG: Cardiac electrophysiologic properties of bupivacaine and lidocaine compared with those of ropivacaine, a new amide local anesthetic. Anesthesiol 72: 322, 1990.
[6] Liu P et al: Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized, ventilated dogs. Anesth Analg 61:317, 1982.

Table 1: Equilibrium blocks on sheathed sciatic nerves of the frog. Each value represents the mean reduction in the amplitude of the compound action potential ± 1.5×SEM. (Numbers of nerves tested are in parentheses.)

Compound	1×10^{-4}M	5×10^{-4}M	10×10^{-4}M
Ropivacaine	30 ± 4 (3)	60 ± 13 (5)	78 ± 10 (9)
Bupivacaine	27 ± 7 (5)	46 ± 8 (6)	67 ± 10 (9)

The lowest concentration does not exclude the possibility of a 30% decreased potency of ropivacaine *in vitro*, the other two concentrations do.

II. Clinical comparisons of the sensory nerve blocking potencies of ropivacaine and bupivacaine.

Despite this *in vitro* evidence against a difference, it is still possible that there are significant *in vivo* differences between the potencies of the two drugs when administered epidurally.[7,8] Ideally, to detect these effects one would like to fit the study data to a formula which could serve to filter out effects other than those due to drug concentration and volume.

There is minimal agreement among clinicians regarding what dose is required as a function of height, weight, and age. There is at least some agreement that: 1) mass of drug injected (concentration x volume) is more important than concentration or volume separately; 2) that age is not a factor in the 20 y to 40 y age group; but 3) that excessive weight is a factor although probably only when the anesthetic is administered with the patient in the sitting position. Bromage[9] has suggested a rule to estimate mass dose of lidocaine as a function of height. (Cousins and Bridenbaugh[10] point out, though, that some studies have shown anesthetic volume as well as mass dependence.)

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[7] Gissen AJ, Covino BG. Differential sensitivity of fast and slow fibres in mammalian nerve. III. Effect of etidocaine and bupivacaine on fast/slow fibres. Anesth Analg 61:570, 1982

[8] Scott DB et al: Effects of concentration of local anaesthetic drugs in extradural block. Br J Anaesth 52: 1022, 1980.

[9] Bromage, P.R.: Spread of analgesic solutions in the epidural space and their site of action: A statistical study. Br. J. Anaesth., 34:161, 1962.

[10] Cousins, M.J. and Bridenbaugh P.O.: Neural Blockade, 2nd Edition. Philadelphia, J. B. Lippincott Company, 1988.

The question of volume dependence can be avoided if a postulated ratio of the potency of two different anesthetics is to be tested. In this case the injected volumes for a given patient height can be made equal by adjusting the concentration of the two drugs.

Based on Bromage's height-mass rule, and the available data on the potency of ropivacaine, an acceptable protocol would be to compare, in a double-blinded crossover study, the rate of successfully producing a T6 sensory level block injecting a volume of 0.5% bupivacaine

$$V\,[ml] = 16 + 0.8\,(height\,[in]-60)$$

with an equal volume of 0.65% ropivacaine via Tuohy needle (not catheter) at the L3-4 interspace. The advantage in looking at the incidence of anesthesia at a particular level, rather than measuring the mean dermatomal level of anesthesia, is that it is more clinically relevant.

None of the current studies fit this design. None of the current studies separately demonstrate any statistically significant difference in potency between the two drugs.

The current group of studies might be used to look for an answer to a simpler question: How large a study group is required to demonstrate that 0.5% bupivacaine is more potent than 0.5% ropivacaine? The data presented by the sponsor indicate that the effects at the T6 level, for the dosages used in supporting studies, would be most likely to show the desired difference. The following table lists the numbers calculated for comparing success rates in achieving a sensory level block at T6 in the lower-extremity orthopedic surgery studies.

Table 2: Required sample size tabulations for representative orthopedic studies utilizing equal volumes (20 cc) of 0.5% bupivacaine and 0.5% ropivacaine.

Study	N_{ropiv}	% Ropiv success	N_{bupiv}	% Bupiv success	Total N required for statistical significance
K5	21	88	19	92	3600
K7	23	65	25	86	200
K9	29	86	25	64	200
K10	17	63	11	71	1800

The required numbers of patients are large compared to the numbers actually studied in support of the NDA. However, as an exercise in pseudo-meta-analysis, one could combined the numbers to approach the minimum estimated required numbers. The results of this combination are shown in Table 3.

Table 3: Composite success rate for T6 analgesia in representative orthopedic studies utilizing equal volumes (20 cc) of 0.5% bupivacaine and 0.5% ropivacaine.

Study	N_{ropiv}	% Ropiv success	N_{bupiv}	% Bupiv success
Combo-a	90	78	94	77

In this case, the combination suggests (without statistical significance) that the potencies of bupivacaine and ropivacaine are equal.

When all orthopedic studies using equal volumes of 0.5% bupivacaine and ropivacaine are compared, the results are no different (Table 4).

Table 4: Composite success rate for T6 analgesia in all orthopedic studies utilizing equal volumes (20 cc) of 0.5% bupivacaine and 0.5% ropivacaine.

Study	N_{ropiv}	% Ropiv success	N_{bupiv}	% Bupiv success
Combo-b	139	71	156	71

Nor do they differ when the abdominal surgery results are added in (Table 5).

Table 5: *Composite success rate for T6 analgesia in all non-obstetrical studies utilizing equal volumes (20 cc) of 0.5% bupivacaine and 0.5% ropivacaine.*

Study	N_{ropiv}	% Ropiv success	N_{bupiv}	% Bupiv success
Combo-c	161	71	178	70

In fact, it begins to appear that there is no difference between the effects of equal doses (masses) of the two anesthetic agents although this has not been proven.

The epidural for labor pain relief studies necessarily involved tailoring to inter-patient variations both in degree of pain because of varying fetal presentations and in duration of

labor. The c-section studies involved either very large doses supplying nearly 100% anesthesia at T6 or variable doses depending upon patient need. Under such circumstances, results of an analysis regarding relative potencies would be far more open to question. Given the apparent equipotency shown by the composite studies that were examined, it does not seem profitable to consider the obstetrics studies here.

III. Clinical comparisons of the motor nerve blocking potencies of ropivacaine and bupivacaine.

Studies K3, K5, K6, K9, K10, and K11 involved epidural administration of equal and relatively large doses of ropivacaine and bupivacaine — sufficient to supply analgesia for lower extremity surgery. The frequency of motor block was determined using the simplified Bromage scale.

0 No block
1 Just able to flex knees, still full flexion of feet possible.
2 Unable to flex knees. Still flexion of feet
3 Unable to flex knees or feet.

No statistically significant differences in the frequency of different degrees of motor blockade were found in studies K3, K5, K9, K10, or K11. Only in study, K6, was a statistically significant difference detected. Here, it was found that the frequency of Bromage degree 2 motor block was greater for bupivacaine 0.5% than for ropivacaine 0.5% ($0.05>p>0.02$).

In spite of the inadequate power of these studies, there did seem to be a trend towards a greater motor blocking potential for bupivacaine than for ropivacaine. However, a composite analysis, Table 6, suggests that over 1200 patients would be necessary to be 95% certain of proving this hypothesis with $p<0.05$.

Table 6: Composite frequencies of motor block of degrees 1,2, and 3 (number of patients reaching each degree/number of patients evaluated for each degree) for studies K6, K9, K10, and K11.

	Degree 1 Block	Degree 2 Block	Degree 3 Block
Ropivacaine 0.5%	77/106 (73%)	38/104 (37%)	16/103 (16%)
Bupivacaine 0.5%	87/114 (76%)	53/113 (47%)	25/113 (22%)
p-value for a Difference	p>0.5	0.5>p>0.1	0.5>p>0.1

IV. Summary.

The sponsor has provided no evidence to support a reduced sensory block potency of ropivacaine. Consequently, there is no evidence to support marketing ropivacaine in concentrations other than those marketed for bupivacaine.

Likewise, the sponsor has provided no evidence to support a reduced motor block potency of ropivacaine. But there may actually be a difference and this may lead anesthesiologists to use increased doses of ropivacaine for this purpose as they gain more experience with the drug. However, just as in the case with bupivacaine, this would be an inappropriate response. Bupivaciane is the only local anesthetic known to show a relative specificity for sensory fibers.[11] Etidocaine — a long-acting local anesthetic without sensory fiber specificity — is the appropriate drug to substitute when augmentation of the motor block potential of bupivacaine is desired. It should also be the substitute for ropivacaine for this purpose. Consequently the possibility of reduced motor blocking potential does not justify marketing ropivacaine in concentrations other than those marketed for bupivacaine

Furthermore, the sponsor has submitted an ovine toxicology study which suggests that

[11] Bromage, P.R.: Mechanism of action of extradural analgesia. Br, J. Anaesth., 47;199:1975.

inadvertent intravenous bolus doses of ropivacaine might be just as toxic as equal doses of bupivacaine (This study is reviewed in my report entitled NDA Safety Issue Review — Naropin) Consequently there is no justification for permitting higher dosing limits for ropivacaine than for bupivacaine. The table in the sponsor's package insert — Dosage Recommendations — should be changed accordingly

I L. Tyler, Ph.D., M.D — date 11/6/95

Peer Reviewer — date 11-6-95

PILOT DRUG EVALUATION STAFF
NDA SAFETY ISSUE REVIEW

NDA #: 20-533
NAME: Naropin
SPONSOR: Astra
SUBMISSION TYPE: Commercial NDA
CSO: D Morgan
REVIEWER: I.L. Tyler, Ph.D., M.D.

The Relative Toxicity of Ropivacaine *vs.* Bupivacaine

Introduction:

The long-acting local anesthetics, bupivacaine and etidocaine, began to see wide usage in the mid 1970's. Bupivacaine, especially, was popular because of its relative specificity for sensory fibers.[1]

In 1979, Prentiss[2] reported a case of sudden cardiac arrest in a healthy 31 year old male following bolus injection of 25 ml of etidocaine 1% for caudal anesthesia. Soon thereafter, Albright[3] summarized several anecdotal reports of sudden cardiovascular collapse after inadvertent intravascular injection of etidocaine or bupivacaine. Numerous similar incidents followed. The preponderance of these involved pregnant women receiving boluses of 0.75% bupivacaine for epidural anesthesia. In some cases, the arrest was preceded by convulsions. In others, arrest occurred immediately after rapid injection.

Subsequently Morishima[4] and co-workers demonstrated that, unlike other amide local anesthetics, the dose and plasma concentration of bupivacaine required to produce cardiovascular collapse were lower in pregnant than in nonpregnant sheep. This finding led the FDA to issue a "not recommended in pregnant patients" designation for the use of 0.75% bupivacaine — the highest concentration on the market.

Ropivacaine, a homologue of bupivacaine, is thought to be less cardiotoxic than bupivacaine while retaining bupivacaine's desirable properties. The sponsor proposes marketing a 1% concentration. The issue at hand is whether sufficient data exist to support the need for and safety of this concentration. In an accompanying review,

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[1] Bromage, P.R.: Mechanism of action of extradural analgesia. Br. J. Anaesth 1975., 47;199.
[2] Prentiss JE. Cardiac arrest following caudal anesthesia. Anesthesiology 1979; 50:51.
[3] Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285.
[4] Morishima HO et al. Bupivacaine toxicity in pregnant and nonpregnant ewes. Anesthesiology 1985;63:134.

entitled NDA Efficacy Review — Naropin, we conclude that the sponsor has not demonstrated ropivacaine is less potent than bupivacaine. Consequently a need for a 1% concentration has not been proven. In this report we consider whether the sponsor has demonstrated that ropivacaine is 30% less toxic than bupivacaine.

Relevant Data:

The NDA for ropivacaine includes a new study by Morishima's group comparing the ovine toxicity of ropivacaine 0.5% with bupivacaine 0.5%.[5] It is a refinement of their study design which led to the proscription of 0.75% bupivaciane in pregnant patients. In the new protocol, chronically prepared unmedicated sheep were randomized to receive a "blinded" intravenous infusion of either bupivacaine or ropivacaine at a constant rate of 0.5 mg/kg/min until they collapsed. The toxic manifestations occurred in the usual sequence when toxic serum levels develop slowly: convulsions, hypotension, apnea, and finally circulatory collapse. There were no resuscitation efforts. The sponsor's conclusions were: (1) contrary to the findings of the previous study, pregnancy did not enhance the toxicity of either drug; and (2) the doses required to produce signs of CNS and cardiac toxicity in pregnant ewes were greater for ropivacaine than for bupivacaine.

The supporting data for onset of convulsions are presented in Table 1. Data for samples obtained at the onset of hypotension, apnea, and circulatory collapse were statistically similar.

Table 1: Doses in mg/kg administered up to the time of onset of convulsions.

	Pregnant	Nonpregnant	Difference ± sedm*	p-value for difference
Ropivacaine ± sd (N)	7.5 ± 1.8 (12)	6.1 ± 2.2 (12)	0.4 ± 0.7	(0.5>p>0.2)
Bupivacaine ± sd (N)	5.0 ± 2.2 (12)	4.6 ± 1.1 (12)	1.4 ± 0.8	(0.5>p>0.2)
Difference ± sedm*	2.5 ± 0.8	1.5 ± 0.7		
p-value for difference	(0.01>p>0.001)	(0.05>p>0.02)**		

* standard error in difference between means

** p-values calculated by reviewer. The sponsor's more sophisticated calculation demonstrated p>0.05 for the difference in nonpregnant ewes.

These data do support the sponsor's conclusions but seem too selective. The important safety issue is whether there are significant differences in the toxicity of bolus doses of the two drugs. In the current study the drugs were infused at the relatively slow rate of about 5 ml/min. The bupivacaine toxicity manifested in clinical practice occurred after bolus injections of 15 to 40 ml over probably less than 5 seconds — 35 to 100 times the injection rate for the sheep studies. Differences in clearance rates to other compartments

[5] Astra Report No 802-550-LF-0219: Pharmacokineteics, protein binding and systemic toxicity of ropivacaine and bupivacaine in pregnant and nonpregnant ewes; systemic toxicity evaluation.

can significantly alter the anesthetic concentration in the central compartment during the ten or so minutes elapsing between the beginning of the infusion and the onset of toxic symptoms. Only in the absence of significant clearance rates are total doses by slow infusion relevant. In that case, greater ropivacaine doses would certify a greater central compartment volume — a parameter which does imply greater safety for ropivacaine boluses (if equal total serum concentrations are equally toxic). In the current experimental design, anesthetic serum concentrations seem the more appropriate parameter; and serum concentrations were measured at the onset of each toxic symptom.

Data for serum concentrations in μg/ml at the onset of convulsions are presented in Table 2. Again, data from samples obtained at the onset of the other toxic manifestations were statistically similar. They are not presented because they have less clinical relevance. (One expects that resuscitation efforts including assisted ventilation would, in the clinical setting, be instituted at the onset of the first toxic symptom. No resuscitation efforts were made on these sheep.)

Table 2: Serum concentration in μg/kg at the onset of convulsions.

	Pregnant Serum Concentration in μg/ml	Nonpregnant Serum Concentration in μg/ml
Ropivacaine ± sd (N)	(11)	(11)
Bupivacaine ± sd (N)	(12)	(12)
Difference ± sedm	(p>0.5)	(p>0.5)

These data do not support a reduced toxicity for ropivacaine. In fact, there is a slight trend in the opposite direction.

One might argue that free — rather than total — serum concentrations are the important parameter to examine because only free drug crosses neural membranes. But this argument is not clinically relevant to bolus toxicity. Only total — not free — drug concentrations are under the direct control of the clinician. If equal bolus doses of ropivacaine and bupivacaine result in equal total serum concentrations and the onset of toxic reactions are known to occur at equal total serum concentrations then the drugs are equally toxic. Nevertheless, free drug concentrations were also determined by the investigators. For completeness, the results for samples obtained at the onset of convulsions are presented in Table 3. Data from samples obtained at onset of the other toxic manifestations were statistically similar but of even less clinical relevance because respiratory acidosis — avoidable in the clinical setting — can strongly affect free drug concentration.

Table 3: Free drug serum concentration in µg/kg at the onset of convulsions.

	Pregnant Free Drug Concentration in µg /ml	Nonpregnant Free Drug Concentration in µg /ml
Ropivacaine ± sd (N)	(11)	(11)
Bupivacaine ± sd (N)	(12)	(11)
Difference ± sedm	(0.1>p>0.05)	(0.001>p)
Confidence Limits		

Conclusion:

We have presented data from a laboratory experiment which is a refinement of the toxicity study that lead the FDA to re-label bupivacaine regarding acceptable concentrations. In this refined experiment, there is indirect evidence that equal bolus doses of ropivacaine and bupivacaine may be equally toxic. No other studies ruled out this possibility. It seems logical, therefore, to expect the FDA to treat ropivacaine and bupivacaine labels equally regarding acceptable concentrations.

This conclusion is supported by the fact that the sponsor was also unable to demonstrate that ropivacaine was less potent in the production of sensory blockade than bupivacaine (see NDA Efficacy Review — Ropivacaine). This probable equipotency of the two drugs supports our conclusion in two ways: First, Liu has demonstrated in a dog model that the potency-to-toxicity ratio is a constant for the amide local anesthetics[6] — additional support for the probable equal toxicity of the two drugs. Second, equipotency implies that there is no real need for higher concentrations of ropivacaine if there is no real need for higher than the currently permitted concentrations of bupivacaine.

Finally, it should be emphasized that these conclusions were based more on lack of proof of inequivalency rather than proof of equivalency. If there is, in fact, inequivalency, will this put the sponsor's drug at a significant disadvantage? Probably it will not. Total dose (mass) of local anesthetic rather than concentration has been shown to determine the clinical effect. If, in the clinical setting, it is found that the initial dose was not adequate, additional dosing to the desired total dose will therefore solve the problem with greater safety. As more experience is gained, increased initial volumes, administered slowly, can be substituted for additional dosing. This is a safe approach because interpolation of data[7,8] from previous epidural anesthetic volume/concentration studies indicate that a 30% increase in volume of a 30% weaker solution of local anesthetic will increase the spread of analgesia by at most one dermatome.

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[6] Liu P et al: Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized, ventilated dogs. Anesth Analg 61:317, 1982.

[7] Erdmir HA et al: Studies of factors affecting peridural anesthesia. Anesth Analg 44:400, 1965.

[8] Crawford O.B.: Comparative evaluation in peridural anesthein of lidocaine, mepivacaine, and L-67, a new local anesthetic agent. Anesthesiology, 25: 321, 1964

I L. Tyler, Ph.D., M.D — date 11/6/95

Peer Reviewer — date 11-6-95

Medical Officer Safety Update Review

NDA #: 20-513

PRODUCT TRADE NAME: Naropin (ropivacaine HCl)

SPONSOR: Astra Pain Control

LETTER/SUBMISSION DATE: July 16, 1996

REVIEWER: Robert F. Bedford, M.D.

COMPLETION DATE: August 4, 1996

CSO: David Morgan

1. RESUME:

This NDA is for a new, long-acting local anesthetic drug that has been shown to have less neuro and cardiac toxicity in animal models. It is anticipated that its primary clinical use will be for obstetrical and postoperative analgesia, delivered via a continuous epidural infusion technique. The purpose if this submission is to update safety information obtained in clinical trials that was not included in the original NDA or the safety update filed 6-months after NDA filing.

Background

During my integrated safety review dated March 21, 1996, there were several items of concern noted: First, the major observed complication associated with epidural anesthesia was hypotension. This was clearly dose-related, both in terms of absolute dosage and also in terms of dosage *vis a vis* patient size. Secondly, it was noted that there was a dose-related tendency for patients to sustain temperature elevations >38.5° C. with prolonged analgesic infusions of ropivacaine. Finally, there was a 10% incidence of urinary retention associated with prolonged epidural ropivacaine infusions. No comparative data with bupivacaine were available for prolonged analgesic infusions at the time of the integrated safety review, but these are now available with the information submitted in the present report.

Clinical Studies:

Clinical trials reported are as follows:

1) 92RO64: A double-blind comparison between epidural ropivacaine 0.25% and bupivacaine 0.25% given as top-up doses for pain relief during labor.

2) 94RO79: Continuous epidural infusion of ropivacaine, 2 mg/ml, for pain relief during labor - a volume-response study.

3) 94RO80: An open study using 150 mg and 187.5 mg ropivacaine (7.5 mg/ml) in epidural anesthesia for Cesarean delivery: a clinical and pharmacokinetic evaluation.

4) 94RO86: An open study using 300 mg, 375 mg and 450 mg ropivacaine for postoperative pain relief after hernia repair: a clinical and pharmacokinetic evaluation.

The sponsor indicates that there are an additional 16 ongoing clinical trials for which safety data are included in the form of line-listings. One trial was discontinued due to slow recruitment.

Deaths: One death was reported in a patient who initially underwent radical cystectomy with creation of an ileal conduit under ropivacaine epidural anesthesia. The patient then required reoperation several months later under general anesthesia and subsequently died from complications of the reoperation. There was clearly no relationship to ropivacaine.

Serious Adverse Reactions: There were no drop-outs related to serious drug-related AE's. Line listings are provided for the serious AE's noted in trials where patients were known to have received ropivacaine or where the study code has not been broken. The AE's are the usual array of complications to be expected with the trials currently underway. This reviewer could not identify any unexpected complications that have not been addressed in the product labeling. Urinary retention was identified only in a single patient.

Study 94RO80: Comparison of 150 mg and 187.5 mg ropivacaine for C-Section: Currently, ropivacaine is only approved for C-Section in the 0.5% strength. This is the first study undertaken to document the safety and efficacy of 0.75% strength. While only 16 patients have been recruited as of the date of this safety update, there is still a strongly dose-dependent pattern emerging, with more hypotension (13 vs 75%) and its resulting nausea (13 vs 38%) occurring intraoperatively with the larger dose of ropivacaine. This issue is well-addressed in the present package insert and is not surprising considering that more than 20 ml of epidural local anesthetic is excessive for most patients undergoing C-section.

Studies 92RO64 and 94RO79: Use of ropivacaine for obstetrical pain relief: Cardiovascular Effects: As was the case in 94RO80, these trials also demonstrate a dose-dependent incidence of early-onset hypotension: (12%, 19% and 25%) for dosages of <76 mg, 76-150 mg, and >150 mg, respectively. This is clearly a dose-related

phenomenon that has been dealt with at great length in the package insert. In study 92RO64, the incidence of hypotension for ropivacaine-treated patients as compared to those who received bupivacaine 21 vs 11% . This difference is probably a function of the greater range of doses administered to the ropivacaine patients, whereas the bupivacaine patients only received a single, relatively conservative, epidural infusion rate.

Fever with prolonged infusion: The incidence of temperature elevations >38.5°C associated with these prolonged epidural infusions also increases with dosage: 7% and 4% for the lower rates of infusion, but equal to 29% at the higher dosage. This is in accordance with data previously observed with higher-rate infusions of ropivacaine for long-term postoperative pain relief. It is probable that patients who received the highest doses of ropivacaine also were in labor the longest, a recognized cause of temperature elevation associated with epidural anesthesia. Fever was most common during the first stage of labor (before complete cervical dilatation). While there was a higher incidence of fever >38.5°C. in ropivacaine vs bupivacaine patients (18 vs 11%), this is probably related to the fact that ropivacaine dosage was pushed higher than the single infusion rate administered to the bupivacaine patients.

Fetal effects: Study 94RO79 shows that fetal effects of ropivacaine appear unlikely, since there was no dose-dependency for adverse event such as fetal bradycardia, fetal distress, fetal tachycardia, meconium aspiration or neonatal jaundice. These observations were confirmed in study 92RO64, which compared ropivacaine and bupivacaine, (n = 77 patients) for labor analgesia in a blinded fashion. The incidence of fetal distress (bradycardia and tachycardia) and neonatal jaundice was identical in the two groups.

Urinary retention: There was no difference in the incidence of urinary retention following epidural anesthesia with either ropivacaine or bupivacaine (3% in both groups), thus minimizing concern about this AE expressed during my review of the integrated safety report.

Prolonged Labor and the need for Cesarean Section:
In study 92RO64, the incidence of routine labors converting to C-Section was 21% and 15% for the ropivacaine and bupivacaine groups, respectively. While this difference is not statistically significant, there is a clear trend from the studies submitted to the NDA that patients receiving epidural ropivacaine for labor analgesia may have a higher incidence of impaired labor requiring Cesarean delivery (see Table 1).

Table 1: Number (%) of obstetrical patients in labor going on to C-section

	All Ropivacaine OB patients	All Bupivacaine OB patients	Ropivacaine C-S patients	Bupivacaine C-S patients
All NDA Studies	n = 231	n = 196	26 (12.6%)	18 (9%)
92RO64	n = 38	n = 39	8 (21%)	6 (15%)

These data are unexpected, since the original NDA studies demonstrated, if anything, a higher incidence of spontaneous vaginal deliveries in patients receiving ropivacaine as compared to bupivacaine. There are two primary indications for converting a routine labor to a C-Section delivery: fetal distress and desultory labor. The available data clearly show that the incidence of fetal distress was not different between ropivacaine and bupivacaine-treated patients. Therefore, the question in this reviewer's mind is simply whether ropivacaine epidurals result in a higher incidence of delayed vaginal delivery that "necessitated" conversion to C-Section. Given the vague indications for performing C-Section in the face of prolonged labor (maternal fatigue, office hours, a pressing social event, etc.), this reviewer suggests that these data should be approached with healthy skepticism.

This opinion is supported by the following observations: If the patients who went to C-section are not counted, then the incidence of poor progression of labor was actually slightly higher for the bupivacaine treated patients (26%) as compared with the ropivacaine patients (18%). Furthermore, in study 94RO79, ropivacaine patients who had prolonged labor received higher ropivacaine dosages and had a consistently higher incidence of dystocia (11% vs 2%) and poor progression of labor (21% vs 7%) as compared with the low-dose ropivacaine groups. To some extent, then, the higher incidence of delayed vaginal deliveries may have been simply a result of excessive ropivacaine dosing and inability of the mothers to actively cooperate during normal spontaneous vaginal delivery.

Study 94RO86: 300 mg, 375 mg and 450 mg ropivacaine for local infiltration for hernia repair analgesia: The incidence of complications was <1% with this route of administration and no difference in AE's was seen between these doses.

Preclinical Studies:

One preclinical study was submitted: **Astra report 802-50 T3062** is a 4-week continuous epidural infusion study comparing neurotoxicity of ropivacaine and bupivacaine in beagles. Of importance, given the concerns about fevers observed with prolonged human exposure,

is the fact that there was no evidence of neurotoxicity related to either drug. Only normal tissue reaction to the epidural catheter foreign body was seen.

2. CONCLUSIONS:

a. Urinary retention does not appear to be a complication specifically related to ropivacaine epidural anesthesia, and occurs with the same frequency in association with bupivacaine epidurals.
b. Fever >38.5° C. continues to be observed and remains a dose-dependent issue during continuous epidural infusions for analgesia. It does not appear to be the result of neurotoxicity. This matter is well-addressed in the current product labeling.
c. There is no difference between ropivacaine and bupivacaine with regard to the incidence of fetal distress or neonatal complications during obstetrical analgesia. Likewise, there does not appear to be any dose relationship between ropivacaine infusion rate and the incidence of neonatal/fetal complications.
d. During obstetrical epidural analgesia for labor, higher infusion rates of ropivacaine will result in desultory labor and a higher incidence of dystocia and Cesarean Section delivery. This dose-dependency is a well-recognized problem in obstetrical anesthesia and is not specifically related to ropivacaine. Therefore, no change in the labeling is indicated.
e. The most serious AE related to epidurally administered ropivacaine continues to be arterial hypotension. The data in this update demonstrate that this is clearly a dose-related phenomenon, and the current labeling abundantly addresses this issue with cautions and warnings.

3. Recommendations regarding labeling:

It is recommended that no major changes be made in the current product labeling, based on the information provided in this safety update.

NDA # 20-533
HFD-170/Div File
HFD-170/RBedford
HFD-170/
HFD-502
HFD-340
F/T by

Robert F Bedford

Robert F. Bedford, MD

MEDICAL OFFICER REVIEW

NDA #: 20-533

NAME: NAROPIN: Safety Update Report to NDA

SPONSOR: Astra
PO Box 4500
Westborough, MA 01581-4500
phone (508)366-1100, fax (508) 366-7406

SUBMISSION DATE: Nov 6, 1995.
REVIEWER: Robert F. Bedford, M.D., Medical Officer.
REVIEW DATE: Nov 16, 1995.
SUBMISSION TYPE: 6 - month safety update
RECEIVED: CDER: 11/6/95; Reviewer:11/15/95.
CSO: David Morgan

1. RESUME:

Background

Ropivacaine is a new local anesthetic agent that has been under NDA review since March 29, 1995. A meeting of the Anesthetic and Life Support Advisory Committee will review the previously-submitted clinical trials and discuss the labeling and approvability of this product in 4 week's time. This submission consists of retrospective meta-analyses of 2 important issues identified in studies previously reviewed for the NDA: 1) neonatal neurologic function following maternal epidural anesthesia and 2) a higher incidence of postoperative fever (9.5% vs 1.0%) observed in patients receiving higher doses of epidurally infused ropivacaine (16-30 mg/hr vs 0 or 10-12 mg/hr) for long-term analgesia following major surgical procedures. Also submitted is another study report (there are already 8) on the use of 0.25% ropivacaine vs 0.25% bupivacaine for pain relief during labor and delivery.

2. OBSTETRICAL ANESTHESIA:

Neonatal Neurobehavioral Function: Vaginal Delivery

This report summarizes the data from 391 pregnant women enrolled in 6 studies that evaluated safety and efficacy of epidurally administered ropivacaine vs. bupivacaine for labor and delivery: 201 patients received ropivacaine, 2.5 mg/ml, and 190 received bupivacaine, 2.5 mg/ml. Duration of epidural local anesthetic infusion was not different: 5.3 vs 5.4 hr, respectively. One and 5-minute Apgar scores and neonatal adaptive capacity scores (NACS) at 2 and 24 hours post-partum were performed (n=147 ropivacaine; 144 bupivacaine). The only significant difference was the 24 hr NACS, where,

with regard to scores < 35, there were more babies in the bupivacaine group (n=11) as compared with the ropivacaine group (n=4). These results may refect a higher incidence of spontaneous vertex deliveries in the ropivacaine group (58% vs 49%) as compared with the necessity for more forceps delivery in the bupivacaine group (22% vs 14%). In any event, there appears to be no evidence for adverse effect on babies of mothers anesthetized with ropivacaine. It is possible that better motor strength in the mothers receiving ropivacaine improves their chances of delivering spontaneously.

Neonatal Neurobehavioral Function: Cesarean Section

155 patients received ropivacaine, 0.5%, and 150 received bupivacaine, 0.5%, with 137 and 129 neonates, respectively, available for evaluation (meaning weight > 2500g and mother received no other analgesics). The doses of study drug, duration of surgery, 1 and 5 min Apgar scores and 2 and 25 hr NACS were not different. There appears to be no adverse impact on neonates whose mothers received ropivacaine for Cesarean section delivery. This observation is currently addressed in the draft package insert.

3: POSTOPERATIVE FEVER REPORT:

Data from 8 studies totaling 572 patients who received epidural infusion of ropivacaine or placebo (in combination with opioid PCA) for postoperative analgesia were used for this analysis. The postoperative study period was 21 hours. Patients were judged to be febrile when temperatures were above 38.5° or 39°C (depending on the protocol) or if antipyretics were administered. The patients were divided into 4 groups: placebo infusion or ropivacaine infusion at rates of 10-12 mg/hr; 16-20 mg/hr or 24-30 mg/hr. Although there were no reports of infection during the 21 hr study period, the incidence of fever was 3,4,13 and 11%, respectively. Of note in this meta-analysis is the dose-dependent reduction in median postoperative morphine PCA requirement: 52, 30, 28 and 21 mg, respectively.

The attached figure demonstrates the separation of temperatures between the four groups over the first 21 postoperative hours. The figure highlights the greater number of febrile temps in the higher-dose ropivacaine groups. In the absence of an active comparator group, it is impossible to determine whether this is a function of ropivacaine per se, or a function of the prolonged, more profound epidural block afforded by the higher ropivacaine concentrations. Whether higher morphine doses in the placebo and low-dose ropivacaine groups augment heat loss due to vasodilation (in contrast to lower morphine doses in the higher-dose ropivacaine groups, which might prevent heat loss), is totally conjectural. This reviewer believes that an important feature from this analysis is the lack of difference in the incidence of postoperative

infections between groups. At the present time, it appears that there is no appreciable increased risk to use of low-dose ropivacaine for postoperative analgesia following epidural anesthesia.
Recommendation: At the NDA labeling day, it will be suggested that language be added to the package insert to describe the increased frequency of postoperative fever when infusions of ropivacaine greater than 12 mg/hr are administered for 24 hours.

4: OBSTETRICAL STUDY REPORT:
76 women in active labor were randomized to receive infusions of 0.25% ropivacaine or bupivacaine for epidural analgesia (n = 38 in each group). Total volumes of local anesthetic administered were 30 and 34 ml, respectively. There was no difference between the groups with regard to onset or height of sensory block or discomfort during labor. Motor block (weak legs) was present in 25% of ropivacaine patients and 53% of bupivacaine patients ($P<.05$). Mean time from first injection to delivery was 3.3 and 5.6 hr, respectively, resulting in fewer "top up" doses of ropivacaine being needed. Operative deliveries were the same in both groups. No differences were seen between the groups with regard to complications or adverse outcomes in either mothers or neonates. No other unanticipated complications occurred in either drug.
Conclusions: There are no new safety issues raised by this study that are not already adequately addressed in the current draft package insert.

5. CONCLUSIONS:
The only new safety issue raised by these reports is the higher incidence of postoperative fever identified in patients receiving prolonged ropivacaine infusions for postoperative epidural analgesia. This will be addressed at the up-coming NDA-day review.

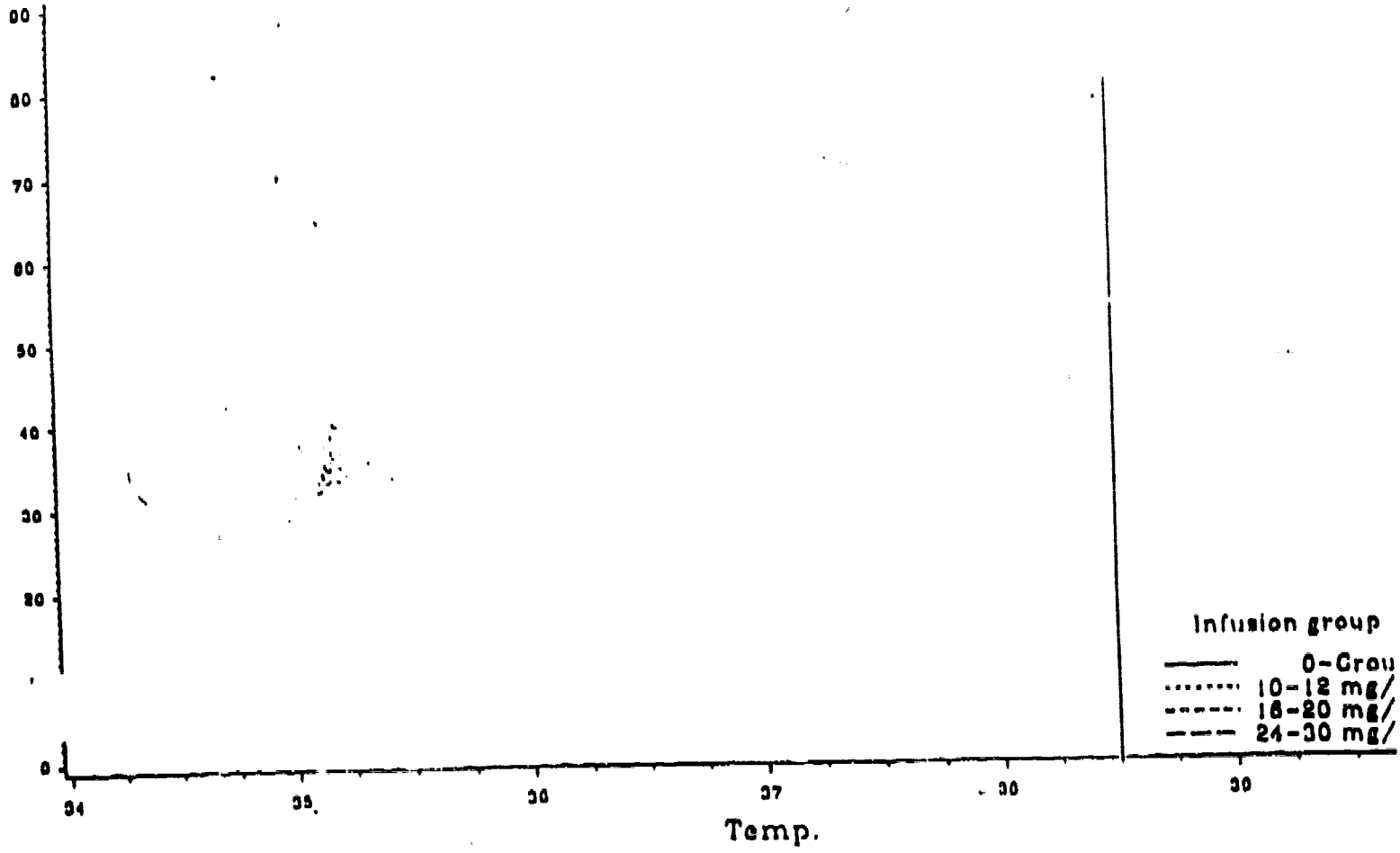
Orig NDA # 20-533
HFD-007/Div File
HFD-007/RBedford
HFD-007/Morgan
HFD-502
HFD-340
F/T by

Robert F. Bedford, MD 11/21/95

Peer Reviewer 11/21/95

Group=Valid for safety Time period=0-21 hrs

Threshold definition fever



DIVISION OF ANESTHETIC, CRITICAL CARE AND
ADDICTION DRUG PRODUCTS

Ropivacaine Integrated Safety Review

NDA #: 20-533
Drug: Ropivacaine (NAROPIN)
Sponsor: Astra USA, Inc.
Reviewer: Robert F. Bedford, M.D.
CSO: David Morgan
Date: March 21, 1996

Background

This NDA is for a new, long-acting local anesthetic agent that was developed because animal toxicity studies suggested that it was less cardiotoxic than the current standard drug, bupivacaine. Shortly after its approval, bupivacaine was associated with reports of unresuscitatable cardiac arrest due to inadvertent intravascular injection, usually occuring during obstetrical epidural anesthetics. After relabeling that included a black-box warning regarding appropirate use of bupivacaine in obstetrical analgesia, this problem has largely disappeared and has not been reported to the Agency's Spontaneous Reporting System in the past 5 years. Because ropivacaine has a longer duration of action and possible lower cardiotoxicity than bupivacaine, the approval of this product has been widely anticipated in the anesthetic practice community.

1.0 Background and Methodology for Safety Review

Clinical Studies:

The sponsor submitted a total of 73 clinical studies to the NDA, in which 2252 patient received ropivacaine. 902 active control patients received corresponding doses of bupivacaine. The following trials were performed using regional anesthesia for a variety of surgical, obstetrical or analgesic procedures:

Epidural Anesthesia for Surgery/Cesarean Section: (32 trials);
Epidural Analgesia for Labor/Delivery: (9 trials)
Epidural Analgesia for Postoperative Pain Control: (9 trials)
Spinal Anesthesia: 2 trials with 80 patients.
Local Infiltration for post-op pain relief: 7 trials
Major nerve block for surgery: 9 trials:
Human Pharmacokinetics and Clinical Pharmacology: 5 studies.

Review of the Clinical Trials:

Eight special government employees with expertise in the above anesthetic subspecialties were recruited to perform the primary reviews of the clinical trials in their respective disciplines. Dr. Robert Merin, an expert on cardiovascular pharmacology of anesthetic agents, was recruited specifically to examine the relative cardiotoxicity of ropivacaine versus bupivacaine. Dr. Israel Tyler, FDA Medical Officer in this Division, performed an integrated review of the relative potency of ropivacaine versus bupivacaine based on information derived from the clinical trials where bupivacaine and ropivacaine were compared for epidural anesthesia. Finally, this Medical Officer reviewed the sponsor's 6-month Safety Update submitted in November, 1995, which addressed neonatal neurologic function following aternal epidural anesthesia, the incidence of postoperative fever (9.5% vs 1.0%) observed in patients receiving higher doses of epidurally infused ropivacaine (16-30 mg/hr vs 0 or 10-12 mg/hr) for long-term analgesia following major surgical procedures and an additional study on the use of 0.25% ropivacaine vs 0.25% bupivacaine for pain relief during labor and delivery.

1.1 Deaths

Three patients who received ropivacaine during the clinical trials died. In each case, the patient was elderly (68-76 years) and at risk for postoperative cardiorespiratory complications. All received ropivacaine epidurally for major surgical procedures and 2 of the 3 had continuation therapy for postoperative analgesia. The causes of death were acute renal failure, bowel obstruction and acute multiorgan failure, occurring 48, 92 and 368 hours postoperatively. No relationship to ropivacaine administration was apparent.

Two patients in comparator groups died. One was a 74 year old patient who received saline placebo as part of the postoperative epidural analgesia study. Cause of death was acute MI 22 hours postop. The other was an infant of a mother who received bupivacaine for C-Section. The baby died of SIDS 12 days after delivery.

1.2 Dropouts

No patient dropped out of any study due to death. The most common cause of dropout was technical failure of the regional anesthetic technique, meaning that the local anesthetic was administered and there was no anesthetic effect due to misplacement of the injection needle or catheter. These patients subsequently received general anesthesia for their scheduled operation and no further analysis comparing adverse effects of ropivacaine and bupivacaine was appropriate.

The most serious adverse reactions resulting in patients' dropping out were caused by apparent intravascular injection. There were 6 inadvertent IV injections of ropivacaine while regional anesthetics were being performed (dose range: 75-200 mg; average 125 mg) . All resulted in typical local-anesthesia-induced CNS symptoms (tinnitus, numbness of the lips, a metallic taste, light-headedness). One patient had a convulsion that was brief and self-limited. There was no evidence of cardiotoxicity from either ropivacaine or bupivacaine in the clinical trials and all patients' recovered from the intravascular injection without sequellae.

In the obstetrical analgesia studies, the most common cause of dropout was evidence of fetal distress (tachycardia or bradycardia) that lead to Cesarean Section. There was no greater incidence of fetal distress in the ropivacaine-treated patients. Furthermore, after ropivacaine and bupivacaine epidural anesthesia, the delivered babies were essentialiy identical with regard to their neonatal adaptive capacity scores, regardless of the method of delivery. Ropivacaine was associated with more spontaneous vaginal deliveries and fewer forceps/vacuum extraction deliveries, perhaps because of less motor blockade and better ability of mothers to voluntarily push during delivery.

1.3 Other Serious Adverse Events

The overall incidence of serous adverse reactions was similar in the ropivacaine and bupivacaine-treated patients: 5.5% for the 2244 ropivacaine patients in non-comparative trials, and 7.8% vs 8.3% for ropivacaine (n=1163) and bupivacaine (n=721), respectively, in the double-blind trials.

Because the serious adverse event profiles, particularly cardiovascular and neurologic events, are related to the route of local anesthetic administration and the operative indication, these are subdivided accordingly. Furthermore, since age and patient size influence dose-requirement for epidural anesthesia, one might expect a higher incidence of complications related to excessive epidural block in the elderly and in smaller, and/or female, patients. These consistent patterns are demonstrated in the following tables for each anesthetic indication.

1.31 Serious AE's related to General Surgical Procedures

Arterial hypotension due to blockade of spinal sympathetic outflow is the most common adverse reaction related to epidural anesthesia. This, in turn, may lead to CNS symptoms (lightheadedness, loss of consciousness) and nausea and vomiting . The following table indicates the close correlation between the incidence of these events and epidural dosage in mg/kg of ropivacaine administered via the epidural route.

Table 1.311: % Incidence of SAE's: Epidural Anesthesia for General Surgery

Ropivacaine Dose (mg/kg body weight)

Adverse Reaction	≤1.51	1.51-2.25	≥2.25
Hypotension	39.6	44.5	56.6
Bradycardia	9.1	18.1	18.6
Nausea	8.6	15.0	31.8
Vomiting	5.6	8.4	12.0

As expected, there was a close correlation between patient age and the incidence of cardiovascular and related adverse events for all patients receiving ropivacaine.

Table 1.312: % Incidence of SAE's: Epidural Anesthesia for General Surgery by Patient Age

Adverse Reaction	<39 years	39-55 years	>55 years
Hypotension	28.9	46.3	62.2
Bradycardia	11.8	8.6	25.3
Nausea	20.6	27.9	9.4
Vomiting	7.0	11.9	7.6

Also, as expected, given the difference in patient size, there was a higher incidence of SAE's in women as compared to men among patients who received ropivacaine.

Table 1.313: % Incidence of SAE's: Epidural Anesthesia for General Surgery: Males vs Females

Adverse Reaction	Males	Females
Hypotension	38.9	54.3
Bradycardia	15.8	16.0
Nausea	6.5	29.4
Vomiting	2.3	14.6

Given the differences in responses to dosage, age and sex of patients, there was, however, no significant difference between the incidence of these events and the type of local anesthetic used in the double-blind clinical trials.

Table 1.314: % Incidence of SAE's: Epidural Anesthesia for General Surgery: Ropivacaine vs Bupivacaine

Adverse Reaction	Ropivacaine	Bupivacaine
Hypotension	44.3	41
Bradycardia	7.1	10.5
Nausea	19.5	18.3
Vomiting	9.9	7.5

1.32 Serious AE's during Cesarean Section:

All these patients are grouped together, since they are female and below the age of 35 years. In terms of critical events, it is important to emphasize that there was no difference in neonatal NACS scores or outcome between patients receiving ropivacaine and bupivacaine in the blinded trials.

Again, dose-dependency was clearly demonstrated, not only in terms of height of epidural block, but also in the incidence of complications resulting from the high block. However, there was no difference between bupivacaine and ropivacaine in terms of serious adverse events (see Tables below).

Table 1.321: % Incidence of SAE's: Epidural Anesthesia for Cesarean Section according to ropivacaine dosage (mg):

Adverse Reaction	≤126 mg	126-225 mg
Hypotension	53.6	69.5
Nausea	17.3	27.4
Vomiting	4.5	9.5

Table 1.322: % Incidence of SAE's: Epidural Anesthesia for Cesarean Section Ropivacaine vs Bupivacaine:

Adverse Reaction	Ropivacaine	Bupivacaine
Hypotension	56.3	57.6
Bradycardia (maternal)	2.8	0.7
Nausea	14.8	22.3
Vomiting	6.3	7.2

1.33 Serious AE's during epidural anesthesia for labor and delivery:

The most critical issue for this indication is that the incidence of fetal distress was, if anything, lower in the patients receiving ropivacaine (2.1%) versus those receiving bupivacaine (3.9%) in the double-blind clinical trials. Again, there was no difference between the anesthetics with regard to neonatal Apgar scores or NACS evaluations. In addition, there was no relationship seen between dosage of ropivacaine and neonatal complications or fetal distress. Unlike the surgical indications for epidural anesthesia, no dose-dependency was seen for cardiovascular adverse events. This is probably due to the fact that supine hypotension is likely to occur in this setting, thus confounding the role of epidural-induced sympathectomy.

1.34 Serious AE's during epidural analgesia following surgery:

Postoperative analgesia via continuous epidural infusion was performed as an extension of intraoperative epidural anesthesia, except that control patients received saline placebo infusions rather than active drug during the first 24 hours postoperatively. All patients received opioid PCA, thus confounding the interpretation of the adverse events because placebo-treated patients self-administered greater doses of opioids.

3 patients died in the postoperative period, one who received placebo (myocardial infarction) and 2 who received ropivacaine (cardiorespiratory failure). All of these patients were high-risk surgical candidates and none of these events was thought due to the analgesic regimen. The overall incidence of serious AE's unrelated to surgery was 3.6% for the ropivacaine groups versus 2% for the saline group. Specifically, there was no difference between the 2 treatment regimens with regard to the incidence of serious cardiorespiratory complications.

Arterial hypotension and hypertension appeared to be age-related in the patients who received ropivacaine for postoperative analgesia.

Table 1.341: Postoperative Analgesia:

Incidence of complications by age-group

Adverse Reaction	<39 years	39-55 years	>55 years
Hypotension	34.1	57.5	72.8
Hypertension	1.1	5.2	13.3
Bradycardia	11.0	14.9	20.4
Tachycardia	6.6	4.5	6.8

1.35 Serious AE's associated with brachial plexus nerve blocks and local infiltration:

Unlike epidural anesthesia, there is no issue of sympathectomy with brachial plexus nerve block or local infiltration anesthesia. The major potential complication related to the local anesthetic is inadvertent intravascular injection and this did not occur during the clinical trials with either of these techniques. There was no difference between patients receiving ropivacaine and those receiving bupivacaine with regard to serious AE's and no evidence of dose-dependent increases in AE's among patients receiving ropivacaine. The only serious AE's in the brachial plexus block studies were two postoperative complications related to surgery (venous thrombosis and would infection). In the local infiltration studies, the SAE's included 1 case each of postoperative bleeding and peritoneal abcess, neither related to the anesthetic.

1.4 Other Search Strategies: Overall Analysis of Clinical Trials

Adverse events related to local anesthetics can be divided into acute episodes, usually CNS or cardiovascular, which occur within the first few minutes of injection, or delayed complications related to peripheral neurological complications which may or man not improve over time. Comparing the number of these complications in patients receiving either ropivacaine or bupivacaine, there is a suggestion that ropivacaine is safer with regard to cardiac toxicity and occurrence of peripheral neuropathy. It can be concluded with reasonable certainty that there is no evidence for increased risk from use of ropivacaine.

Table 1.41 Adverse reactions reported for Ropivacaine and Bupivacaine

Adverse Reactions: n and (%)	Ropivacaine n=2330	Bupivacaine n=902
Acute CNS Toxicity	5 (0.2%)	3 (0.3%)
Acute Cardiac Toxicity (other than epidural-induced hypotension)	3 (0.1%)	17 (1.9%)
Peripheral Neuropathy (Improved over time)	7 (0.3%)	10 (1.1%)
Peripheral Neuropathy (Unimproved over time)	9 (0.4%)	11 (1.2%)

1.5 Laboratory Findings

All patients and volunteers in the clinical trials were subject to routine monitoring of hematologic and clincal chemistry tests. Values outside the normal range were reported as adverse drug reactions. Unfortunately, these data are often confounded by the impact of the surgical procedures performed and the myriad medications that patients received. Within the above constraints, however, it can be concluded that there was no evidence for a difference between ropivacaine and bupivacaine with regard to any of the laboratory parameters examined. Furthermore, there is no historical suggestion that the long-acting amide-linked local anesthetics might be responsible for post-single dose laboratory abnormalities.

In the case of the prolonged (21 hr) epidural infusion studies in volunteers, again there was no difference between ropivacaine, bupivacaine and placebo with regard to any of the above laboratory values.

In the obstetrical analgesia trials, neonatal laboratory values for blood gases and pH were determined after each delivery. Again, there was no difference between ropivacaine and bupivacaine exposure.

1.6 Vital Signs

Pulse and blood pressure data were obtained and reviewed for virtually all patients in the epidural anesthesia, peripheral nerve block, obstetrical analgesia and long-term postoperative epidural infusion studies. As expected, blood pressure and heart rate were affected by height of epidural blockade which was directly related to the dosage of local anesthetic relative to patient size. Comparing the ropivacaine and bupivacaine-treated patients, however, there was no tendency for vital signs to be different between the two drug treatments, except for the occasional episodes of cardiovascular toxicity that were noted in the bupivacaine group (see above).

1.7 Overdose Experience

Clinical trials demonstrated that there was significantly greater CNS tolerance for ropivacaine than for equal doses and blood levels of bupivacaine. There was a distinct leftward shift of the dose-response curve for dosage of local anesthetic vs. muscle twitching and/or dysarthria, two early indicators of local anesthetic-induced CNS toxicity. In clinical trials where maximal doses of ropivacaine were administered by epidural or nerve blocks, peak blood levels never exceeded 3 ug/ml, well below the range of CNS toxicity.

The relative potency of ropivacaine versus bupivacaine was repeatedly addressed. For most peripheral nerve blocks and for analgesic epidurals, the drugs were considered to be equipotent. However, for high epidural blocks designed to provide muscle relaxation, 1.0% ropivacaine was thought to be approximately equivalent to 0.75% bupivacaine. The information currently available suggests that the higher dose requirement for producing muscle relaxation with ropivacaine is nearly equally balanced by its slightly lower cardiotoxicity.

2. Review of Systems

2.1 Cardiovascular

As repeatedly noted above, the cardiovascular effects of local anesthetic administration is primarily related to the dosage and route. Hypotension due to high sympathetic blockade from epidural anesthesia was frequently seen in the clinical trials, with no evidence that ropivacaine was different from bupivacaine in this regard. Hypotension during epidural anesthesia was clearly related to dose of drug in relationship to the size of the patients. Review of the overall blood pressure and heart rate data both for patients and for infants born to mothers who received obstetrical anesthesia with either ropivacaine or bupivacaine showed no difference between the two drugs when used for the same indication.

2.2 Gastrointestinal system

Nausea and vomiting were the most frequent GI side-effects seen during the clinical trials. These symptoms were usually directly related to arterial hypotension in the epidural anesthesia studies, and occurred intraoperatively. By contrast, nausea and vomiting are also common occurrences following intraperiotoneal surgery and following administration of opioids given for postoperative analgesia. Most of the postoperative symptomatology could be attributed to the latter confounding factors. Once again, comparing the incidence of nausea and vomiting following either ropivacaine or bupivacaine, there was no difference between the two drugs.

2.3 Hemic/Lymphatic

Local anesthetic agents have never been implicated in causing abnormalities in hematopoetic or lymphatic function, and there is no reason to suspect that ropivacaine is different from other drugs in this class. Reduction in hematocrit resulting from perioperative blood loss and crystalloid fluid infusion is a common finding in the clinical trials. In the double-blind trails comparing ropivacaine and bupivacaine, there was no difference in laboratory data obtained following administration of either of these agents.

2.4 Metabolic/Endocrine (Fever Reports)

At the 6-month NDA safety update, a detailed analysis of fever (temperatures >38.5^{0}) following prolonged epidural infusion for postoperative pain relief was presented. This phenomenon was found to occur with a higher incidence in patients receiving ropivacaine at an infusion rate >16 ml/hr as compared with those receiving placebo or ropivacaine infusions <12ml/hr. While the exact etiology of this phenomenon is unknown, it was hypothesized to be similar to the temperature increase seen in laboring women during prolonged epidural anesthesia for obstetrical pain relief. An alternative suggestion might be postoperative fever resulting from atelectasis in patients with higher levels of epidural block, although no evidence for this was actually presented. In any event, there was no corresponding change in leukocyte counts, or other indices suggestive of an infectious or immunologic process. Since there was no comparator drug administered in the postoperative epidural infusion studies, it is not possible to say if this was related to prolonged exposure to ropivacaine, although this seems unlikely. The labeling for the product describes this finding and the recommended dosing schedule suggests that only lower doses be given for postoperative infusion.

2.5. Musculoskeletal

23 cases of back pain were described as complications of epidural adminstration of ropivacaine. 20/23 patients were women undergoing gynecologic procedures. The incidence was not related to ropivacaine dose and, most likely, was the result of muscular strain due to patient positioning in lithotomy position. Backache is a common side-effect after gynecological procedures performed under general anesthesia as well.

2.6 Nervous

As noted above under serious AE's, there was no evidence for an increased incidence of transient or prolonged neurologic findings after ropivacaine as compared with bupivacaine.

Another common symptom following regional anesthesia is hypesthesias and/or numbness. In the case of circumoral or lingual symptoms, these symptoms are commonly related to anxiety and/or hyperventilation syndrome. High-thoracic sensory levels induced by epidural anesthesia often cause hypesthesias/numbness of the hands and arms and are not, per se, an adverse reaction. Likewise, delayed offset the the epidural block frequently results in several hours of numbness/hypesthesias in the lower extremities.

2.7 Respiratory

No specific respiratory complications were noted in the clinical trials apart from those widely recognized as being due to postoperative respiratory complications.

2.8 Dermatological

Rash was reported in 1.4% of patients who received ropivacaine for epidural anesthesia for general surgery, compared with 0% of patients who received bupivacaine. The overall incidence of rashes in patients receiving ropivacaine was 0.8%, with no relationship to the site of injection. This is unlikely to be due to ropivacaine specifically, but, rather, due to contact dermatitis from exposure to antiseptic solutions, adhesive tape or other contact allergens during the perioperative period. Local anesthetic agents of the amide variety are notably free from allergic reactions.

2.9 Genitourinary

Of particular note in the postoperative analgesia studies was in incidence of urinary retention = 10.2% in patients receiving epidural ropivacaine versus a 1% incidence in the saline placebo group. This complication was clearly dose-related, increasing as the infusion rate or ropivacaine increased. As opposed to an adverse reaction related to a specific local anesthetic, this is a well-recognized complication of prolonged epidural block resulting in denervation of the bladder, particularly in elderly males with subclinical prostatic hypertrophy. In any event, this is listed in the labeling as a potential complication of prolonged epidural block for pain relief.

3. Summary of Key Adverse Findings

The primary probable adverse reactions tc ropivacaine are summarized in the following table:

Frequency of Adverse Drug Reaction	Method of Calculation
Arterial Hypotension (10-62%)	Applicable to all epidural administration of ropivacaine, depending on dose and height of block.
Temperature Elevation (10%)	Applicable to long-term epidural infusion for postoperative pain relief. Less frequent with infusion rate <12 ml/hr.
Urinary Retention (1-2%; 10.2%)	Postoperative epidural infusion for pain relief associated with 10.2% incidence. Epidural anesthesia for general surgical, C-section and analgesia during labor and delivery associated with 1-2% incidence.
Hypesthesias/dysesthesias (0.3-2.0%)	Occurred in all indications, primarily related to epidural administration of ropivacaine.

4: Labeling review:

The following changes to the submitted draft package insert for Naropin were recommended by the advisory committee and incorporated into the final PI.

5: Conclusions:

Data from the extensive clincal trial experience demonstrate that ropivacaine is at least as effective and safe as bupivacaine for the production of local anesthesia via both infiltration and major nerve block. Both animal and human studies suggest that it may have a lower neurotoxicity and cardiotoxicity than bupivacaine, but this may be obviated by a slightly lower potency, at least in epidural administration, which, therefore, requires additional dosing to acheive a similar level of anesthesia. The side-effect profile and incidence of adverse reactions for ropivacaine is, if anything, less problematic than bupivacaine. The most common adverse reactions are clearly dose-related and the labeling gives considerable guidance regarding proper administration of the drug to avoid these problems.

6: Recommendations:

Based on the extensive safety and efficacy profile of Naropin, this reviewer concurs with the recommendation of the Anesthetic and Life Support Drug and supports approval of this product, as labeled in the final package insert.

Robert F Bedford 3/21/96

Robert F. Bedford, MD

Orig NDA # 20-533
HFD-170/Div File
HFD-170/RBedford
HFD-170/DMorgan
HFD-502
HFD-340
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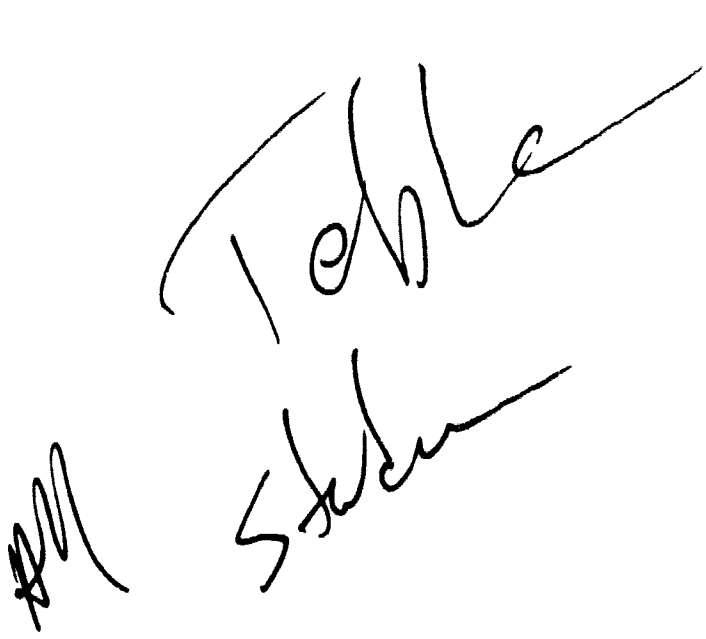

Ropivacaine HCl Injection
FDA Study List

* = Pivotal Study

Study No.	Astra No.	# Ctr.	Pt. Plan	Pt. Ent	Study Design	Comparator Drug	Ropivacaine Dose
K1	87Ro06	1			Open, dose response	None	0.75%: 15, 20, 25 mL
K2	87Ro10	3			Open, dose response	None	0.5%, 0.75%, 1.0%: 20 mL
K3	88Ro02	1			DB, Comparative	Bupi 0.75%: 20 mL	0.75%: 20 mL
K4	88Ro03-00	1			DB, Comparative	Bupi 0.75%: 15 mL	0.75%: 15 mL
K5	88Ro03-01	1			DB, Comparative	Bupi 0.75%: 20 mL	0.75%: 20 mL
K6	88Ro04	1			DB, Comparative	Bupi 0.5%: 20 mL	0.5%: 20 mL
K7 *	88Ro07	1			DB, Comparative	Bupi 0.5%: 20 mL	0.75%: 20 mL
K8 *	88Ro11	1			DB, Comparative	Bupi 0.75%: 15 mL	1.0%: 15 mL
K9 *	90Ro16	3			DB, Comparative	Bupi 0.5%: 20 mL	0.5%, 0.75%, 1.0%: 20 mL
K10	90Ro25	1			DB, Comparative	Bupi 0.5%: 20 mL	0.5%: 20 mL
K11	90Ro29	1			DB, Controlled	Bupi 0.5%: 20 mL	0.5%: 20 mL
L1	87Ro04/05/08	3			Open, dose-response	None	0.5%, 0.75%, 1.0% +adr 5 µg/mL: 20 mL
L2	87Ro07	1			Open, dose-response	None	0.75%, +adr 5µg/mL: 15, 20, 25 mL
L3	87Ro09	1			Open, dose-response	None	0.5%, 0.75% w/ & w/o adr 5 µg/mL: 20 mL
L4	87Ro12/13/14	3			Open, dose-response	None	0.5%, 0.75%, 1.0%: 20 mL
L5	88Ro01	1			DB, Comparative	Bupi 0.75% w/ adr 5 µg/mL: 20 mL	0.75% w/ 5 µg/mL adr: 20 mL
L6 *	88Ro05	1			DB, Comparative	Bupi 0.5%, 0.75%: 15 mL	0.5%, 0.75%, 1.0%: 15 mL
L7	88Ro06	1			DB, Controlled	None	0.75% w/ & w/o adr, 5 µg/mL: 20 mL
L8	88Ro10	1			DB, Comparative	Bupi 0.75%: 20 mL	1.0%: 20 mL
L9	88Ro14	1			DB, Controlled	None	0.5%, 0.75%: w/ & w/o 5 µg/mL adr: 20 mL
L10	88Ro15	1			DB, Comparative	Bupi 0.75%: 20 mL	1.0%: 20 mL
L11*	89Ro07	1			DB, Comparative	Bupi 0.5%: 20 mL	0.5%: 20 mL 1.0%: 10 mL

Ropivacaine HCl Injection
FDA Study List
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Study No.	Astra No.	# Ctr.	Pt. Plan	Pt. Ent	Study Design	Comparator Drug	Ropivacaine Dose
L12*	90Ro14	1			DB, Comparative	Bupi 0.5%: 25 mL	0.5%, 0.75%, 1.0%: 25 mL
L13*	90Ro21	3			DB, Comparative	Bupi 0.75%: 20 mL	0.75%: 20 mL
L14	90Ro41	1			DB, Comparative	Bupi 0.5%: 25 mL	0.5%: 25 mL
M1	90Ro33-00	1			Open	None	0.5%: 30 mL
M2*	90Ro33-01	1			DB, Comparative	Bupi 0.5%	0.5%: 30 mL
M3*	90Ro35	4			DB, Comparative	Bupi 0.5%: 20-30 mL	0.5%: 20-30 mL
M4	91Ro47	1			Open	None	0.75%: 20 mL
M5	92Ro57	1			DB, Comparative	Bupi 0.5%: 20-30 mL	0.5%: 20-30 mL
M6	92Ro65	2			DB, Comparative	Bupi 0.5%: 20-30 mL	0.5%: 20-30 mL
M7	92Ro66	4			DB, Comparative	Bupi 0.5%: ≤ 30 mL	0.5%: ≤ 30 mL
N1	90Ro28	1			DB, Comparative	Bupi 0.5% +0.25%: 10 mL + 10 mL	0.5% +0.25%: 10 mL + 10 mL
N2	90Ro34-03,04	2			Open, Cont Infusion	None	0.25% +0.25%: 12 mL +6-12 mL/h
N3*	90Ro34-01,02	2			DB, Comparative Cont Infusion	Bupi 0.5% +0.25%: 12 mL + 6-12 mL/h	0.25% +0.25%: 12 mL +6-12 mL/h
N4*	90Ro36	3			DB, Comparative	Bupi 0.25%: 10-15 mL + 5 x 10 mL top-up	0.25%: 10-15 mL + 5 x 10 mL top-up
N5	92Ro56	1			DB, Comparative	Bupi 0.25% 10-15 mL +5 x 10 mL top-up	0.25% 10-15 mL +5 x 10 mL top-ups
N6	92Ro64	1			DB, Comparative	Bupi 0.25%: 10-15 mL +5 x 10 mL top-up	0.25%: 10-15 mL +5 x 10 mL top-ups
N7	92Ro67	1			DB, Comparative Cont Infusion	Bupi 0.25%: max 70mL/3h; max 160mL/24h	0.25%: max 70mL/3h; max 160mL/24h
N8	92Ro75	1			DB, Comparative	Bupi 0.25%: 10-15 mL + 5 x 10 mL top-ups	0.25%: 10-15 mL + 5 x 10 mL top-ups
O1*	92Ro58	1			DB, dose response, Cont Infusion	Saline	(0.5% bolus for surg) +0.1%, 0.2%, 0.3%: 10 mL/h; 21h
O2*	92Ro59	3			DB, dose response, Cont Infusion	Saline	(0.5% bolus for surg) +0.1%, 0.2%, 0.3%: 10 mL/h; 21h

Ropivacaine HCl Injection
FDA Study List
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Study No.	Astra No.	# Ctr.	Pt. Plan	Pt. Ent	Study Design	Comparator Drug	Ropivacaine Dose
O3	92Ro60	2			DB, dose response, Cont infusion	Saline	(0.5% bolus for surg) +0.1%, 0.2%, 0.3%: 10 mL/h; 21h
O4	92Ro61	2			DB, dose response, Cont infusion	Saline	(0.5% bolus for surg) +0.1%, 0.2%, 0.3%: 10 mL/h; 21h
O5	92Ro62	2			DB, dose response, Cont infusion	Saline	(0.5% bolus for surg) +0.1%, 0.2%, 0.3%: 10 mL/h; 21h
O6	92Ro63	2			DB, dose response, Cont infusion	Saline	(0.5% bolus for surg) +0.1%, 0.2%, 0.3%: 10 mL/h; 21h
O7*	92Ro71	7			Open, dose response	Saline	(0.5% bolus for surg) +0.2%: 6, 8, 10, 12 mL/h; 21h
O8	92Ro72	6			Open, dose response	Control: no infusion	(0.5% bolus for surg) +0.2%: 6, 8, 10, 14 mL/h; 21h
P1	87Ro11	2			Open, dose response	None	0.5% w/ & w/o 5 µg/mL adr: 28 mL
P2*	88Ro08	1			Blind, Comparative	Bupi 0.5%: 35 mL	0.5%: 35 mL
P3	88Ro09	2			Blind, Comparative	Bupi 0.25%: 40 mL	0.25%: 40 mL
P4	88Ro13	1			Open	None	0.25%: 33 +5 mL
P5	89Ro09	1			DB, Comparative	Bupi 0.5%: 35-45 mL	0.5%: 35-45 mL
P6	90Ro13	1			DB, Comparative	None	0.25%, 0.5% ≤ 80 kg: 40 mL > 80 kg: 50 mL
P7	90Ro20	1			DB, Controlled	Bupi 0.5%: 35 mL	0.5%: 35 mL
P8	90Ro26	1			DB, Controlled	Bupi 0.5%: 40 mL	0.5%: 40 mL
P9*	91Ro53	1	..		Open, Dose response	None	0.5%: 30-60 mL
O1	89Ro02	1			DB, comparative	Bupi 0.25%: mL	0.25%: 40 mL
O2	90Ro12	2			DB, Controlled	Saline	0.25%, 0.125%: 70 mL
O3	90Ro18	1			3rd party blind	None	0.25%: 60-80 mL
O4*	90Ro19	2			DB, Controlled	Saline	0.125%, 0.25%, 0.5%: 30 mL
O5	90Ro22	1			DB, Comparative	Bupi 0.25%: 60 mL	0.25%: 60 mL
O6	91Ro49	1			DB, Comparative	Mepi 1.0%	0.5%

Ropivacaine HCl Injection
FDA Study List
* = Pivotal Study

Study No.	Astra No.	# Ctr.	Pt. Plan	Pt. Ent	Study Design	Comparator Drug	Ropivacaine Dose
Q7 *	91Ro50	4			DB, Controlled	Saline	0.25%, 0.5%: 40 mL
R1	90Ro38	1			DB, Controlled	None	0.5%, 0.75%
R2	90Ro40	1			DB, Controlled	None	0.25%, 0.75%: 3 mL

Study No.

K	=	Orthopaedic surgery (OL)
L	=	Other surgery (GG, UR, LA, VV, MS)
M	=	Caesarean section
N	=	Labour
O	=	Post-operative pain relief (epidural)
P	=	Brachial plexus
Q	=	Infiltration
R	=	Spinal

Study Code - Abbreviations

Code 1 ROUTE OF ADMINISTRATION

E	Epidural
B	Brachial Plexus
I	Infiltration
S	Spinal

Code 2/3 SURGICAL AREA OR PROCEDURE

OL	Orthopedic Surgery (Lower Limb)
OU	Orthopedic Surgery (Upper Limb)
GG	General Gynecological
CS	Cesarean Section
LD	Labor & Delivery
UR	Urologic Surgery
LA	General Surgery (Lower Abdominal)
UA	General Surgery (Upper Abdominal)
HR	Hernia Repair
CH	Cholecystectomy
VV	Varicose Vein Stripping
MS	Multiple Surgical Procedures
DA	Dermatological Surgery

Code 4 SPECIAL DESIGNATION

P	Post-Operative Pain

BIO Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-533 **CODE:** 1S
SUMISSION DATE: 31 March 1995 **REVIEW DATE:** 15 November 1995
GENERIC NAME: S-(-)-Ropivacaine HCL **BRAND NAME**: Naropin™-MPF
DOSE AND FORMULATION: Single dose containers in 2.0, 2.5, 5.0, 7.5, and 10.0 mg/mL concentrations to be administered parenterally
SPONSOR: Astra USA, Inc., Westborough, MA
TYPE OF SUBMISSION: Orginal NME
REVIEWER: Suresh Doddapaneni, Ph.D.

SYNOPSIS

The sponsor submitted 30 human pharmacokinetics studies involving about 675 subjects in support of this NDA, characterizing the biotransformation, pharmacokinetics and dose proportionality after the different modes of administration for different surgical procedures. Of these 30 studies, 14 were identified as pivotal with the remaining 16 studies used as supportive in the review process. Human metabolism, excretion and protein binding of ropivacaine have been adequately studied. Ropivacaine is extensively metabolized with only about 1% of the dose excreted in the urine unchanged. 3-Hydroxy ropivacaine was the major metabolite found in the urine and formed about 37% of the total dose (total radioactivity) excreted. α_1-Acid glycoprotein was the major plasma protein to which ropivacaine was bound with only a small plasma unbound fraction of about 0.06 in healthy volunteers. The unbound fraction increased with decreasing α_1-acid glycoprotein concentrations and at term in pregnancy it was of the order of 0.09, and in fetal plasma it was about 0.2. The pharmacokinetics of ropivacaine was adequately characterized. After iv infusion, ropivacaine's disposition was best described by a biexponential model with mean half-lives of 0.33 hours and 1.9 hours for the distribution and terminal phases respectively. Mean plasma clearance was about 440 mL/minute, steady state volume of distribution was about 47 liters, and the renal clearance was about 1 mL/minute. After epidural administration, systemic absorption of ropivacaine from the epidural space was biphasic with an initial rapid phase (absorption half-life of 14 minutes) followed by a slower phase (absorption half-life of 4.2 hours), each contributing about 50% to the overall absorption. The terminal half-life was about 4.3 hours which was longer than that seen after iv administration indicating that its elimination is absorption dependent after epidural administration. Dose proportionality of ropivacaine was adequately established. Ropivacaine followed linear pharmacokinetics upto the highest intravenous dose studied, 80 mg corresponding to a mean C_{max} of about 1.8 mg/liter. Dose proportionality was also demonstrated upto 250 mg after epidural administration, 150 mg after local infiltration, and 250 mg after rectal administration.

RECOMMENDATION

The sponsor's NDA 20-533 is acceptable for meeting agency's Biopharmaceutics requirements (21 CFR 320). However, Comments 1-4 need to be satisfactorily addressed.

1.0. BACKGROUND

Ropivacaine is a member of the amino amide class of local anesthetics and is intended for the production of local or regional anesthesia during surgery (epidural block for surgery including caesarean section, major nerve block, local infiltration), for post-operative pain management and for obstetrical procedures (epidural continuous infusion or intermittent bolus and local infiltration). Currently bupivacaine is the most widely used long-acting local anesthetic drug of its class although incidents of cardiac toxicity (accentuated in pregnancy) i.e., cardiac arrest following unintended intravascular injection of a large amount of drug or due to the premature release of a tourniquet following iv regional anesthesia have been reported. It is claimed that ropivacaine is superior to bupivacaine in both safety and effectiveness. This claim of improved safety comes from the lower cardiodepressant effect and a higher dose requirement to produce seizures in animal studies. The anesthetic effectiveness comes from the lower potential for producing motor blockade and a superior dose response for duration of infiltration anesthesia. Improved safety of ropivacaine is due to the use of the optically pure **S-(-) -ropivacaine** enantiomer which is less toxic and/or has a longer duration of action than the R-(+)-enantiomer.

Ropivacaine has a distribution ratio between n-octanol and phosphate buffer at pH 7.4 of 141 and a pKa of 8.07 in 0.1 M KCL solution. It is proposed to be marketed as a sterile, isotonic solution in single dose containers in 2.0, 2.5, 5.0, 7.5, and 10.0 mg/mL concentrations. The doses administered depend on the indication and cover a dose range of 25-200 mg through epidural route for surgical anesthesia and labor pain management and 5-200 mg for minor nerve blocks and infiltration. Ropivacaine has been recently approved for use in Sweden in 2.5 and 5.0 mg/mL concentrations and applications have been submitted and are pending in several other countries.

Ropivacaine is not dependent on the general circulation for exerting the local anesthesia. However, ropivacaine administered for producing local anesthesia through epidural and local infiltration is absorbed into systemic circulation where the secondary pharmacological effects such as CNS and cardiovascular toxicities occur. This NDA has been extensively documented with pharmacokinetic studies such as biotransformation, pharmacokinetic characterization and dose proportionality after the different modes of administration for different surgical procedures from the perspective of the secondary effects.

2.0 BIOTRANSFORMATION, PHARMACOKINETICS, AND DOSE-PROPORTIONALITY

2.1. BIOTRANSFORMATION;

In an open-label study, 6 male healthy volunteers were administered 50 mg [^{14}C] ropivacaine intravenously to characterize the biotransformation(17). Ropivacaine was found to be extensively metabolized with only about 1% excreted unchanged in urine. The major metabolite found in the urine was 3-hydroxy ropivacaine (37%). The half-life of 3-hydroxy ropivacaine calculated from its urinary excretion rates was about 6.0 hours. Minor amounts of 4-hydroxy ropivacaine, N-despropyl ropivacaine (PPX), 3-hydroxy-N-despropyl ropivacaine (3-hydroxy PPX) were also found in urine. In addition 2-hydroxy methyl ropivacaine (LEA166) was also isolated and identified but not quantitated. No *in vivo* metabolic racemization of the therapeutically important S-(-)-ropivacaine to the more toxic R-(+)-ropivacaine occurred (<0.2% in urine). The amide hydrolysis metabolic pathway leading to the production of the potential carcinogen 2,6-xylidene was

absent in ropivacaine. The proposed metabolic pathway is shown in Figure 1. The mean plasma terminal half-life was about 5.4 hours for total radioactivity. The mean half-life of 3-hydroxy ropivacaine calculated from its urinary excretion data was 6.0 hours. and is probably the main contributor to the longer terminal half-life of plasma radioactivity. All the metabolites except 3-hydroxy ropivacaine were present at or below determination limits in the plasma. The racemate of 3-Hydroxy ropivacaine produced successful motor and sensory block while 4-hydroxy ropivacaine produced only successful motor block with a shorter duration than ropivacaine in animal models. However, at the low plasma concentrations found, their activity *in vivo* may not be of significance relative to ropivacaine (802-550 LF-0228-01).

In vitro, ropivacaine is metabolized to 3-hydroxy-ropivacaine by the CYP1A isozyme. The formation of 4-hydroxy-ropivacaine, 2-hydroxy-methyl ropivacaine and PPX is catalyzed by CYP3A isozyme. CYP2D6 and CYP2C19 did not contribute to the metabolism of ropivacaine and therefore poor metabolizers of debrisoquine or mephenytoin will not have an impaired metabolism of ropivacaine.

Figure 1. Proposed metabolic scheme of ropivacaine.

2.2. PROTEIN BINDING;

Protein binding of ropivacaine determined *in vivo* showed that it is extensively bound to plasma proteins with only a small plasma free fraction of 0.06. α_1-Acid glycoprotein was the protein to which ropivacaine was bound to extensively. Mean blood/plasma ratio was 0.7 and the

mean fraction of ropivacaine in blood distributing into blood cells was 0.2, again indicating its preference for plasma. The binding was linear in the range of mg/liters (I31). *In vitro* results were similar. The unbound fraction of ropivacaine at delivery in pregnancy seems to be higher than in non-pregnant patients. Mean unbound fractions ranged from 0.07-0.08 in maternal plasma and 0.17-0.25 in fetal venous plasma. The considerably higher unbound fraction in fetal plasma may be due to the lower fetal concentration of α_1-acid glycoprotein (I18). See page 11 for further discussion on protein binding under NONMEM analysis.

2.3. PHARMACOKINETICS OF ROPIVACAINE:

2.3.1. IV PHARMACOKINETICS;

A total of five studies involved the characterization of iv pharmacokinetics of ropivacaine in male healthy volunteers of which three studies were reviewed. After the iv infusion of 50 mg ^{14}C-ropivacaine over 15 minutes in 6 volunteers, ropivacaine was found to have a mean CL of 397 mL/minute, V_{ss} of 60.0 liters, $t_{1/2}$ of 2.0 hours, CL_R of 1 mL/minute, and an extraction ratio of 0.39 (I7). Pharmacokinetics of ropivacaine and [$^2H_3$]ropivacaine were determined after the iv infusion of 40 mg over 25 minutes in 8 volunteers in an open-label, simultaneous cross-over study (I5). This study was conducted to find out if ropivacaine and [$^2H_3$]ropivacaine have similar pharmacokinetics *in vivo*. No statistically significant differences were found between the two drugs. Pharmacokinetics of 40 mg [$^2H_3$]ropivacaine infused intravenously over 30 minutes as a part of a study characterizing absorption through epidural route in 9 subjects also gave essentially similar results (I2). Significant arterio-venous plasma concentration differences were found in this study. Initially the arterial concentrations were higher than venous concentrations, reached equilibrium by about 1 hour after which the venous concentrations were higher and declined in parallel with the arterial concentrations. The pharmacokinetic parameter values were; CL of 313 mL/minute, V_{ss} of 43 liters, and $t_{1/2}$ of 1.7 hours. Between the three studies, mean CL varied from 313 to 478 mL/minute, mean V_{ss} varied from 43 to 60 liters, mean $t_{1/2}$ values ranged from 1.7 to 1.97 hours.

Table 1. Pharmacokinetic parameters of ropivacaine administered intravenously in healthy volunteers (mean (% CV)).

Pharmacokinetic parameters	Study I7 (50 mg [^{14}C]ropivacaine)	Study I5 (40 mg ropivacaine)	Study I2 40 mg [$^2H_3$]ropivacaine
C_{max}, mg/mL	1.61 (45)	0.97 (19)	1.27 (13)
$t_{1/2}$, hours	1.97 (14.7)	1.86 (32)	1.7 (18)
AUC, mg minute/liter	132 (34)	82 (21)	117 (22)
CL, mL/minute	397 (32)	478 (20)	313 (27)
V_{ss}, liter	60 (37)	54 (15)	43 (19

2.3.2. EPIDURAL PHARMACOKINETICS;

Two studies were conducted in healthy volunteers and fourteen studies were conducted in patients to characterize the pharmacokinetics after epidural administration. Of these sixteen studies, one study involved characterization of the absorption of ropivacaine into systemic circulation after epidural administration (I2). After the epidural infusion of 150 mg of ropivacaine and iv infusionof 40 mg [$^2H_3$] ropivacaine in 9 healthy subjects in a cross-over study designed to evaluate the absorption, ropivacaine was absorbed slowly into the systemic circulation from the epidural space in a biphasic fashion. The two phases were an initial rapid absorptive phase characterized by a half-life of 14 minutes and a slow absorptive phase characterized by a half-life of 4.2 hours (I2). Each of the absorptive phases comprised about 50% of the absorption. The terminal half-life was about 4.2 hours and reflects the absorption dependent elimination of ropivacaine. The fraction of ropivacaine absorbed was about 87% based on venous data. Clearance of ropivacaine was similar to that obtained in iv studies (363 mL/minute) but steady state volume of distribution was about 3.5 times higher (153 liters).

2.4. DOSE PROPORTIONALITY OF ROPIVACAINE;

A double-blind cross-over study in 9 healthy male volunteers was conducted to determine the dose proportionality at 20, 40, and 80 mg doses after iv infusion (I6).The mean plasma concentration-time profiles of ropivacaine after the iv infusion of 20, 40, and 80 mg doses, adjusted for the doses were close to each other at most time points (Figure 2). Dose normalized AUC's at the three doses plotted as a function of the dose yielded a flat line. Dose normalized C_{stop}'s (plasma concentration when infusion of ropivacaine is stopped) however decreased slightly with increasing doses. Anova analysis on the dose normalized C_{stop}'s and AUC's gave good fit for AUC but not C_{stop} data. None of the factors for period, carry-over, direct dose effect or between subject variance were significant for C_{stop}. This might be explained by C_{stop} being a point estimate depending on the infusion rate and time at which infusion is stopped among other factors resulting in a large intra-individual variability in the data interfering with the ANOVA analysis. On a mean basis however rough dose proportionality in C_{max} is still indicated. For AUC, in the reduced ANOVA model eliminating the factors for period and carry-over effects (which were not significant) no significant differences between dose levels were seen. Linear regression lines fitted to the individual data with zero intercepts fitted well to the non-normalized AUC data. These results taken together show dose proportionality of ropivacaine in the range of mg for C_{stop} and AUC.

The mean $t_{1/2}$, CL, and V_{ss} were similar for all the three doses (Table 2). The period and carry-over effects were not significant when ANOVA was performed on the $t_{1/2}$, CL, and V_{ss} data. In the reduced ANOVA model eliminating the factors for period and carry-over effects no significant differences were seen between these parameters at these dose levels.

As the dose increased from mg, the mean fraction of ropivacaine unbound in plasma, f_u, increased slightly from % (Table 1). Also, a weak trend was observed for the f_u to increase with increasing total plasma concentration. The concentration of α_1-acid glycoprotein, which is the main protein to which ropivacaine binds in the plasma, was in the normal range. This indicates that at the higher dose levels the plasma concentrations are reaching the lower limits of

saturation of the protein binding capacity. CL_R and f_e were also similar between the doses further supporting the dose proportionality of ropivacaine in this dose range. See sections 3.1, 3.2, 3.7, and 3.8 for additional discussion on dose-proportionality.

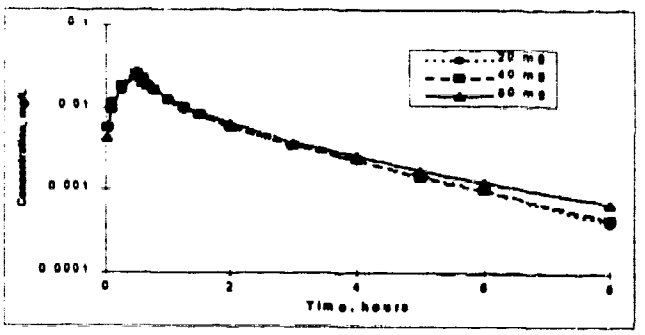


Figure 2. Mean plasma concentration-time profiles of ropivacaine after dose correction of 20, 40, and 80 mg doses.

Table 2. Pharmacokinetic parameter values of ropivacaine after the iv infusion of separate doses of 20, 40, and 80 mg over 30 minutes (mean (% CV)).

Pharmacokinetic parameters	20 mg ropivacaine	40 mg ropivacaine	80 mg ropivacaine
C_{stop}, mg/liter	0.55 (13)	1.03 (23)	1.92 (17)
C_{stop}/dose	0.0275 (13)	0.0258 (23)	0.024 (17)
AUC, mg minute/liter	47 (26)	94 (27)	198 (34)
AUC/dose	2.35 (26)	2.35 (27)	2.48 (34)
CL, mL/minute	395 (25)	402 (27)	387 (28)
V_{ss}, liter	38 (21)	39 (21)	41 (17)
$t_{1/2}$, hours	1.6 (31)	1.6 (25)	1.8 (39)
f_u, %	4.8 (1.3)	5.1 (2.0)	5.5 (2.3)
f_{e1} %	0.4 (122)	0.8 (148)	0.6 (53)
CL_R, mL/minute	1.4 (84)	1.7 (114)	2.5 (54)

3.0. SPECIAL STUDIES:

Several studies were conducted to detemine the pharmacokinetics of ropivacaine in patients scheduled for different surgical procedures such as abdominal hysterectomy and orthopaedic surgery, labor, cesarean section, brachial plexus block for orthopaedic surgery, intercostal block, local infiltration for pain relief after lower abdominal surgery, and potential use of ropivacaine for

ulcerative colitis as a rectal enema. Many of these studies, also included comparison with the currently marketed regional anesthetic, bupivacaine.

3.1. CONTINUOUS EPIDURAL INFUSION FOR POST-OPERATIVE PAIN RELIEF IN LOWER ABDOMINAL SURGERY PATIENTS;

In 44 patients scheduled for major lower abdominal surgery at two centers, anesthesia was administered using a combination of epidural block with 65-90 mg ropivacaine (5mg/mL) and general anesthesia (I21). During surgery, 25 mg ropivacaine was injected epidurally every 2 hours. Additional 25 mg doses were given in between at sign/symptoms of inadequate block. The total dose of ropivacaine before and during surgery was 90 to 150 mg. Within 40 minutes after completion of surgery a 21-hour epidural infusion was started with 10, 20, 30 mg/hour ropivacaine or placebo using ropivacaine solutions of 1 mg/mL, 2 mg/mL, and 3 mg/mL. The corresponding mean total doses during the infusion period were 220, 440, and 630 mg ropivacaine.

Plasma concentrations of ropivacaine increased with time during the last 11 hours of epidural infusion. Since the terminal half-life of ropivacaine through epidural infusion is about 4-5 hours, presumably steady state was not achieved at the end of 21 hours of infusion resulting in the rising plasma concentrations that were seen. The mean plasma C_{max}'s were 1.1, 1.7, and 2.3 mg/liter at the three different infusion rates of 10, 20, 30 mg/hour of ropivacaine. The increase in C_{max} was not proportional to the infusion rate of ropivacaine but plateaued off. The mean $AUC_{10\text{-}21\ hours}$'s were also not proportional to the dose and levelled off (599, 941, and 1205 mg minute/liter). Several complicating factors that could have contributed to this dose non-proportionality are; (1) different loading doses in the patients (90-140 mg) (2) systemic volume changes due to the infusion of electrolyte solutions and possible loss of blood during the surgical procedures, and (3) concurrent administration of a long list of several different drugs. The significance of these results is unknown given the confounding factors. Comparing the plasma concentrations of ropivacaine obtained in study I21 with that obtained in study I9 (total concentrations over 10-21 hours and free concentration at 21 hours) with identical infusion rates used in healthy volunteers with loading doses of single epidural injections of 10, 20, and 30 mg, the plasma concentrations were twice as high in study I21, presumably because of the higher loading doses of 90-150 mg. Dose proportionality was also reported for both C_{max} and AUC in study I9.

3.2. EPIDURAL INJECTION IN PATIENTS SCHEDULED FOR HYSTERECTOMY;

Four groups of 13 patients each, were administered 125, 187.5, and 250 mg ropivacaine and 125 mg bupivacaine epidurally to evaluate dose-proportionality (I14). C_{max} increased proportionally with the dose and C_{max}/dose also increased slightly with dose. The linear regression analysis of C_{max} vs dose resulted in an intercept not significantly different from zero. AUC and AUC/dose increased as the dose increased from 125 to 187.5 mg but plateaued as the dose increased from 187.5 to 250 mg complicating the intrepretation of dose proportionality of AUC with dose (Table 3). However, AUC/dose at 125 mg and 250 mg doses were very close (0.047 and 0.044). Regression analysis of AUC against dose resulted in an intercept significantly different from zero intercept and with an r^2 value for the regression line of 0.28. The $t_{1/2}$ and CL values were close between 125 and 250 mg doses of ropivacaine while those of 187.5 mg ropivacaine differed

somewhat.

Table 3. Pharmacokinetic parameter values (mean (% CV)) of ropivacaine after the epidural administration of single doses of 125, 187.5, and 250 mg ropivacaine.

Pharmacokinetic parameters	125 mg ropivacaine*	187.5 mg ropivacaine#	250 mg ropivacaine•
C_{max}, mg/liter	0.75 (32)	1.2 (30)	1.77 (35)
C_{max}/dose	0.006 (32)	0.0064 (30)	0.0071 (35)
T_{max}, hours	0.65 (63)	0.99 (34)	0.51 (35)
AUC, mg hour/liter	5.82 (34)	11.37 (37)	10.98 (34)
AUC/dose	0.047 (34)	0.061 (37)	0.044 (34)
$t_{1/2}$, hours	4.74 (21)	6.53 (52)	4.07 (45)
CL, mL/minute	344 (27)	283 (45)	367 (27)

*n=11, #n=9-11, •n=10-11

3.3. EPIDURAL INJECTION IN PATIENTS SCHEDULED FOR ORTHOPAEDIC SURGERY (EFFECT OF INJECTION VOLUME);

30 Patients undergoing surgery for elective varicose vein or inguinal hernia were administered 100 mg ropivacaine, as 20 mL of a 5 mg/mL solution or 10 mL of a 10 mg/mL solution or 100 mg bupivacaine as 20 mL bupivacaine 5 mg/mL epidurally (I17). Mean plasma concentration-time profiles of ropivacaine in 10 mL and 20 mL groups and in bupivacaine 10 mL group is shown in Figure 2. Ropivacaine plasma profiles seem to be similar between the two treatments, with concentrations at most time points being very close. Plasma concentrations of bupivacaine were however lower initially and seemed to decline slowly in the terminal phase. The t_{max} was the same between the three treatments, about 25 minutes. The C_{max} was similar between 5 mg/mL and 10 mg/mL ropivacaine but that of 5 mg/mL bupivacaine was significantly lower than that of ropivacaine at both concentrations. The mean $t_{1/2}$ was similar for ropivacaine at both concentrations (about 5 hours) which were shorter than of bupivacaine (10.6 hours) and significantly different between the two drugs. Mean AUC was identical for the two concentrations of ropivacaine (345 mg minute/liter) while that of bupivacaine was slightly lower (333 mg minute/liter). Mean apparent CL was almost similar between the three treatments.

Ropivacaine undergoes absorption rate-limited elimination when given epidurally. Similar $t_{1/2}$'s between 100 mg ropivacaine given in 10 mL or 20 mL indicates similar absorption. This together with similar concentration-time profiles, C_{max}'s, and AUC's indicates the independency of ropivacaine pharmacokinetics of the injected volume/drug concentration. Significantly longer $t_{1/2}$ of bupivacaine over ropivacaine indicates relatively slower absorption which is consistent with the higher lipophilicity of bupivacaine (higher lipophilicity results in slower absorption from epidural space).

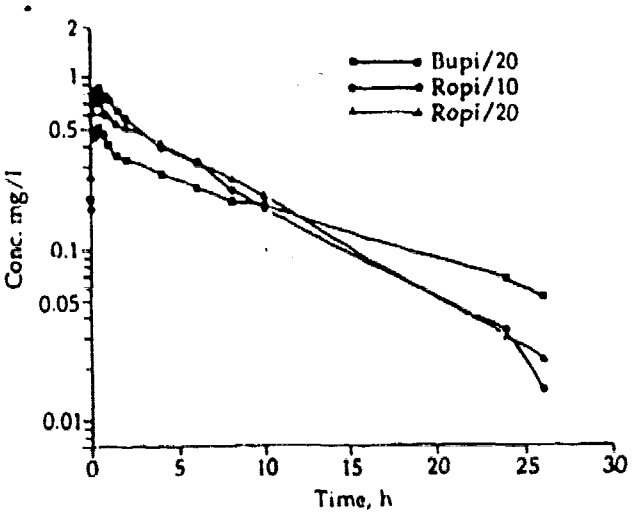


Figure 3. Mean total plasma concentration-time profiles of ropivacaine and bupivacaine after 100 mg dose given epidurally in patients.

Table 4. Pharmacokinetic parameters of ropivacaine (5 and 10 mg/mL) and bupivacaine 5 mg/mL after the administration of a standard dose of 100 mg epidurally in patients undergoing surgery for varicose veins or inguinal hernia (mean (% CV)).

Pharmacokinetic parameters	5 mg/mL ropivacaine	10 mg/mL ropivacaine	5 mg/mL bupivacaine
C_{max}, mg/liter	0.76 (32)	0.93 (32)	0.55 (20)
t_{max}, minute	27 (44)	24 (46)	26 (42)
AUC, mg minute/liter	345 (53)	346 (35)	333 (33)
$t_{1/2}$, hours	5.5 (15)	5.3 (51)	10.6 (41)
CL, mL/minute	314 (47)	282 (33)	301 (44)

3.4. DISPOSITION IN PREGNANCY;

Along with the increased volume of distribution associated with pregnancy, there is an engorgement of the vertebral veins and a hyperkinetic circulation which may affect absorption of ropivacaine from the epidural space. Ropivacaine is lipophilic and therefore equilibrates rapidly across the placenta. Also, the α_1-acid glycoprotein levels are low in neonates and there is a possibility of free levels of ropivacaine being high in them during pregnancy. Three studies were

conducted in pregnant women, both during labor when ropivacaine was administered for pain relief and during cesarian section when ropivacaine is administered for regional anesthesia, evaluating ropivacaine plasma levels in the mother and in the umbilical cord.

3.4.1. CONTINUOUS EPIDURAL INFUSION FOR PAIN RELIEF IN LABOR;

Two studies were conducted to evaluate the effect of administering ropivacaine epidurally for pain relief during labor and one study was reviewed (I23). Using a parallel study design, 30 pregnant women were administered a continuous lumbar epidural infusion of ropivacaine 12.5 mg/hour, 25 mg/hour or bupivacaine 25 mg/hour until delivery. 12.5 mg/hour ropivacaine group of patients were dropped from the study due to insufficient analgesia and consequently only ropivacaine 25 mg/hour and bupivacaine 25 mg/hour groups were evaluated in this study. The mean duration of infusions were 6.2 hours and 8.2 hours, corresponding to mean doses of 180 mg and 227 mg of ropivacaine and bupivacaine respectively. The mean C_{max}'s were 1.05 and 0.8 mg/liter for ropivacaine and bupivacaine (Table 5). The mean $t_{1/2}$ was shorter after ropivacaine than after bupivacaine, 5.1 vs. 8.6 hours, and the total plasma clearance was lower, 223 vs. 299 mL/minute. The mean umbilical venous unbound fraction was 0.17 with ropivacaine and 0.12 with bupivacaine and the unbound umbilical vein/maternal vein (UV/MV) ratios did not seem to increase with the duration of the infusion indicating rapid equilibrium. The umbilical total plasma concentrations of the two drugs were similar in both venous and arterial plasma. The umbilical unbound venous plasma concentration was higher after ropivacaine than after bupivacaine.

Table 5. Pharmacokinetic parameters after the continuous epidural infusion of 25 mg/hour ropivacaine and bupivacaine during labour (mean (% CV)).

Pharmacokinetic parameters	Ropivacaine	Bupivacaine
Dose administered, mg	179.2 (24)	226.7 (38)
C_{max}, mg/liter	1.05 (27)	0.8 (28)
Time to delivery, hours	6.26 (27)	8.17 (42)
AUC, mg hour/liter	12.4 (29)	12.3 (45)
$t_{1/2}$, hours	5.1 (35)	8.6 (38)
Cl_{tot}, mL/minute	223 (27)	299 (31)
Cl_u, liter/minute	3.35 (41)	6.4 (39)
f_u	0.07 (29)	0.05 (20)

3.4.2. EPIDURAL INJECTION FOR CESAREAN SECTION;

Two studies involving 114 women in labor were conducted to evaluate the pharmacokinetics of ropivacaine administered during cesarean section of which one study was reviewed. In an open-label study, ropivacaine 150 mg and bupivacaine 150 mg were given as an epidural injection to 29 and 31 subjects respectively for elective cesarean section (I18). At the time of delivery, both total and unbound concentrations in the mother were higher than in the neonate.

The mean total concentration was 1.25 mg/liter in the mother and 0.37 mg/liter in the neonate. The corresponding unbound concentrations were 0.089 mg/liters and 0.06 mg/liters. The mean ratio of unbound concentrations in umbilical vein/maternal vein at the time of delivery was 0.74. The mean unbound fraction was 0.07 in maternal and 0.18 in fetal plasma. Total C_{max} in maternal plasma was similar after both drugs, as was total plasma clearance but the terminal half-life was shorter after ropivacaine (Table 6). The mean unbound plasma clearance of ropivacaine was lower, 2.8 liter/minute, compared to that of bupivacaine, 4.8 liter/minute. The unbound concentrations of ropivacaine were twice as high as the unbound concentrations of bupivacaine. The mean unbound fraction of ropivacaine in maternal plasma, 0.09, was also higher than for bupivacaine, 0.06. the unbound fraction of both drugs was higher in the umbilical vein, 0.25 vs 0.17. The maternal total drug concentration was higher than in the neonate for both ropivacaine and bupivacaine. The total umbilical vein concentration was also somewhat higher than the arterial concentration. The unbound concentration of the two drugs in the neonate was about 70-75 % of the unbound concentration in the mother, and the unbound concentrations in the umbilical vein and umbilical artery were almost the same. The umbilical vein/maternal vein ratios as well as the umbilical artery/umbilical vein ratios were similar after ropivacaine and bupivacaine for both the total and unbound drug at the time of delivery, indicating a similar transplacental passage of the drugs (Table 7). The umbilical vein/maternal vein ratio (UV/MV) of both the total and unbound drug as well as the umbilical artery/umbilical vein ratio (UA/UV) did not seem to be related to the time from drug administration to delivery.

Table 6. Pharmacokinetic parameters of ropivacaine and bupivacaine after the epidural administration of 140 mg dose for patients undergoing cesarian section (mean (% CV)).

Pharmacokinetic parameters	Ropivacaine	Bupivacaine
C_{max}, mg/liters	1.3 (22)	1.1 (29)
t_{max}, hours	0.71 (37)	0.43 (38)
AUC, mg hour/liter	9.8 (40)	8.4 (32)
$t_{1/2}$, hours	5.2 (37)	10.9 (31)
CL, mL/minute	256 (36)	286 (25)
CL_u, liters/minute	2.8 (100)	4.8 (106)

Table 7. Umbilical vein/maternal vein (UV/MV) and umbilical artery/vein (UA/UV) ratios (mean (% CV)) for ropivacaine and bupivacaine (total and free concentrations).

Parameter	Ropivacaine	Bupivacaine
UV/MV (total)	0.29 (41)	0.32 (44)
UV/MV (free)	0.72 (18)	0.76 (21)
UA/UV (total)	0.72 (104)	0.70 (19)
UA/UV (free)	0.92 (8)	0.89 (16)

NONMEM analysis

The pharmacokinetic submodel used to describe the data was a one-compartment model with two parallel first-order absorption rates (corresponding to slow and rapid absorptive phases) and a first order disposition constant. By using the unbound and total concentration obtained at the same time points in this study, a covariate submodel for the protein binding was produced. For both ropivacaine and bupivacaine, a significant relationship was found between the unbound, total, and α_1-acid glycoprotein concentrations. In the case of ropivacaine a saturable relationship best described the data, whereas for bupivacaine, a linear relationship was adequate. These models were then combined in order to use all the maternal vein data relating the total concentrations to the unbound concentrations via the protein binding models. The absorption half-lives were estimated to be 7.7 minutes and 6.5 hours for ropivacaine and the fraction of drug absorbed by the slow route was estimated to be 80%. The disposition half-life was 41 minutes. The absorption half-lives for bupivacaine were estimated to be 5.3 minutes and 10.3 hours with the slow absorption phase estimated to comprise 86% of absorption. The unbound clearances were 3.3 and 4.2 liters/minute and the unbound volume of distribution was 192 and 212 liters respectively for ropivacaine and bupivacaine. The dissociation constant (Kd) for the binding of ropivacaine to α_1-acid glycoprotein was estimated to be 0.29 mg/liter and the number of binding sites 1. However, the precision regarding these estimates was poor, with very large standard errors (30-40%).

3.5. BRACHIAL PLEXUS BLOCK FOR ORTHOPAEDIC SURGERY;

Three studies involving 54 patients were conducted of which one study was reviewed. An open label study involving 17 patients was conducted to determine the pharmacokinetics of ropivacaine both with and without epinephrine (I24). On a mean basis, the parameter values of C_{max}, t_{max}, $AUC_{0\text{-}12\ hours}$ and $t_{1/2}$ were similar between ropivacaine administered for brachial plexus block with and without epinephrine (Table 8). There was no statistical difference in any of the pharmacokinetic parameters indicating that presence of epinephrine did not produce any effect on the pharmacokinetics of ropivacaine. Very high C_{max}'s of 10 to 23 mg/mL were seen in four patients. Inspite of these very high C_{max}'s no adverse events were reported by these patients. However, midazolam was one of the concurrently administered drugs and potentially it could have blocked the CNS side effects ropivacaine causes at toxic concentrations. The sponsors claim that these high C_{max}'s could have been an artifact (samples were re-analyzed but came out the same) as results from a similar study at another center in 17 patients gave small mean C_{max}'s (I25). The mean C_{max}'s with and without epinephrine were 1.59 ± 40 and 1.26 ± 33 mg/liter respectively. The maximum C_{max} found was 2.91 mg/liter in this latter study (Table 8). The $t_{1/2}$ of ropivacaine obtained in this study (6 hours) was longer than after iv infusion (2 hours) indicating that ropivacaine is undergoing absorption dependent elimination, absorption being very slow. Comparing the effect of epinephrine on ropivacaine obtained in this study with that on bupivacaine, lower peak concentrations resulted in the presence of epinephrine for bupivacaine. Earlier reports showed that ropivacaine increases vascular smooth muscle activity and decreases blood flow at the site of injection. Since, blood flow is already reduced, presence of epinephrine did not change the pharmacokinetics of ropivacaine. On the other hand presence of epinephrine reduced the blood flow resulting in lower plasma levels for

bupivacaine.

Table 8. Pharmacokinetic parameter values after the administration of 190 mg ropivacaine with or without epinephrine for brachial plexus anesthesia.

Pharmacokinetic parameters	Study I24,87Ro11-02		Study I25,87Ro11-02	
	With epinephrine	Without epinephrine	With epinephrine	Without epinephrine
C_{max}, mg/liter				
mean	5.82	5.81	1.59	1.26
% CV	109	143	40	33
maximum	20.7	23.05	2.91	1.98
minimum	1.04	0.71	0.82	0.85
t_{max}, hours				
mean	0.54	0.5	0.8	0.79
% CV	109	130	53	36
maximum	2.0	2.0	1.5	1.0
minimum	0.08	0.08	0.42	0.42
$AUC_{0\text{-}12\ hours}$, mg liter/hour				
mean	8.69	11.55	7.66	6.95
% CV	43	98	47	49
maximum	14.93	32.51	13.26	12.64
minimum	4.4	2.78	3.11	3.95
$t_{1/2}$, hours				
mean	6.78	5.74	5.8	8.0
% CV	72	47	52	49
maximum	18.58	10.82	11.1	13.8
minimum	3.05	2.15	2.8	4.3

3.6. INTERCOSTAL BLOCK;

One study was undertaken to study the pharmacokinetics of ropivacaine and its comparison with bupivacaine after intercostal block (I10). The mean plasma concentration-time profiles after the intercostal administration of 140 mg ropivacaine and bupivacaine in two parallel healthy groups of 7 volunteers each show that both ropivacaine and bupivacaine were absorbed quite rapidly followed by a relatively short terminal elimination phase for ropivacaine and a relatively longer elimination phase for bupivacaine (Figure 4). Although the mean C_{max} was slightly higher for ropivacaine over bupivacaine (1.06 mg/liter vs. 0.92 mg/liter), they were statistically insignificant (Table 9). The mean t_{max} calculation for ropivacaine was complicated by the presence of secondary peaks in three of the 7 subjects. Inclusion of the secondary peak in subject 12 gave a mean value of 53 ± 160(CV) minutes while inclusion of the first peak in the same subject, the t_{max} was 21 ± 43(CV) minutes. The t_{max} for bupivacaine was 30 minutes. The $t_{1/2}$ of ropivacaine was 2.3 hours and was considerably shorter than that of bupivacaine (4.6 hours). The CL value (425 mL/minute) was

slightly lower for ropivacaine when compared with that of bupivacaine (549 mL/minute). Comparing the $t_{1/2}$ and CL values of ropivacain : obtained in this study after intercostal block with those obtained after iv infusion, the CL was slightly lower and the $t_{1/2}$ was similar.

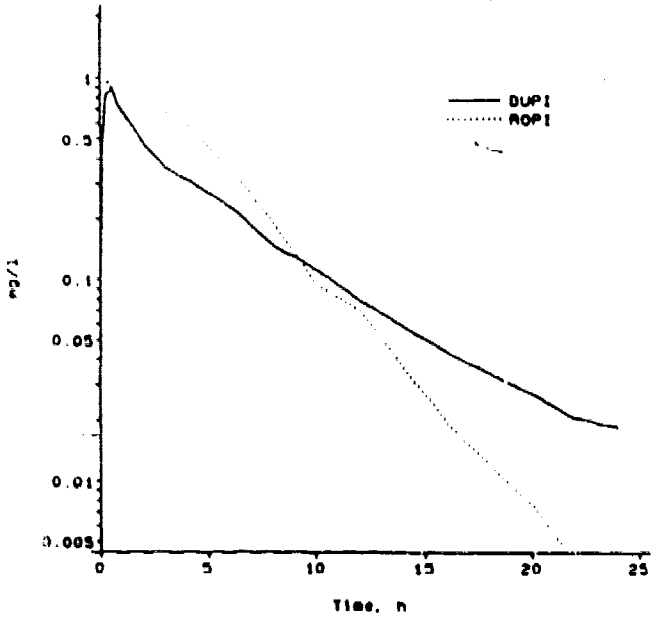


Figure 4. Mean total plasma concentration-time profiles of ropivacaine (n=7) and bupivacaine (n=7) after intercostal administration of 140 mg.

Table 9. Pharmacokinetic parameters after the intercostal administration of 140 mg each of ropivacaine and bupivacaine in healthy subjects (mean (% CV)).

Pharmacokinetic parameters	140 mg ropivacaine (intercostal)	140 mg bupivacaine (intercostal)
C_{max}, mg/liter	1.06 (34)	0.92 (24)
T_{max}, minutes	53 (160)	30 (27)
AUC, mg minute/liter	306 (25)	243 (28)
$t_{1/2}$, hours	2.3 (35)	4.6 (57)
CL, mL/minute	425 (24)	549 (30)

3.7. LOCAL INFILTRATION FOR POST-SURGERY PAIN RELIEF;

Two studies involving 74 patients were conducted to study the pharmacokinetics of ropivacaine after local infiltration of which one was reviewed. In a parallel study involving 38 patients, three groups of subjects were administered 37.5, 75, and 150 mg doses of ropivacine via

local infiltration (129). The mean plasma concentration-time profiles of ropivacaine at 37.5, 75, and 150 mg doses rise to plateau concentrations around 45 minutes and remained at the plateau level for the remainder of the sampling period (75 minutes). Incomplete sampling period did not permit the observation of a declining phase and its associated terminal half-life at any of the three doses (Figure 5). The C_{max}'s and AUC_{0-2}'s of ropivacaine increased with increasing doses (Table 10). A linear regression model with an intercept fitted the C_{max} (r^2=0.962) and AUC (r^2=0.958) data well with the intercept not significantly different from zero. This indicates dose-proportional behaviour of ropivacaine in the dose range of 37.5 -150 mg when administered by local wound infiltration The mean C_{max} at the highest dose of 150 mg was 0.46 mg/liter, which is very much smaller than 1.92 mg/liter through iv infusion (80 mg dose), 1.09 mg/liter through epidural infusion (150 mg dose), and 1.1 mg/liter after intercostal administration (140 mg dose).

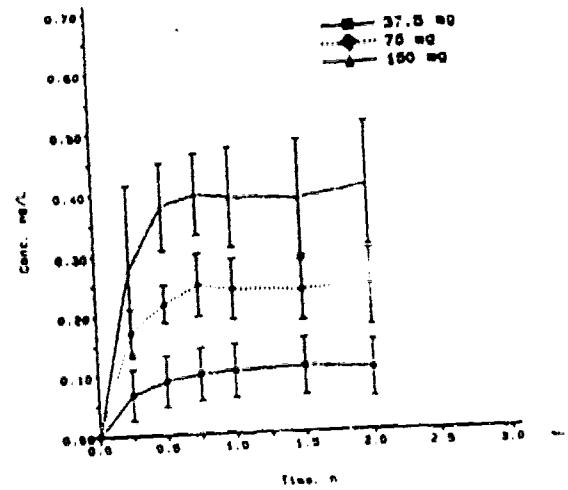


Figure 5. Mean plasma concentration-time profiles over the first two hours after post-surgery wound infiltration with 37.5, 75, and 150 mg of ropivacaine.

Table 10. Mean pharmacokinetic parameters (mean (% CV)) after post-surgery wound infiltration with 37.5, 75, and 150 mg ropivacaine given in 30 mL over 2 minutes.

Pharmacokinetic parameter	37.5 mg ropivacaine	75 mg ropivacaine	150 mg ropivacaine
C_{max}, mg/liter	0.11 (45)	0.27 (15)	0.46 (17)
T_{max}, minutes	81 (52)	63 (57)	70 (63)
AUC_{0-2}, mg minute/liter	10.7 (45)	26.9 (18)	42.8 (19)

3.8. RECTAL ADMINISTRATION;

Although not included in the proposed package insert, data pertaining to the use of rectal administration of ropivacaine in ulcerative colitis was briefly reviewed. Two (2) studies conducted in 36 healthy volunteers were submitted in support of this indication and one study was reviewed. An open, cross-over study was conducted in 20 healthy volunteers to assess the bioavailabilty, tolerability, effect of rectal gel volume, and dose proportionality of 50 mg in 20 mL, 100 mg in 40 mL, and 200 mg in 80 mL gel (I4). The mean plasma concentration-time profiles after the three rectal doses of 50, 100, and 200 mg ropivacaine showed (Figure 6) that the absorption was relatively slow with similar mean t_{max}'s over the dose range (2.77 - 3.35 hours). Mean C_{max} at the highest dose of 200 mg ropivacaine was 0.88 mg/liter (Table 11). C_{max} exhibited dose proportionality over the dose range with the equation describing the mean regression line being C_{max} = 0.004*dose. The hypothesis of zero intercept was not rejected at the 5% level. AUC was also proportional to the dose with the hypothesis of zero intercept not being rejected. The mean regression line was given by the regression equation, AUC = 0.027*dose. The mean terminal half-lives were consistent at the three doses and were 2.7, 2.6, and 2.4 hours respectively. The variability between individuals was approximately 3 and 2.5 times higher than the intra-individual variability for AUC and C_{max} when evaluating the dose normalized parameters. The inter-individual variability for AUC was statistically significantly greater than the intra-individual variability. The results obtained in this study were consistent with those of part 2 of study I4. Between the two parts the intercepts and slopes of the individually fitted regression lines (C_{max} and AUC) did not show any significant differences. Thus the volume of the rectal formulation did not seem to have an effect on the absorption. Examination of the rectal mucosa and anal canal through rectoscopy did not reveal any changes of clinical significance. The mean bioavailability, studied by co-administration of intravenous [$^2H_3$]ropivacaine was about 60%.

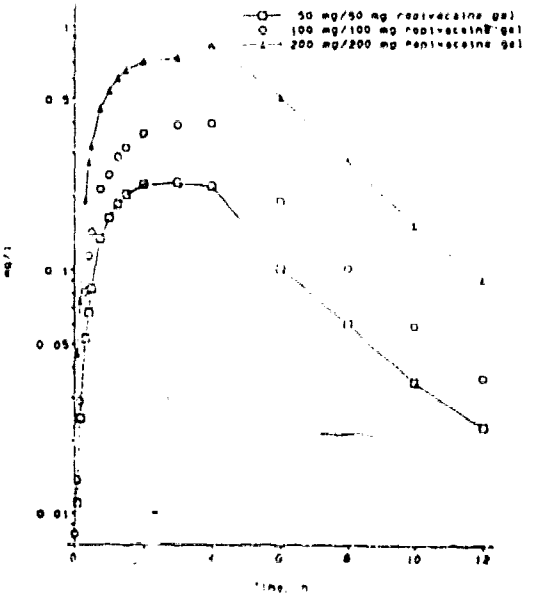


Figure 6. Mean plasma concentration-time profiles of 50, 100, and 200 mg of ropivacaine administered rectally in 20, 40, and 80 mL gel respectively in healthy subjects.

Table 11. Pharmacokinetic parameters of ropivacaine at 50, 100, and 200 mg doses administered rectally in healthy subjects (mean (% CV)).

Pharmacokinetic parameters	50 mg ropivacaine	100 mg ropivacaine	200 mg ropivacaine
C_{max}, mg/liter	0.26 (50)	0.44 (43)	0.88 (41)
t_{max}, hours	2.77 (40)	2.8 (35)	3.35 (37)
$t_{1/2}$, hours	2.69 (35)	2.64 (21)	2.43 (13)
AUC, mg hour/liter	1.47 (52)	2.52 (46)	5.48 (41)
f_e (0-12 hours)	0.34 (176)	0.25 (84)	0.47 (136)

4.0. SPECIAL POPULATIONS:

4.1. RENAL FAILURE;

No special studies were conducted in renal failure patients. The CL_R of ropivacaine is 1 mL/min and forms only a small fraction of its total clearance. The elimination $t_{1/2}$ of its major metabolite 3-hydroxy ropivacaine was longer (5.7 hours) than that of ropivacaine (2.0 hours). Ropivacaine's metabolites are excreted in the urine (total radioactivity excreted in the urine was about 80% of the dose) but the plasma levels of these were very low or below detection limits. In light of this information, the sponsors claim that renal failure should not have clinical significance. Even though ropivacaine might not, some of its metabolites might accumulate to a greater extent because of their primary elimination being via renal route. The systemic effects of these metabolites is not known at the present time and as such the consequences of such an accumulation is unknown.

4.2. PEDIATRICS:

There is no information available at this stage regarding pharmacokinetics of ropivacaine in children. During a communication with the FDA, the sponsors informed that a phase IV program is underway to approach this issue. However, at this time the proposed label contains a recommendation that until further experience is gained in this age group ropivacaine should not be used.

4.3. HEPATIC FAILURE:

No special studies were conducted in liver failure patients. Ropivacaine is eliminated primarily by hepatic metabolism and changes in hepatic function may have significant consequences. Ropivacaine has an intermediate to low extraction ratio and therefore its clearance depends on its unbound fraction and intrinsic metabolic clearance. The proposed label contains a statement that repeated doses of ropivacaine should be used cautiously in patients with hepatic disease.

4.4. NURSING MOTHERS:

It is known that some local anesthetic drugs are excreted in human milk and excretion of ropivacaine or its metabolites in human milk has not been studied when it is administered to a

nursing woman. Based on the milk/plasma concentration ratio in rats, the estimated daily dose to a pup will be about 4% of the dose given to the mother. Assuming that the milk/plasma concentration in humans is of the same order, the total ropivacaine dose to which the baby is exposed by breast feeding is far lower than by exposure in utero in pregnant women at term.

4.5. DRUG-DRUG INTERACTIONS:

No special drug-drug interaction studies were conducted as the list of drugs that are likely to be administered concomitantly with ropivacaine is extensive. In vitro studies indicate that cytochrome P4501A is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. Thus agents likely to be administered concomitantly with ropivacaine, which are metabolized by this isozyme family may potentially interact with ropivacaine. Such interaction might be a possibility with drugs known to be metabolized by P4501A2 via competitive inhibition such as theophylline, acetaminophen, imipramine and with potent inhibitors such as fluvoxamine, verapamil and furafylline.

5.0. DISPOSITION OF ROPIVACAINE AS A FUNCTION OF SEX, BODYWEIGHT, AND AGE:

The relationship between certain pharmacokinetic variables (AUC, C_{max}, CL, and $t_{1/2}$) and some predictors (age, sex, weight etc.) was investigated using stepwise regression methods at a statistical significance level of 0.10. The relationships were also examined using plots of the variables versus the predictors. However, due to the confounding factors in which regional anesthesia is used during and after surgery, the relationships that were isolated should be regarded with caution.

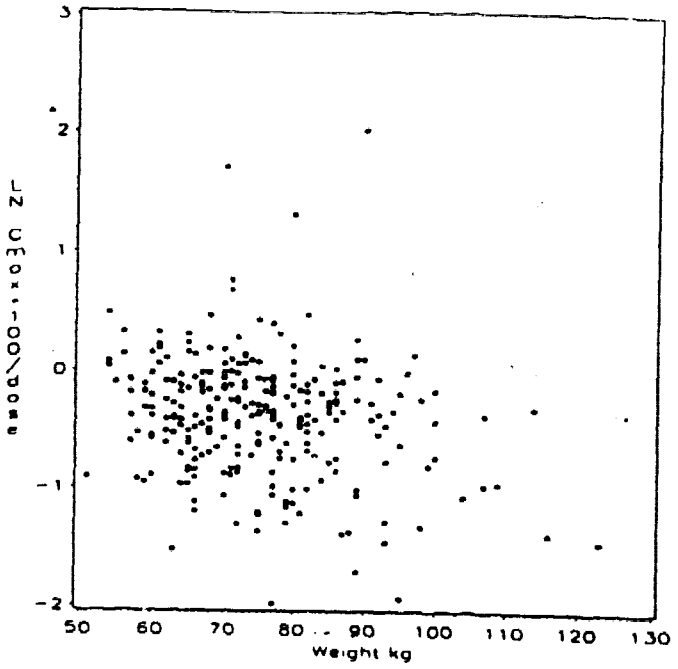
5.1. SEX;

There appeared to be no sex differences in the pharmacokinetics of ropivacaine. When selected, sex came out as the last predictor in the stepwise regression procedure for clearance (4th of 4, R^2=0.34).

5.2. BODYWEIGHT;

Although bodyweight did come out as a significant predictor on the dose-normalized C_{max} and the log dose-normalized C_{max} in the stepwise regression procedure, its contribution to the variation in these variables was only marginal, 2nd of 4, R^2=0.24, and 2nd of 3, R^2=0.19. In descriptive plots, bodyweight versus log dose-normalized C_{max} and dose normalized AUC after ropivacaine given for various regional blocks did not reveal any trend indicating that the plasma concentration of ropivacaine does not seem to be influenced much by bodyweight (Figure 7).

(a)



(b)

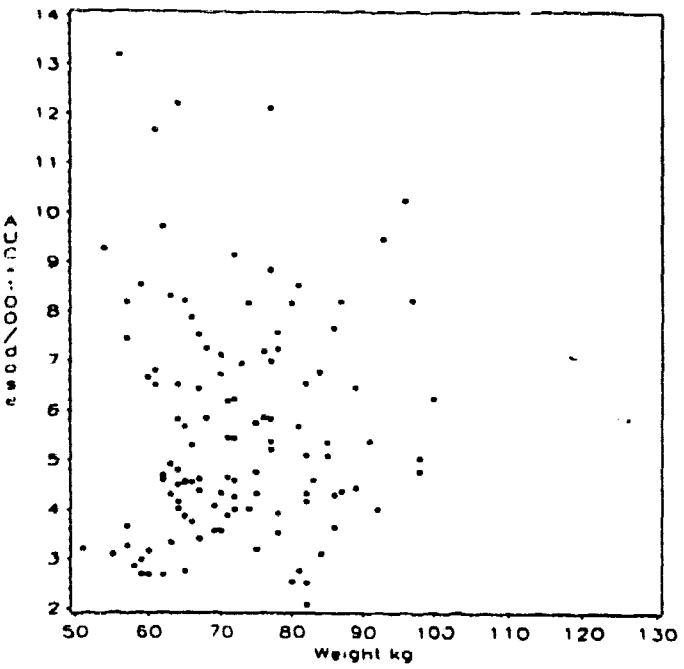


Figure 7. Plot of (a) bodyweight versus log dose-normalized C_{max} and (b) bodyweight versus dose-normalized AUC, after ropivacaine given for various regional blocks.

5.3. AGE;

Both hepatic blood flow and the intrinsic ability are probably reduced in the elderly. The excretion of the metabolites is also probably slower in elderly than in younger patients. This may not be of major clinical significance as the major metabolite 3-hydroxy ropivacaine has a short half-life (≈ 6.0 hours), shows low plasma concentrations and ropivacaine is used for single dose or short-term treatment. Figure 8 shows the plots of age versus $t_{1/2}$ and CL respectively with no apparent

relationship between age and $t_{1/2}$ and age and CL. Stepwise regression procedure of dose-normalized AUC yielded age as a significant predictor although its contribution to the variation in AUC was only marginal, 3rd of 4, R^2=0.24.

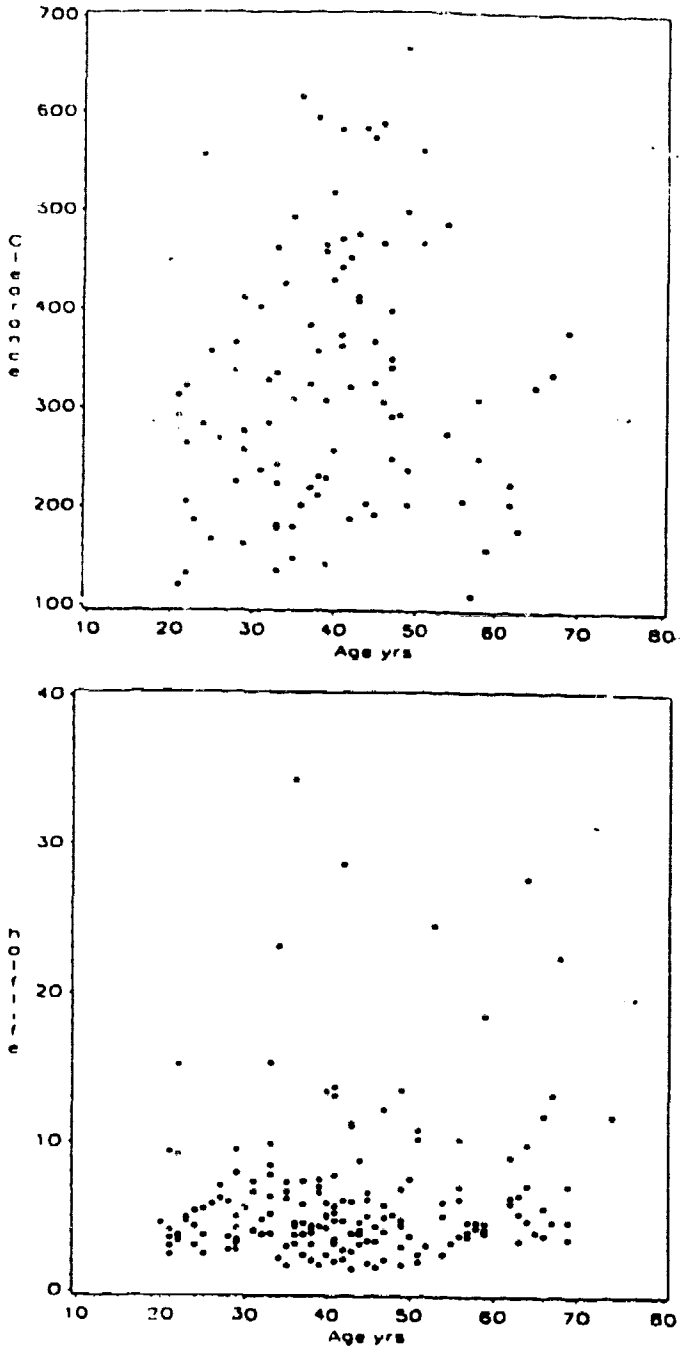


Figure 8. Plot of (a) age versus total plasma clearance and (b) age versus terminal half-life, after ropivacaine given for various regional blocks.

6.0 CONCLUSIONS

1 [^{14}C]Ropivacaine and its metabolites were mainly excreted in the urine after iv administration, with a mean total recovery of 86% in urine and 9% in feces after 96 hours. Most of the radioactivity was excreted within 12 hours in the urine, 68%. The elimination half-life of total radioactivity in plasma was 5.4 hours.

2 Ropivacaine was extensively metabolized and about 1% of the dose was excreted unchanged in the urine. The major metabolite was 3-hydroxy ropivacaine about 37% of which was excreted in the urine, mainly conjugated, and most likely with glucuronic acid. Conjugated + unconjugated 3-hydroxy ropivacaine showed detectable concentrations in plasma (5.5 ng/mL). Urinary excretion of 4-hydroxy ropivacaine, the N-dealkylated metabolite (PPX), and 4-hydroxy-PPX accounted for 1-3%.

3 No *in vivo* racemization of S-(-)-ropivacaine to the corresponding R-form was observed.

4 2,6-Xylidene, a suspected carcinogen and a likely metabolite of amide linked local anesthetics was not found.

5 Ropivacaine was highly bound to serum proteins (94%) predominantly to α_1-acid glycoprotein and to some extent to serum albumin. Binding was linear in the concentration range mg/liter. Blood to plasma concentration was of the order of 0.7.

6 The unbound fraction varied between 0.03 and 0.10 in volunteers and adult patients, but decreased with an increase in α_1-acid glycoprotein concentration. The unbound fraction at term in pregnancy was of the order of 0.09, and in fetal plasma about 0.2.

7 After intravenous administration, the mean plasma clearance was about 313 mL/minute, the steady state volume of distribution was 43 liters, and the terminal half-life was about 1.7 hours. Renal clearance was about 1 mL/minute.

8 Ropivacaine followed linear pharmacokinetics upto the highest intravenous dose studied, 80 mg, corresponding to a maximum plasma concentration of about 1.8 mg/liter.

9 C_{max} and AUC were proportional to the dose after single epidural administration in the range of clinical doses used (up to 250 mg). t_{max} was unchanged between doses suggesting constant absorption rate from the epidural dose with the dose.

10 The systemic absorption from the epidural space was biphasic with an initial rapid phase followed by a slower phase, each contributing about 50 % to the overall absorption. The half-life of the slower absorption phase was similar to the terminal half-life of ropivacaine after epidural absorption i.e., 4.3 hours. The bioavailability after epidural administration was of the order of 90%.

11 The pharmacokinetics of ropivacaine were not influenced when the same epidural dose (100 mg) was given in different volumes (10 or 20 mL).

12 There was no major decrease in the plasma concentration regardless of whether ropivacaine was combined with epinephrine or not in major nerve blocks.

13 The total clearance of ropivacaine at term in pregnancy was somewhat lower and the unbound clearance markedly lower than after epidural ropivacaine in non-pregnant patients. Accordingly, total C_{max} and unbound C_{max} were higher in pregnancy. The umbilical vein/maternal vein ratios of unbound plasma concentrations seemed to be in equilibrium within one hour of ropivacaine administration.

14 Ropivacaine gave lower plasma concentrations after infiltration than after epidural block and

exhibited dose-proportional behaviour in the dose range of 37.5 - 150 mg.

7.0. PROPOSED PACKAGE INSERT

The pharmacokinetics section of the proposed package insert submitted by the sponsor did not conform to the format (ADME) preferred by the Office of Clinical Pharmacology and Biopharmaceutics. The proposed package insert rewritten by this reviewer to reflect the ADME format along with other related changes is included here.

8.0. COMMENTS

1 **Metabolism**

Mass balance studies indicate excretion of about 85% total radioactivity in the urine and of that, 43% was accounted in terms of 3-hydroxy ropivacaine, 4-hydroxy ropivacaine, PPX, 3-hdroxy PPX and 4-hydroxy ropivacaine. The remaining 40-43% is unaccounted for, although 2-hydroxy methyl ropivacaine may account for part of it. Composition of the remaining radioactivity and the cytochrome P-450 isozymes involved should be explored. Samples from previous studies can be used if possible or a separate study can be undertaken as a Phase IV commitment.

2 **Hepatic failure patients**

Ropivacaine is highly metabolized in the liver. The fraction of [^{14}C]ropivacaine excreted unchanged in the urine after iv infusion was only about 1%. As such, potentially ropivacaine and/or its metabolites plasma levels could be very high resulting in toxicity when used in hepatic failure patients. No supporting studies have been provided addressing this issue. Therefore, the sponsor should put forward a proposed phase IV development plan to address this issue. Plasma levels of ropivacaine and its metabolites should be followed in this study. Ideally the protocol should be discussed with FDA before the trial begins.

3 **Renal failure patients**

Even though ropivacaine, because of it small renal clearance might not accumulate, some of its metabolites might accumulate to a greater extent because of their primary elimination being via

renal excretion. The consequences of such an accumulation is unknown and the sponsor has not conducted any special studies to investigate this. Therefore the sponsor should put forward a proposed phase IV development plan to address this issue. Plasma levels of ropivacaine and its metabolites should be monitored in a long term continuous epidural infusion study (simulating a 21 hour continuous epidural infusion for pain relief). Ideally the protocol should be discussed with FDA before the trial begins.

4 **Pediatric patients**

The sponsor should submit the pharmacokinetic data in pediatric patients to FDA once the phase IV studies in this sub population are completed.

12/15/95

Suresh Doddapaneni, Ph.D.
Pharmacokineticist

Peer Reviewer: John Hunt 12/15/95

CC:
NDA 20-533 (Original)
HFD-170 (Division of Anesthetic, Critical Care & Addiction Drug Products)
HFD-860 (Division of Pharmaceutical Evaluation I)
HFD-860 (Bashaw)
HFD-870 (Division of Pharmaceutical Evaluation II)
HFD-870 (Doddapaneni, Hunt, Lockwood, Mei-Ling Chen)
HFD-880 (Division of Pharmaceutical Evaluation III)
HFD-340 (Viswanathan)
HFD-850 (Chron, Drug, Reviewer)
HFD-205 (FOI)

STUDY I7

STUDY TYPE: HUMAN METABOLISM **STUDY:** I7 90Ro27

STUDY TITLE: Biotransformation and excretion of ropivacaine in man following single intravenous administration of a ^{14}C-labelled compound

NDA: 20-533 **SUBMISSION DATE:** March 29, 1995 **VOLUME:** 1.45

CLINICAL INVESTIGATOR:

ANALYTICAL INVESTIGATOR: T.Arvidsson, Ph.D. Bioanalysis Astra Pain Control AB S-151 85 Södertälje, Sweden

STUDY DESIGN:

Single Dose: Yes **Multiple Dose:** No **Washout Period:** No

Cross-over: No **Parallel:** No **Other Design:** Open, ^{14}C-labelled ropivacaine

Fasted: Yes **If fasted, how long (hours)?** Overnight

SUBJECT BREAKDOWN:

Normal Yes **Patients:** no **Young** Yes **Number=** 6 **Male=** 6 **Female=**none

Sex Type Male

Weight **Mean** 82 **Range** kg

Age **Mean** 33 **Range** yrs

FORMULATION:

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
Normal	50 mg ^{14}C-ropivacaine	Injection (Intravenous)	2.5 mg/mL	470-22-2	23 (50 mL)

SAMPLING TIMES:

Plasma: Before (0) and 10 minutes after start of infusion and 5, 10, 20, 30, 45, 60 and 90 minutes and 2, 3, 4, 6, 10, 24, 48, 72 and 96 hours after end of infusion.

Urine: Blank, 0-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 hours

Faces: Blank, 0-24, 24-48, 48-72, 72-96 hours

ASSAY METHOD: Ropivacaine in plasma gas-chromatography method with nitrogen-phosphor detector. Radioactivity by liquid scintillation. Ropivacaine in urine and the metabolites in plasma were determined by reversed-phase liquid chromatography.

ASSAY SENSITIVITY: The limit of determination was 0.03 μmol/liter (10 μg/Liter) for plasma. Limit of determination in urine was 0.3 μmol/Liter for ropivacaine, 0.7 μmol/Liter for PPX, 0.4-0.5 μmol/Liter for 3-OH-PPX, 0.7 μmol/Liter for 4-OH-ropivacaine, 0.4-0.6 μmol/Liter for 3-OH-ropivacaine. In the determination of 2,6-xylidine the limit was 0.1 μmol/Liter for plasma.

ASSAY ACCURACY: Plasma: Ropivacaine, the recovery was 97% and the inter-assay precision 2.3% at 0.3 μg/Liter. 3-OH-PPX, the recovery was 98% and the inter-assay precision 4.1% (0.45 μmol/Liter). 3-OH-ropivacaine, the recovery was 97% and the inter-assay precision 1.9% (0.50 μmol/Liter) 4-OH-ropivacaine, the recovery was 97% and the inter-assay precision 1.8% (0.53 μmol/Liter). 2,6 xylidine, the recovery was 95% and the inter-assay 3.9% precision (0.68

µmol/Liter). Urine: Ropivacaine, the recovery was 104% and the inter-assay precision 2.1% (30 µmol/Liter). 3-OH-PPX, the recovery was 99% and the inter-assay precision 3.0% (3.6 µmol/Liter). PPX, the recovery was 98% and the inter-assay precision 3.1% (3.5 µmol/Liter). 3-OH-ropivacaine, the recovery was 102% and the inter-assay precision 0.9% (30 µmol/Liter). 4-OH-ropivacaine, the recovery was 98% and the inter-assay precision 3.4% (3.3 µmol/Liter).

LABELING CLAIMS FROM STUDY: Ropivacaine was excreted unchanged in the urine to <1%. The major metabolite was 3-OH-ropivacaine (37%). Totally 43% of dose was recovered as identified metabolites. No 2,6-xylidine was found.

OBJECTIVES

(1) To determine the excretion routes of ropivacaine and its metabolites.
(2) To elucidate the metabolic pattern of ropivacaine.
(3) To evaluate the pharmacokinetic parameters of ropivacaine and its main metabolites.

STUDY DESIGN

The blood samples and plasma were analyzed for total radioactivity while plasma was analyzed for ropivacaine on GC and for major metabolites on reverse phase HPLC. Additional blood samples taken at pre-infusion, and at 30 minutes and 6 hours after infusion were used for isolation and identification of possible metabolites in plasma.

The urine samples were analyzed for total radioactivity as well as ropivacaine and its metabolites. Unchanged ropivacaine and major metabolites were quantified using reverse phase HPLC. Urine samples collected in the interval 2-4 hours were also subjected to analysis for isolation and identification of metabolites. Feces was subjected to total radioactivity analysis.

RESULTS AND DISCUSSION

Pharmacokinetics of ropivacaine;

Ropivacaine pharmacokinetic parameters determined using non-compartmental methods of analysis showed that it had a mean clearance of 0.397 liters/minutes, a steady state volume of distribution value of 60.0 liters, and an intermediate extraction ratio of 0.39 (Table 1). The plasma concentrations of metabolites, except for 3-hydroxy ropivacaine, were below or just above the limit of determination for unconjugated as well as after the hydrolysis of the metabolites (Limit of quantitaton was 10 ng/mL). 3-Hydroxy ropivacaine showed detectable mean plasma concentrations of 137.0 and 55.0 ng/mL at 30 min and 6 hours respectively corresponding to about 20% and 66% of ropivacaine plasma concentrations at these time points. The mean half-life of 3-hydroxy ropivacaine calculated from its urinary excretion data was 6.0 hours. and is probably the main contributor to the longer terminal half-life of plasma radioactivity.

The pharmacokinetic parameters were analyzed in this study using only non-compartmental methods of analysis. Compartmental methods of analysis were utilized in study I1, 802-50 AC-007-1, 86 LE 02 and the results of study I1 are presented here for comparison with those obtained after non-compartmental methods of analysis in the current study. The plasma concentration-time profile after iv infusion of 50 mg ropivacaine over 15 minutes gave a best fit to a biexponential function with half-lives of 0.33 and 1.9 hours for the rapid and slow disposition phases. The mean CL was about 501 mL/minute, mean Vss was about 41 liters.

Total radioactivity ;

Urine comprised the major route of excretion for total radioactivity (Table 2). After 96 hours about 86 % was excreted in the urine and about 9% in the feces. Most of the radioactivity in the

urine was excreted within 12 hours. Unchanged ropivacaine formed only about 1% of the total radioactivity excreted in the urine while 3-hydroxy ropivacaine formed the major component (about 37%) with minor amounts of 4-hydroxy ropivacaine (0.4%), the N-dealkylated metabolite, PPX (2.8%), and 3-hydroxy-PPX (2.1%). In addition 2-hydroxy methyl ropivacaine was also isolated and identified but not quantitated. The proposed metabolic pathway for ropivacaine is shown in Figure 1. All identified metabolites comprised about 43% (not including 2-hydroxy methyl ropivacaine) of the excreted radioactivity while the remaining 40-43% includes 2-hydroxy methyl ropivacaine and other unknown metabolites. Since the urine samples were subjected to acidic hydrolysis during sample processing, the above mentioned amounts for 3-hydroxy ropivacaine, 4-hydroxy ropivacaine, and 3-hydroxy-N-despropyl ropivacaine might include both unconjugated as well as conjugated forms. The mean plasma total radioactivity levels were higher and could be quantitated much longer when compared to the mean plasma radioactivity corresponding to ropivacaine (Figure 2). The C_{max}'s for both total radioactivity and ropivacaine were the same and occurred at the end of infusion indicating that the radioactivity at the peak could be accounted for by ropivacaine alone. The mean terminal half-lives were about 5.4 hours for total radioactivity and 2.0 hours for ropivacaine. This indicates that one or more metabolites of ropivacaine have a longer terminal half-life than ropivacaine. Because of the presence of amide linkage, hydrolysis of this amide linkage producing 2, 6-Xylidene is a possibility. However, 2, 6-Xylidene was not detected in this study indicating the absence of this metabolic pathway. Regarding the pharmacological activity of the metabolites, 3-hydroxy ropivacaine and 4-hydroxy ropivacaine were found to be active in animal models (F6, 802-550 LF-0228-01). A 1% solution of 3-hydroxy ropivacaine and 4-hydroxy ropivacaine when used for sciatic nerve block in the guinea-pig gave durations of 28% and 14% respectively of that of a 1% solution of ropivacaine for motor block. For sensory block 4-hydroxy ropivacaine did not produce any block while 3-hydroxy-ropivacaine had a duration of 22% of that of ropivacaine.

***in vivo* racemization of the S-(-)-enantiomer of ropivacaine to R-(-)-enantiomer;**

Urine samples obtained at different time intervals from subjects administered ropivacaine rectally in a different study and intravenously from this study, when examined for the two enantiomers, S-(-)-ropivacaine and R-(+)-ropivacaine showed that ropivacaine existed predominantly as S-(-)-enantiomer. Less than 0.2% of R-(+)-ropivacaine was detected in the urine samples. Since ropivacaine administered is pure S-(-) ropivacaine, this finding indicates that no *in vivo* metabolic inversion of the enantiomer occurs. Similar findings were obtained from urine samples of rat, sheep and the dog.

***In vitro* metabolism studies;**

In vitro metabolism studies were performed to determine the cytochrome P-450 isozymes involved in the metabolism of ropivacaine (Astra report 802-550-LF-0284,1995). The NADPH-dependent metabolism of ropivacaine to its major metabolite 3-hydroxy ropivacaine is catalyzed by CYP1A isozyme. The formation of 4-hydroxy-ropivacaine, 2-hydroxy-methyl-ropivacaine and PPX which are the minor metabolites *in vivo* were catalyzed by CYP3A. Of the two members in the CYP1A family, CYP1A1 is expressed only after exposure to inducers, while CYP1A2 accounts for about 10% of total P450 in the liver. A potential for metabolic drug interaction exists with drugs metabolized by CYP1A2 such as theophylline, acetaminophen (also by CYP2E1), and imipramine and inhibitors of CYP1A2 such as cimetidine, furafylline, and fluvoxamine. CYP2D6 and CYP2C19 did not contribute to the metabolism of ropivacaine and therefore poor metabolizers of

debrisoquine or mephenytoin will not have impaired metabolism of ropivacaine. Although, metabolic interaction of other drugs metabolized by CYP3A isozyme with ropivacaine is possible, minor amounts of ropivacaine's metabolites are produced by this isozyme and therefore any metabolic interaction may not be clinically significant.

CONCLUSIONS

The results obtained support the sponsors labelling claims from this study. Ropivacaine was extensively metabolized with only about 1% excreted unchanged in urine. After iv infusion, it has a fairly short terminal half-life of 2.0 hours, a large steady state volume of distribution of 60.0 liters, and a moderately large clearance of 0.4 liters/minute. Calculated hepatic extraction ratio of ropivacaine was 0.4. The major metabolite found was 3-hydroxy ropivacaine. All the metabolites except 3-hydroxy ropivacaine were present at or below determination limits. The half-life of 3-hydroxy ropivacaine calculated from its urinary excretion rates was about 6.0 hours. Minor amounts of 4-hydroxy ropivacaine, N-despropyl ropivacaine, 3-hydroxy-N-despropyl ropivacaine were also found in urine. A significant fraction of the total radioactivity excreted in the urine (40-43%) was in the form of unknown metabolites. No *in vivo* metabolic racemization of the therapeutically important S-(-)-ropivacaine to the toxic R-(+)-ropivacaine occurred. The amide hydrolysis metabolic pathway was absent in ropivacaine.

COMMENTS

(1) Urinary excretion of total radioactivity was about 86%. Known metabolites accounted for only about 43% of it. It would be good to know what constitutes the remaining 40-43% of the total radioactivity, in addition to the newly identified 2-hydroxy methyl ropivacaine. The sponsors should speculate on the likely nature of the components comprising the unidentified radioactivity and their pharmacological activity if any.

Response from Astra:

Regarding the unidentified part of the total radioactivity, the response was that about 10-20% of the activity could be in the form of 2-hydroxy-methyl ropivacaine and about 20% of the radioactivity is lost during the work-up procedure and could be associated with the already identified metabolites. In addition, the radioactivity tracing is reported to have at least three more radioactive peaks that have to be identified. However, these additional peaks will not correspond to major amounts. The sponsors believe that these compounds have been oxidized in the piperdine ring in addition to the aromatic hydroxylation.

(2) Although the pharmacological activity of the metabolites 3-hydroxy and 4-hydroxy ropivacaine have been determined in animal models, in each case the racemates were used instead of the pure S-enantiomer. Also, the anesthetic activity determined may or may not be important *in vivo* as these are formed outside of the epidural space, but their effects on the CNS and heart (similar to ropivacaine) may be more important from a toxicity standpoint.

Table 1. Pharmacokinetic parameters of ropivacaine after the iv infusion of 50 mg/kg [^{14}C]ropivacaine over 15 min (mean (% CV)).

Pharmacokinetic parameter	**Parameter value**
C_{max}, mg/liter	1.61 (45)
CL, mL/minute	397 (32)
V_{ss}, liters	60 (37)
$t_{1/2}$, hours	1.97 (14.7)
Hepatic extraction ratio	0.39 (30.7)

Table 2. Fractionation of ^{14}C-radioactivity excreted in the urine from 0-96 hours after the iv infusion of [^{14}C]ropivacaine over 15 minutes (mean (% CV)) expressed as % of dose.

Drug	**Cumulative amount excreted in urine**
Ropivacaine	1.02 (56)
3-Hydroxy ropivacaine	36.92 (8.0)
4-Hydroxy ropivacaine	0.42 (57)
N-Desmethyl ropivacaine (PPX)	2.75 (41)
3-Hydroxy N-desmethyl ropivacaine (3-hydroxy PPX)	2.15 (36)
2-Hydroxy methyl ropivacaine	not quantitated
Unidentified	▪ 40-43
Total amount excreted in the urine	86.3 (3.5)

Figure 1. Proposed metabolic scheme for ropivacaine.

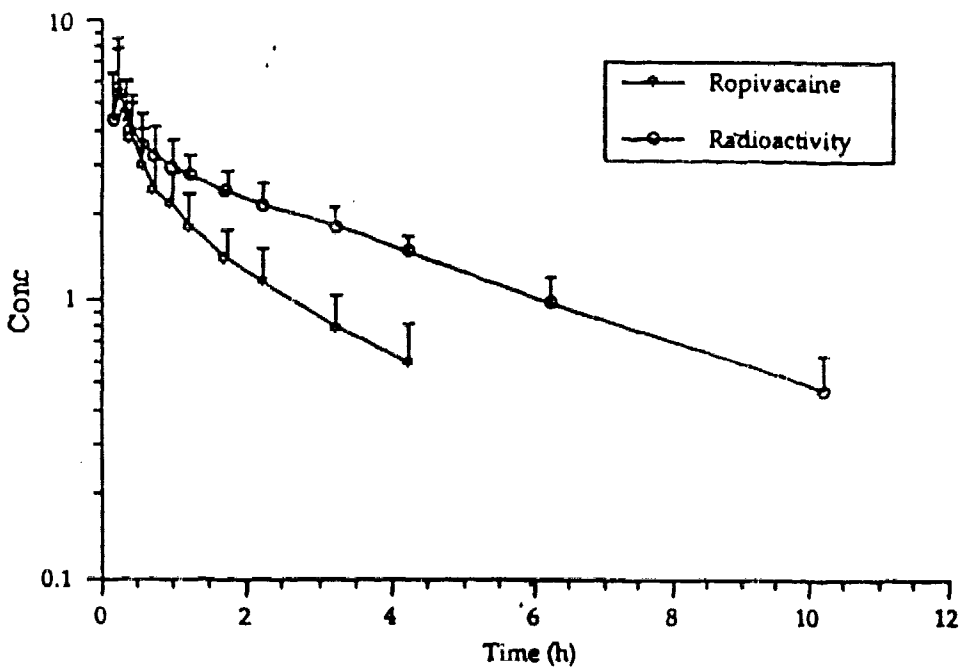


Figure 2. Mean plasma concentration (μmol/liter)-time profile of ropivacaine and total radioactivity following iv infusion of 50 mg [^{14}C] ropivacaine over 15 minutes.

STUDY I31

STUDY TYPE: PLASMA PROTEIN BINDING **STUDY:** I31 AF8674

STUDY TITLE: Blood/Plasma Concentration Ratio of Ropivacaine and Binding to Plasma Protein in Man after an Intravenous Infusion

NDA: 20-533 **SUBMISSION DATE:** March 29, 1995 **VOLUME:** 1.37

CLINICAL INVESTIGATOR

ANALYTICAL INVESTIGATOR: T.Arvidsson, Ph.D. Bioanalysis Astra Pain Control AB S-151 85 Södertälje, Sweden

STUDY DESIGN:

Single Dose: Yes **Multiple Dose:** No **Washout Period:** No
Cross-Over: No **Parallel:** No **Other Design:** One group, open
Fasted: Not specified

SUBJECT BREAKDOWN:

Normal Yes **Young** Yes **Number=** 6 **Male=** 6 **Female=** none
Weight; **Mean** 69 **Range** kg
Age; **Mean** 26 **Range** yrs

FORMULATION:

Treatment	Dose	Dosage	Strength	Lot	Lot Size
Normal	50 mg ropivacaine	Injection (Intravenous)	5 mg/mL	471-3-1	414 (10mL)

PLASMA SAMPLING TIMES: 16 and 30 minutes after the start of the infusion.
ASSAY METHOD: Capillary gas chromatography with nitrogen phosphorus detection.
ASSAY SENSITIVITY: Limit of determination was set at 0.02 µmol/liter (5 µg/liter).
ASSAY ACCURACY: The recovery of the method was 102% and the inter-assay precision was 7.9% (at 1.1 µmol/liter).
LABELING CLAIMS FROM STUDY: The plasma protein binding was estimated to 91-96% and the blood/plasma ratio ranged between
RESULTS AND DISCUSSION

The mean blood concentration of ropivacaine at 16 minutes and 30 minutes after the infusion of 50 mg ropivacaine over 15 minutes was 991 ng/mL and 623 ng/mL respectively. The corresponding values in plasma were 1471 ng/mL and 917 ng/mL.

The mean blood/plasma concentration ratio was 0.7 at 16 minutes and 0.7 at 30 minutes. The mean fraction of ropivacaine bound to plasma proteins was 94% at 16 minutes and 95% at 30 minutes (Table 1). The mean fraction of ropivacaine in whole blood distributing into the blood cells

was 0.21 at 16 minutes and 0.15 at 30 minutes. Although the mean plasma concentrations were 1431 ng/mL and 917 ng/mL at 16 and 30 minutes, the individual concentrations in the six subjects varied from a high of 2048 ng/mL to a low of 580 ng/mL. In this concentration range, the blood/plasma ratio and fraction bound to plasma proteins did not vary much indicating linear binding.

In vitro, the plasma protein binding and blood/plasma ratio determined in the range of ng/mL were slightly lower although no statistically significantly differences were found between the *in vivo* and *in vitro* values.

CONCLUSIONS

This study supports the sponsor's claim regarding ropivacaine's protein binding. Ropivacaine is extensively bound to the plasma proteins with 94% existing in the bound form. It distributes predominantly into the plasma with only about 20% distributing into the blood cells. Mean blood/plasma concentration ratio was 0.7 again indicating ropivacaine's preferential distribution into the plasma. α_1-acid glycoprotein is the protein to which ropivacaine is predominantly bound.

COMMENTS

1 In the present study, only male subjects were included for the determination of protein binding. Since ropivacaine is likely to be used extensively in women (especially pregnant woman for labor), protein binding in pregnant women is of interest because of potential placental transfer implications. Protein binding in pregnant women was determined in studies I23 and I18 and further discussion on this subject can be found in the individual study reviews.

2 In the proposed package insert for ropivacaine, the dose range recommended for ropivacaine was 150-200 mg for lumbar epidural administration (for surgery) and 175-250 mg for major nerve block (e.g. brachial plexus block). If the concentration range covered in this study also covers the concentrations that are likely to be encountered in the proposed dose ranges is not clear from this report. The mean C_{max} at 150 mg ropivacaine after local infiltration was 0.46 mg/liter (I29). The mean C_{max} at 190 mg ropivacaine for brachial plexus block was 1.26 mg/liter (I25). The mean C_{max} at 250 mg ropivacine administered epidurally was 1.77 mg/liter (I14). Thus, at the doses used in these pharmacokinetic studies, the mean C_{max}'s were all within the concentration range used for the determination of protein binding in this study.

3 The potential effect on protein binding of ropivacaine during the concurrent administration of commonly administered drugs such as lidocaine, midolazam, and pentycaine is unknown.

Table 1. Blood/plasma concentration ratio and fraction bound to plasma proteins of ropivacaine *in vivo*.

Subject	Hematocrit	16 Minutes blood sample			30 Minutes blood sample		
		blood/plasma	f_p	fraction bound to blood cells (f_{bc})	blood/plasma	f_p	fraction bound to blood cells (f_{bc})
Mean (% CV)	0.45	0.70 (10.9)	93.9 (1.4)	0.21 (26)	0.69 (15)	94.9 (1.2)	0.15 (52)
Mean of all measurements (16 and 30 minutes); blood/plasma = 0.69, fp = 94.4, f_{bc} = 0.18							

STUDY I5

STUDY TYPE: BASIC IV PHARMACOKINETICS OF ROPIVACAINE AND [$^2H_3$] ROPIVACAINE

STUDY TITLE: Basic pharmacokinetics of ropivacaine and its stable isotope labelled analogue in volunteers.

NDA: 20-533 **SUBMISSION DATE:** March 29, 1995 **VOLUME:** 1.41 **STUDY:** I5 90Ro31

CLINICAL INVESTIGATOR:

ANALYTICAL INVESTIGATOR: T.Arvidsson, Ph.D.
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STUDY DESIGN:

Single Dose: Yes **Multiple Dose:** No **Washout Period:** No

Cross-over: Yes **Parallel:** No **Other Design:** Open, simultaneous cross-over

Fasted: Yes **Food Study:** No

If fasted, how long (hours)? From midnight and until 3 hours after the infusion (minimum 8 hours).

SUBJECT BREAKDOWN:

Normal: Yes **Young:** Yes **Number=** 8 **Male=** 8 **Female=**none

Weight; **Mean** 82 **Range** kg

Age; **Mean** 33 **Range** yrs

FORMULATION:

Treatment	Dose	Dosage Form	Strength	Lot	Lot Size
Normal	40 mg ropivacaine	Injection (Intravenous)	2.5 mg/mL	470-15-1	499 (20 mL)
Normal	40 mg [$^2H_3$]ropivacaine	Injection (Intravenous).	2.43 mg/mL	1046-1-1	155 (20 mL)

PLASMA SAMPLING TIMES: Before (0), 5, 15, 25 (end of infusion), 30, 45, 60, 90 minutes and 2, 3, 4, 6, 8, 10 and 12 hours after start of infusion.

URINESAMPLING TIMES: Blank, 0-2, 2-4, 4-6, 6-8, 8-12 hours

ASSAY METHOD: Gas-chromatography/mass spectrometry (GC/MS) procedure.

ASSAY SENSITIVITY: The limits of determination were set to 0.01 µmol/liter (0.003 mg/liter) for both.

ASSAY ACCURACY: The recovery was for plasma 91-107% (ropivacaine 0.2-1.9 µmol/liter) and 91-120% ([$^2H_3$]ropivacaine) and for urine 80-105% (ropivacaine 0.2-1.9 µmol/liter) and 89-100% ([$^2H_3$]ropivacaine). The intra-assay precision was 3-13% for ropivacaine and 5-11% for [$^2H_3$]ropivacaine (0.2-1.8 µmol/liter) in plasma and 4-13% for ropivacaine (0.2-1.9 µmol/liter), and 5-11% for [$^2H_3$]ropivacaine (0.2-1.8 µmol/liter) in urine.

LABELING CLAIMS FROM STUDY: The basic pharmacokinetics of ropivacaine and [$^2H_3$]ropivacaine were similar.

OBJECTIVES

To determine if pharmacokinetics of ropivacaine and its trideutero-methyl labelled analogue, [$^2H_3$]ropivacaine, are similar.

This study was designed to find out if the disposition of the trideutero-methyl isotope labelled analogue of ropivacaine and its unlabelled form are similar. Similar disposition will facilitate the usage of this labelled analogue in conjunction with the unlabelled ropivacaine in a two-leg, simultaneous cross-over design, to study the rate and extent of absorption of ropivacaine after epidural administration. Ropivacaine can be given epidurally and a smaller dose of [$^2H_3$]ropivacaine can be given intravenously at the same time to characterize the absorptive process of ropivacaine and thus avoiding intra-individual variations.

STUDY DESIGN

This study was an open, single-dose, simultaneous cross-over study of 40 mg each of ropivacaine and [$^2H_3$]ropivacaine infused intravenously over 25 minutes in eight healthy male volunteers. The subjects were selected using appropriate inclusion/exclusion criteria and were subjected to a routine medical-physical examination before and after the study. They were fasted overnight for eight hours before and three hours after the administration of the dose. Ten (10) mL blood samples were taken at pre-infusion, and at 5, 15, 25, 30, 45, 60, 90 minutes, and 2, 3, 4, 6, 8, 10, and 12 hours after the start of the infusion (total amount of blood sampled was 225 mL including 75 mL for clinical chemistry tests). Urine samples to characterize renal clearance were collected at the intervals of 0-2, 2-4, 6-8, 8-12 hours.

RESULTS AND DISCUSSION

The mean plasma concentration-time profiles of ropivacaine and [$^2H_3$]ropivacaine closely matched with each other (Figure 1). The mean pharmacokinetic parameter values of ropivacaine were; CL, 478 mL/min; V_{ss}, 54 liters; $t_{1/2}$, 1.8 hours. The plasma concentration at the end of infusion, C_{stop}, was 0.97 mg/liter. The mean pharmacokinetic parameter values for [$^2H_3$]ropivacaine were similar and were within 10% of the corresponding values for ropivacaine (Table 1). The mean fraction of ropivacaine excreted unchanged in the urine, f_e, was 0.5% while its mean CL_R was 1.8 mL/min. The corresponding values for [$^2H_3$]ropivacaine were 0.6% and 2.2 mL/min.

The pharmacokinetic parameters of ropivacaine and [$^2H_3$]ropivacaine were tested for equivalency using Wilcoxon sign rank test (non parameteric test not requiring the assumption of normal distribution) and paired-sample t-test. Both Wilcoxon test and paired t-test gave similar results in that differences between the pharmacokinetic parameters of ropivacaine and [$^2H_3$]ropivacaine, CL, $t_{1/2}$, V_{ss}, AUC, and C_{stop} were found to be statistically insignificant at 5% level of significance (Table 2). 95% Confidence intervals of the ropivacaine/[$^2H_3$]ropivacaine ratios of CL, V_{ss}, C_{stop} and AUC were within the pre-planned 0.90-1.10 interval (Table 3). The upper limit of the confidence interval of $t_{1/2}$ exceeded the limit 1.10 because of subject 4 who had a slower rate of elimination of ropivacaine compared to [$^2H_3$]ropivacaine from 6-12 hours after start of infusion. However, since the primary parameters CL and V_{ss} were within the pre-set limits of 0.90-1.10, similarity of pharmacokinetics was concluded.

CONCLUSIONS

No direct labelling claims were made from this study. The Plasma concentration-time profiles and the mean pharmacokinetic parameter values for both ropivacaine [$^2H_3$]ropivacaine closely matched with each other. The mean f_e's and CL_R's were also similar between ropivacaine and [$^2H_3$]ropivacaine. The pharmacokinetic parameter values were not significantly different for ropivacaine and [$^2H_3$]ropivacaine when tested using Wilcoxon sign rank test and paired t-test indicating that substitution of a deuterated methyl group has no influence on its disposition in healthy volunteers.

COMMENTS

1 Although C_{stop} was the same as C_{max} for most subjects, they differed in subjects 2, and 7 for both ropivacaine and [$^2H_3$]ropivacaine and in subject 6 for ropivacaine. The sponsors however used the C_{max} values instead of the Cstop's for showing pharmacokinetic equivalency in these subjects and as such in all subjects the values used were Cmax values.

2 The sponsors used Hodges-Lehman estimate and 90% confidence intervals to test the equivalency between the pharmacokinetic parameters of ropivacaine and [$^2H_3$]ropivacaine. The median of the differences between the parameters of ropivacaine and [$^2H_3$]ropivacaine is the Hodges-Lehman estimate. In the calculations, ratio of the parameter values of ropivacaine/[$^2H_3$]ropivacaine were used. The sponsors did not provide an explanation for this transformation. Not withstanding this transformation and its effect on the test statistic, this reviewer demonstrated pharmacokinetic equivalency between ropivacaine and [$^2H_3$]ropivacaine using Wilcoxon sign rank test and paired sample t-test.

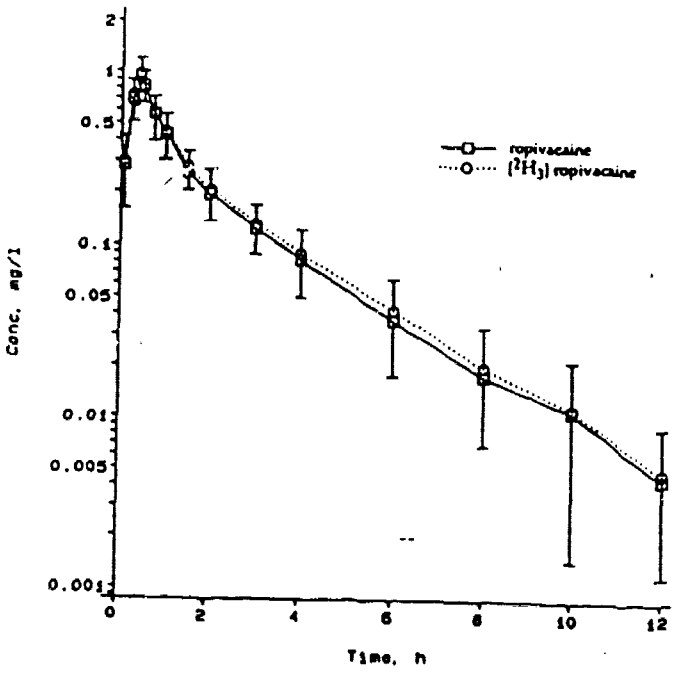

Figure 1. Mean plasma concentration-time profiles of ropivacaine and [$^2H_3$]ropivacaine after the iv infusion of 40 mg each of ropivacaine and [$^2H_3$]ropivacaine over 25 minutes.

Table 1. Pharmacokinetic parameter values of 40 mg each of ropivacaine and [$^2H_3$]ropivacaine infused intravenously over 25 min in 8 subjects (mean (%CV))

Pharmacokinetic parameters	**40 mg iv ropivacaine**	**40 mg iv [$^2H_3$]ropivacaine**
$t_{1/2}$, hours	1.86 (32)	1.73 (24)
CL, mL/minute	478 (20)	472 (21)
V_{ss}, liter	54 (15)	53 (17)
C_{stop} (Concentration at the end of infusion), mg/liter	0.97 (19)	0.98 (21)
AUC, mg minute/liter	82 (21)	86 (22)
$f_e^{\#}$ (%)	0.5 (80)	0.6 (87)
$CL_R^{\#}$, mL/minute	1.75 (80)	2.22 (89)

[#] n=5 subjects

Table 2. Equivalence of pharmacokinetic parameters of ropivacaine and [$^2H_3$]ropivacaine using Wilcoxon sign rank test and paired t-test.

Pharmacokinetic parameters	Paired t-test	Wilcoxon sign rank test
$t_{1/2}$	0.88*	3.5*
CL	1.01*	6.5*
V_{ss}	0.15	15.5*
C_{stop} (Concentration at the end of infusion)	0.23*	19*
AUC	2.0*	15*
Critical Value at 5% level	**2.36**	**3**

* not significant

Table 3. The 95% confidence intervals for the ratio ropivacaine/[$^2H_3$]ropivacaine calculated by Wilcoxon sign rank test. Renal clearance and the fraction of dose excreted unchanged were based on data from five subjects due to incomplete urine collections in the sampling period 0-12 hours.

Pharmacokinetic parameters	Number of subjects	Hodges-Lehmann estimate	Lower limit	Upper limit
AUC	8	0.973	0.916	1.026
C_{stop}	8	1.044	0.962	1.087
CL	8	1.02	0.975	1.052
V_{ss}	8	1.004	0.940	1.095
$t_{1/2}$	8	1.011	0.940	1.315
CL_R	5	0.965	nd	nd
f_e	5	0.947	nd	nd

nd = not determined

STUDY I2

STUDY TYPE: EPIDURAL PHARMACOKINETICS **STUDY:** I2 91Ro46

STUDY TITLE: Pharmacokinetics of ropivacaine following epidural administration in volunteers. Simultaneous investigation of absorption and disposition kinetics using the isotope-labelled analogue [$^2H_3$]ropivacaine

NDA: 20-533 **SUBMISSION DATE:** March 29, 1995 **VOLUME:** 1.38

CLINICAL INVESTIGATOR:

ANALYTICAL INVESTIGATOR: T. Arvidsson, Ph.D.
Bioanalysis
Astra Pain Control AB
S-151 85 Södertälje,
Sweden

STUDY DESIGN:

Single Dose: Yes **Multiple Dose:** No **Washout Period:** Yes
Cross-over: Yes **Parallel:** No **Other Design:** Simultaneous cross-over
Fasted: Yes
If fasted, how long (hours)? From midnight and for at least 4 hours after drug infusion.

SUBJECT BREAKDOWN:

Normal Yes **Young** Yes **Number** = 9 **Male**=9 **Female**=none
Weight; **Mean** 83 **Range** kg
Age; **Mean** 32 **Range** yrs

FORMULATION:

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
Normal	150 mg ropivacaine over 30 minutes	Injection (Epidural)	7.5 mg/mL	172-17-1	400 (20 mL)
Normal	40 mg [$^2H_3$]ropivacine	Injection (Intravenous)	2.5 mg/mL	1046-1-1	155 (20 mL)

PLASMA SAMPLING TIMES: Venous blood: Before (0), 2.5, 5, 10, 15, 20, 25, 30, 40 and, 50 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 22, 24 and 30 hours. Arterial blood: 2.5, 5, 10, 20, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6 and 8 hours (total of 270 mL blood was sampled from each subject).

EFFICACY MEASUREMENTS: Sensory analgesia (pin prick test) and motor block (motor function of lower limbs) were carried out at specified intervals to verify the adequacy of the epidural block.

ASSAY METHOD: Gas-chromatography/mass-spectrometry (GC/MS) procedure.

ASSAY SENSITIVITY: The limit of determination was set at 0.03 µmol/liters (10 µg/liters) for both compounds.

ASSAY ACCURACY. The recovery was 103% (ropivacaine) and 107% ([$^2H_3$]ropivacaine), The between day precision at 1 µmol/liters was 11% and 12% for ropivacaine and [$^2H_3$]ropivacaine,

respectively.

LABELING CLAIMS FROM STUDY: Biphasic absorption after epidural administration with a rapid phase followed by a slower phase. Each phase contributing ~50%. Based on venous data a absorbed fraction of ~85%. Arterio/venous differences after i.v. and epidural administration. Plasma clearance estimated after i.v. [$^2H_3$]ropivacaine was lower than earlier reported after i.v. ropivacaine.

OBJECTIVES

1)To estimate the rate and extent of systemic absorption of ropivacaine after epidural administration.
2)To document any possible differences in the pharmacokinetics based upon arterial and venous drug concentrations and to relate any occurring adverse event to both arterial and venous drug concentrations.

Ropivacaine does not require absorption into the systemic circulation to exert local or regional anesthesia for which it is proposed to be used. However, it can be absorbed into the blood stream after epidural administration to produce regional anesthesia for surgery or labor and potentially result in secondary and unwanted pharmacological effects such as seizures and cardiovascular toxicity. Therefore, the pharmacokinetic characterization of ropivacaine after epidural infusion is important in understanding any toxic effects of its systemic absorption. Also, ropivacaine exhibits arteriovenous concentration differences and in such a case arterial concentrations are the best indicator of its concentration-time profile at the sites of toxicity. This study therefore examines the extent and significance of such arteriovenous differences of ropivacaine.

RESULTS AND DISCUSSION

The mean concentration-time profiles of ropivacaine after epidural infusion and of [$^2H_3$]ropivacaine after intravenous infusion exhibited arteriovenous differences (Figure 1). Initially, the arterial concentrations increased faster and were higher than venous concentrations and reached equilibrium by about 1 hour after which the venous concentrations were higher and declined in parallel with the arterial concentrations. Significant differences were found between the arterial and venous C_{max} values for both ropivacaine (venous C_{max} = 1.09 mg/liter, arterial C_{max} = 1.58 mg/liter) and [$^2H_3$]ropivacaine (venous C_{max} = 0.82 mg/liter, arterial C_{max} = 1.27 mg/liter). No significant difference was found between the terminal half-life, although AUC, clearance, and Vss were significantly different ($p=0.02$) for [$^2H_3$]ropivacaine between arterial and venous plasma data (Table 1). The pharmacokinetic parameter values except V_{ss} were not different for ropivacaine based on arterial or venous plasma data. The extrapolated arterial AUC's comprised a mean of about 26% of the total AUC in the nine subjects and therefore pharmacokinetic parameters calculated using arterial plasma data may not be completely reliable. The mean pharmacokinetic parameter values of [$^2H_3$]ropivacaine estimated using venous plasma data employing non-compartmental methods of analysis were; mean terminal half-life of about 1.7 hours, clearance of about 313 ml/minute, and a steady state volume of distribution of 43 liters. Parameter values determined using compartmental methods of analysis yielded similar values.

For ropivacaine, mean pharmacokinetic parameter values calculated using venous plasma data and employing non-compartmental methods of analysis were; $t_{1/2}$ of 4.2 hours, CL of 363 mL/minute, and V_{ss} of 153 liters. The absorption of ropivacaine from the epidural space into the systemic circulation was estimated by point-area deconvolution procedures using iv unit impulse

response curv s derived from the venous plasma concentration-time profiles of [$^2H_3$]ropivacaine. The mean cumulative fraction of ropivacaine absorbed into the systemic circulation after epidural infusion was 0.85 which corresponded well with the fraction estimated from dose-corrected venous AUC's (0.87) but was smaller than when calculated from arterial AUC's (0.98). The absorption was biphasic with a slow and a long absorptive phases and mean absorption half-lives of 14 minutes and 4.2 hours respectively. Each of these two phases comprised about 50% each of the total absorption. The terminal half-life of ropivacaine which is similar to the absorption half-life reflects the absorption dependent elimination of ropivacaine.

Comparing the pharmacokinetic parameters of [$^2H_3$]ropivacaine and ropivacaine infused intravenously and epidurally respectively, the terminal half-life was about 2.5 times longer with the epidural infusion (4.2 hours) over iv infusion (1.8 hours). Even though ropivacaine is eliminated faster relative to the absorption from the epidural space, because of the slow absorption from the epidural space, its elimination is determined by the absorption and hence is prolonged resulting in a longer half-life. The clearances of [$^2H_3$]ropivacaine and ropivacaine were 310 mL/minute and 360 mL/minute respectively. The clearance of ropivacaine is slightly overestimated because of the assumption of 100% bioavailability and when this is taken into account, the clearances appear to be similar. The steady state volume of distribution for ropivacaine was about 3.5 times higher than that of [$^2H_3$]ropivacaine.

None of the adverse events reported seemed related to the systemic concentrations of ropivacaine/[$^2H_3$]ropivacaine. Efficacy measurements indicate mean times of onset and duration of 23 minutes and 4.2 hours for motor block while for sensory analgesia they ranged from 8-32 minutes for onset and 3.2-6.9 hours for the duration for the different dermatomes.

CONCLUSIONS

The results obtained support the sponsors labelling claims from this study. After the epidural infusion of 150 mg of ropivacaine, it was absorbed slowly into the systemic circulation from the epidural space in a biphasic fashion, with an initial rapid absorptive phase characterized by a half-life of 14 minutes which was followed by a slow absorptive phase characterized by a half-life of 4.2 hours. The terminal half-life was about 4.2 hours and reflects the absorption dependent elimination of ropivacaine. The fraction of ropivacaine absorbed was about 87% based on venous data. Clearance of ropivacaine was similar but steady state volume of distribution was about 3.5 times higher when compared with [$^2H_3$]ropivacaine. Large arteriovenous differences in the plasma concentration were found with significant differences in C_{max} and V_{ss} for both ropivacaine and [$^2H_3$]ropivacaine. The terminal half-life was however similar based on both arterial and venous plasma data.

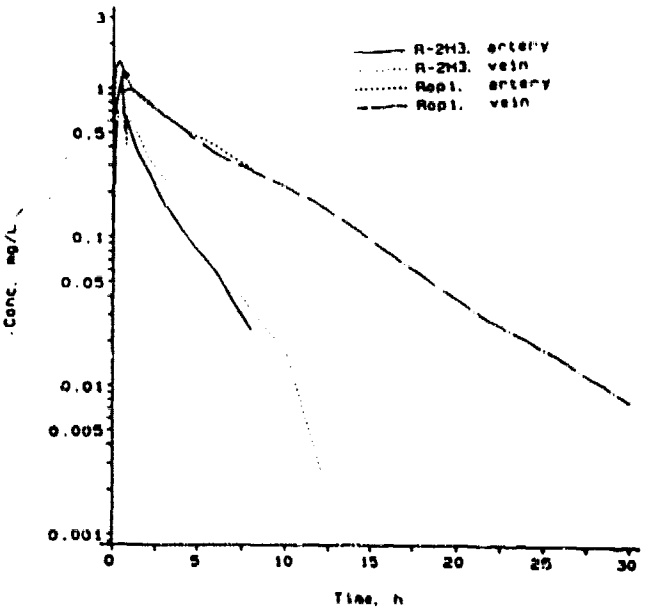

Figure 1. Mean arterial and venous plasma concentrations of ropivacaine and [$^2H_3$]ropivacaine after iv (40 mg) and epidural (150 mg) infusions respectively.

Table 1. Pharmacokinetic parameter values of 40 mg [$^2H_3$]ropivacaine and 150 mg ropivacaine calculated using non-compartmental methods of analysis (mean (% CV) of 9 subjects).

Pharmacokinetic parameters	40 mg [$^2H_3$]ropivacaine		150 mg ropivacaine	
	Venous	Arterial	Venous	Arterial
C_{max}, mg/mL	0.82 (23)*	1.27 (13)*	1.09 (28)*	1.58 (22)*
t_{max}, minute	27 (30)	29 (7)	36 (64)	19 (32)
$t_{1/2}$, hours	1.7 (18)	1.8 (33)	4.2 (24)	4.4 (39)
AUC, mg minute/liter	117 (22)*	110 (25)*	392 (27)	418 (35)
CL, mL/minute	313 (27)*	338 (30)*	363 (29)	360 (39)
V_{ss}, liter	43 (19)*	36 (11)*	153 (34)#,*	98 (32)#,*

* Significant difference between venous and arterial values as determined using Wilcoxon signed rank test (p=0.02).

Not provided in the report and calculated by this reviewer.

STUDY I6

STUDY TYPE: BASIC IV PHARMACOKINETICS AND DOSE PROPORTIONALITY
STUDY TITLE: Pharmacokinetics of ropivacaine in volunteers after three intravenous doses
NDA: 20-533 **SUBMISSION DATE:** March 29, 1995 **VOLUME:** 1.42 **STUDY:** I6 91Ro43
CLINICAL INVESTIGATOR:
ANALYTICAL INVESTIGATOR: T.Arvidsson, Ph.D. Bioanalysis Astra Pain Control AB S-151 85 Södertälje, Sweden

STUDY DESIGN:
Single Dose: Yes **Washout Period:** Yes (one week)
Cross-over: Yes **Other Design:** Double-blind randomized
Fasted: Yes **If fasted, how long (hours)?** From midnight prior to the trial day and until 3 hours after the infusion (minimum 8 hours).
SUBJECT BREAKDOWN:
Normal: Yes **Young:** Yes **Number** = 9 **Male** = 9 **Female** = none
Weight; **Mean** 77 **Range** kg **Age;** **Mean** 26 **Range** yrs
FORMULATION:

Treatment	Dose	Dosage	Strength	Lot	Lot Size
Normal	20 mg as iv infusion over 30 minutes	Injection (Intravenous)	0.125 mg/mL	1106-1-1	44 (250 mL)
Normal	40 mg as iv infusion over 30 minutes	Injection (Intravenous)	0.25 mg/mL	1107-1-1	45 (250 mL)
Normal	80 mg as iv infusion over 30 minutes	Injection (Intravenous)	0.5 mg/mL	1108-1-1	44 (250 mL)

PLASMA SAMPLING TIMES: Before (0), 2, 5, 15, 30 (end of infusion), 35, 40, 45, 60, 75 and 90 minutes and 2, 3, 4, 5, 6, 8 hours after start of infusion. A total of 450 mL blood was drawn from each subject for the entire study including 70 ml for clinical chemistry
URINE SAMPLING TIMES: Blank, 0-0.5, 0.5-2, 2-4, 4-6, 6-8, 8-24 hours
ASSAY METHOD: Total plasma and urine concentration: Gas-chromatography with a nitrogen sensitive detector. Free plasma concentration: Coupled-column liquid chromatography after ultra filtration of plasma samples and detected by UV.
ASSAY SENSITIVITY: The limit of determination was set at 0.03 µmol/liter (10 µg/liter) for both plasma and urine total concentration. and at 0.01 µmol/liter (3 µg/liter) for free plasma concentration.
ASSAY ACCURACY: Total concentration-plasma: The recovery was 100% and the between day precision 2.1% (0.7 mg/liter). Free plasma concentration: The recovery of aqueous controls was close to 100% and the between day precision of plasma ultrafiltrate was 5.2% (36 µg/liter). Total concentration urine: The recovery was 99% and the between day precision 8% (at 0.9 mg/liter).

LABELING CLAIMS FROM STUDY: The results show linear pharmacokinetics up to the highest total plasma concentrations (~2 mg/liter). A slight increase of the free fraction was, however, seen at the highest plasma levels - indicating that the lower levels of concentration dependent protein (at normal alpha-1-acid glycoprotein) may be reached.

RESULTS AND DISCUSSION

The mean plasma concentration-time profiles of ropivacaine after the iv infusion of 20, 40, and 80 mg doses adjusted for the doses were close to each other at most time points (Figure 1). Dose normalized AUC's at the three doses plotted as a function of the dose yielded a flat line (Figure 2). Dose normalized C_{stop}'s however decreased slightly with increasing doses.. Anova analysis on the dose normalized C_{stop}'s and AUC's gave good fit for AUC but not C_{stop} data. None of the factors for period, carry-over, direct dose effect or between subject variance were significant for C_{stop}.. This might be explained by C_{stop} being a point estimate depending on the infusion rate and time at which infusion is stopped among other factors resulting in a large intra-individual variability in the data interfering with the ANOVA analysis. On a mean basis however rough dose proportinality in C_{max} is still indicated. For AUC, in the reduced ANOVA model eliminating the factors for period and carry-over effects (which were not significant) no significant differences between dose levels were seen. Linear regression lines fitted to the individual data with zero intercepts fitted well to the non-normalized AUC data. These results taken together show dose proportionality of ropivacaine in the range of 20-80 mg for C_{stop} and AUC.

The mean terminal half-lives, clearances, and steady state volume of distribution were similar for all the three doses (Table 1). The period and carry-over effects were not significant when ANOVA was performed on the terminal half-life, clearance, and steady state volume of distribution data. In the reduced ANOVA model eliminating the factors for period and carry-over effects no significant differences were seen between these parameters at these dose levels.

As the dose increased from mg, the mean fraction of ropivacaine unbound in plasma, f_u, increased slightly from 4.8%-5.5% (Table 1). Also, a weak trend was observed for the f_u to increase with increasing total plasma concentration. The concentration of α amino glycoprotein, which is the main protein to which ropivacaine binds in the plasma, was in the normal range. This indicates that at the higher dose levels the plasma concentrations are reaching the lower limits of saturation of the protein binding capacity. The unbound clearance decreased slightly from 8.5-7.2 liters/minute, but was not statistically significant between doses. The unbound steady state volume of distribution however did not vary between the doses. Renal clearance and fraction excreted unchanged in the urine were also similar between the doses further supporting the dose proportionality of ropivacaine in this dose range.

CONCLUSION

Dose proportionality of ropivacaine infused intravenously in the range mg corresponding to mean C_{stop}'s of 0.55 to 1.92 mg/liter was adequately demonstrated and supports the sponsor's labelling claims from this study.

COMMENTS

1 All the subjects in this study were males and analysis of any possible gender differences in the dose proportionality of ropivacaine was not possible.

2 Although C_{stop} was used instead of C_{max} for assessing the dose proportionality, C_{stop} was the highest concentration in all the subjects (except two subjects where the next time point the concentration was the same as C_{stop}). Therefore use of C_{stop} in this study was equivalent to using C_{max}.

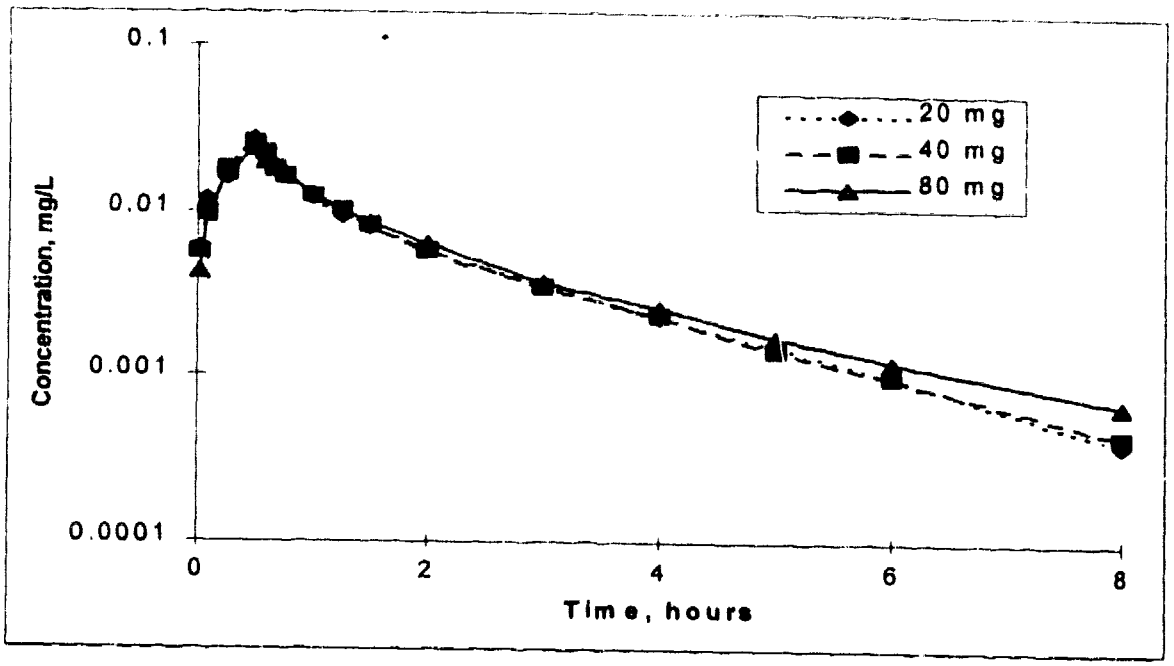

Figure 1. Mean plasma concentration-time profiles of ropivacaine after dose correction of 20, 40, and 80 mg doses.

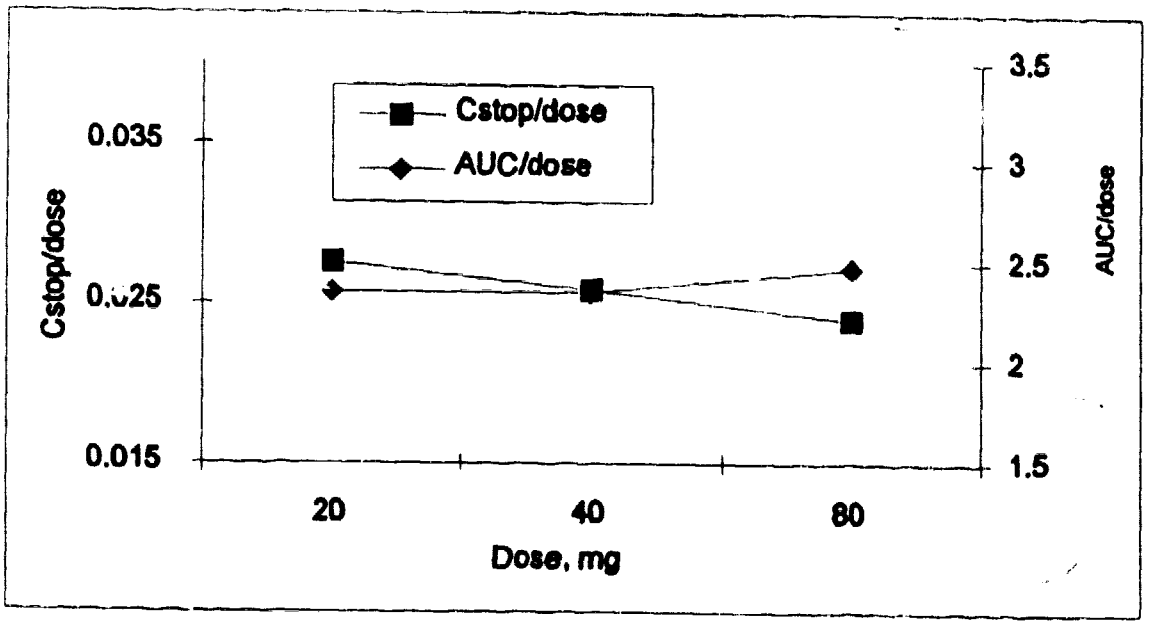

Figure 2. Dose normalized AUC, C_{stop} of ropivacaine at 20, 40, and 80 mg doses.

Table 1. Pharmacokinetic parameter values of ropivacaine after the infusion of separate doses of 20, 40, and 80 mg over 30 minutes (mean (% CV)).

Pharmacokinetic parameters	20 mg ropivacaine	40 mg ropivacaine	80 mg ropivacaine
C_{stop}, mg/liter	0.55 (13)	1.03 (23)	1.92 (17)
C_{stop}/dose	0.0275 (13)	0.0258 (23)	0.024 (17)
AUC, mg minute/liter	47 (26)	94 (27)	198 (34)
AUC/dose	2.35 (26)	2.35 (27)	2.48 (34)
CL, mL/minute	395 (25)	402 (27)	387 (28)
CL_u, mL/minute	8500 (32)	8000 (26)	7200 (22)
V_{ss}, liter	38 (21)	39 (21)	41 (17)
$V_{ss,u}$, liter	827 (40)	813 (34)	816 (40)
$t_{1/2}$, hours	1.6 (31)	1.6 (25)	1.8 (39)
f_u, %	4.8 (1.3)	5.1 (2.0)	5.5 (2.3)
f_e, %	0.4 (122)	0.8 (148)	0.6 (53)
CL_R, mL/minute	1.4 (84)	1.7 (114)	2.5 (54)

STUDY I21

STUDY TYPE: DOSE PROPORTIONALITY IN PATIENTS FOR POSTOPERATIVE PAIN THROUGH CONTINUOUS INFUSION

STUDY TITLE: Continuous epidural infusion of ropivacaine for the prevention of postoperative pain after major lower abdominal surgery: A dose-finding study - the pharmacokinetic evaluation.

NDA:20-533 **SUBMISSION DATE:**March 29, 1995 **VOLUME:**1.58 STUDY:I21 92Ro61

CLINICAL INVESTIGATOR:

ANALYTICAL INVESTIGATOR: T.Arvidsson, Ph.D.
Bioanalysis
Astra Pain Control AB
S-151 85 Södertälje,
Sweden

STUDY DESIGN:
Multiple Dose: Continuous epidural infusion **Washout Period:** No
Parallel: Yes **Other DesignN:** Double-blind, randomized
Fasted: Yes **If fasted, how long (hours)?** From midnight prior the surgery day
PLASMA SAMPLING TIMES: Before (0), 10, 12, 20 and 21 hours after infusion

ASSAY METHOD: Total concentration of ropivacaine in plasma was determined by gas chromatography with a nitrogen-sensitive detector. A coupled-column liquid chromatographic technique with UV-detection was used for free concentration.

ASSAY SENSITIVITY: Limit of determination was set at 0.03 µmol/liter (0.01 µg/mL) for total conc and the limit for free ropivacaine was set at 0.01 µmol/liter (0.003 µg/mL).

ASSAY ACCURACY: Total concentration: The recovery was 105% and the between day precision 5% (0.65 µg/mL). Free concentration: The recovery of aqueous controls was close to 100% (128 ng/mL) and the between day precision of plasma ultrafiltrate was 3.9% (118 ng/mL).

LABELING CLAIMS FROM STUDY: Both total and free plasma concentration increased during the last 11 hours of infusion (the sampling time) and were almost twice as high as the plasma levels in healthy subjects using the same infusion rates.

SUBJECT BREAKDOWN:

Patients Yes		**Young Yes**	**Elderly Yes**		
Subject Type Male			**Number= 44**	**Male= 14**	**Female= 30**
Weight;Mean 80	**Range:**	**kg**	**Group A**	**N= 11 M= 2**	**F= 9**
Age; Mean 67	**Range:**	**kg**	**Group B**	**N= 11 M= 5**	**F= 6**

Subject Type Female Group C N= 11 M= 4 F= 7
Weight; Mean 67 Range: kg Group D N= 11 M= 3 F= 8
Age; Mean 44 Range: kg

FORMULATION:

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
A	10 mg/hour ropivacaine (210 mg)	Injection (Epidural infusion)	1 mg/mL (10 mL/hour)	1201-1-1	575
B	20 mg/hour ropivacaine (420 mg)	Injection (Epidural infusion)	2 mg/mL (10 mL/hour)	1202-1-1	517
C	30 mg/hour ropivacaine (630 mg)	Injection (Epidural infusion)	3 mg/mL (10 mL/hour)	1203-1-1	586
D	Sodium chloride (Placebo)	Injection (Epidural infusion)	9 mg/mL (10 mL/hour)	400-66-1 *(400-67-1)	191 929
A+B+C+D	Bolus ropivacaine (75-140 mg)	Injection (Epidural)	5 mg/mL (15-28 mL)	471-17-1 *(471-29-1) (centre 1)	1399 934
A+B+C+D	Bolus ropivacaine (90-165 mg)	Injection (Epidural)	5 mg/mL (18-33 mL	471-29-1 (centre 2)	934

*)replacement

OBJECTIVES

To evaluate the dose-proportionality of the total and free plasma concentrations of ropivacaine when administered as an epidural infusion for postoperative analgesia after major abdominal surgery.

Post-operative pain is one of the most common forms of acute pain. To prevent post-operative pain, ropivacaine in a low concentration can be infused epidurally continuously. In order to be fully effective, the epidural block has to be established either in connection with the surgical procedure or immediately after surgery. In this study, combination of ropivacaine epidural anesthesia and general anesthesia was used for anesthesia during the surgical procedure and maintenance infusion of ropivacaine at three different rates. As a consequence of this, dose proportionality of ropivacaine at these different doses was assessed.

STUDY DESIGN

The study was a randomized, double-blind, multicentre trial with four parallel treatment groups, ropivacaine 10 mg/hr, 20 mg/hr, and 30 mg/hr and placebo. Forty four (44)

patients scheduled for major lower abdominal surgery (e.g., major colonic surgery, rectal amputation, bladder surgery, hysterectomy etc.) were anesthetized using a combination of epidural block with ropivacaine 5 mg/mL and general anesthesia. During surgery, an additional 25 mg ropivacaine was injected epidurally every 2nd hour after injection of the main dose. Additional 25 mg doses could be administered between signs/symptoms of inadequate block. Within 30 minutes of the end of the surgery an epidural infusion was started with 10 mg/hour, 20 mg/hour, 30 mg/hour, or a placebo of 0.9% sodium chloride in the four treatment groups respectively. The total dose of ropivacaine administered (test dose + bolus dose for induction of anesthesia + additional doses for maintenance) before infusion for post-operative pain relief was started in each treatment group was not kept constant for all patients.

RESULTS AND DISCUSSION

Plasma concentrations of ropivacaine increased with time during the last 11 hours of epidural infusion. Since the terminal half-life of ropivacaine through epidural infusion is about 4-5 hours, presumably steady state was not achieved at the end of 21 hours of infusion resulting in the rising plasma concentrations that were seen. The mean plasma C_{max}'s were 1.1, 1.7, and 2.3 mg/liter at the three different infusion rates of 10, 20, 30 mg/hour of ropivacaine (total doses at these infusion rates were 220, 440, and 630 mg ropivacaine not including ropivacaine administered prior to these infusions). The increase in C_{max} was not proportional to the infusion rate of ropivacaine but levelled off (Table 2). The mean $AUC_{10\text{-}21\ hours}$'s were also not proportional to the dose and levelled off. Comparing the plasma concentrations of ropivacaine (total concentrations over 10-21 hours and free concentration at 21 hours) obtained with identical infusion rates used in healthy volunteers with loading doses of single epidural injections of 10, 20, and 30 mg (study I9), the plasma concentrations were twice as high in this study presumably because of the higher loading doses of 90-150 mg.

Several complicating factors that could have contributed to this dose non-proportionality are; (1) different loading doses in the patients (90-140 mg) (2) systemic volume changes due to the infusion of electrolyte solutions and possible loss of blood during the surgical procedures, and (3) concurrent administration of a long list of several different drugs.

CONCLUSIONS

The objective of dose proportionality of ropivacaine when infused for post-operative pain relief at three different infusion rates of 10, 20, and 30 mg/hour was not realized. However, the results of this study support the labelling claims of the sponsor regarding the comparison of the plasma levels of this study with those of study I9.

COMMENTS

1 Collection of blood samples for only the last 11 hours of infusion did not permit proper characterization of the AUC. Blood samples at time points beginning with the first dose ofropivacaine administered could have facilitated calculation of AUC from time zero to 21 hours through induction of anesthesia, maintenance of anesthesia, and finally during post-operative pain relief and relate it to the dose of ropivacaine each patient received. The study as conducted does not permit the characterization of the AUC during the early periods which might be different in the different subjects.

Table 1. Mean C_{max} and $AUC_{11\text{-}21\ hours}$ parameter values at the three different epidural infusion rates of 10, 20, 30 mg/hour of ropivacaine for post-operative pain relief in patients undergoing lower abdominal surgery (mean (% CV)).

Pharmacokinetic parameters	10 mg/hour ropivacaine	20 mg/hour ropivacaine#	30 mg/hour ropivacaine*
C_{max}, mg/liter	1.1 (48)	1.74 (39)	2.3 (46)
$AUC_{10\text{-}21\ hours}$, mg minute/liter	599 (43)	941 (36)	1205 (48)

† n = 10, # n = 8, * n=10

Table 2. Ratios of C_{max} and $AUC_{10\text{-}21\ hours}$ at three infusion rates of 10, 20, and 30 mg ropivacaine.

Pharmacokinetic parameters	(20 mg/hour)/(10 mg/hour)	(30 mg/hour)/(10 mg/hour)	(30 mg/hour)/(20 mg/hour)
C_{max}, mg/liter	1.58	2.09	1.32
$AUC_{10\text{-}21\ hours}$, mg minute/liter	1.57	2.01	1.28

STUDY I14

STUDY TYPE: DOSE-PROPORTIONALITY IN PATIENTS FOR POST-OPERATIVE PAIN RELIEF THROUGH CONTINUOUS EPIDURAL INFUSION

STUDY TITLE: A clinical and pharmacokinetic comparison between ropivacaine and bupivacaine in epidural anaesthesia: A double-blind multi-centre study in women undergoing hysterectomy using 0.5% and 1% ropivacaine and 0.5% bupivacaine.

NDA: 20-533 **SUBMISSION DATE:** March 29,1995 **VOLUME:** 1.50 **STUDY:** I14 90Ro14

CLINICAL INVESTIGATORS:

ANALYTICAL INVESTIGATOR: T.Arvidsson, Ph.D.
Bioanalysis
Astra Pain Control
S-151 85 Södertälje
Sweden

STUDY DESIGN:

Single Dose: Yes **Multiple Dose:** No **Washout Period:** No
Cross-Over: No **Parallel:** Yes **Other Design:** Double-blind, randomized
Fasted: Yes **If fasted, how long (Hours)?** Not specified

SUBJECT BREAKDOWN:

Patients Yes **Young** Yes **Elderly** Yes

Subject Type: Female **Number=** 52 **Female=** 52 **Male=** none
Weight; Mean 68 **Range** **Groups** A, B, C, D **Number=** 13
Age; Mean 42 **Range**

FORMULATION:

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
A	125 mg ropivacaine	Injection (Epidural)	5 mg/mL (25 mL)	471-14-1	949
B	187.5 mg ropivacaine	Injection (Epidural)	7.5 mg/mL (25 mL)	472-17-1	400
C	250 mg ropivacaine	Injection (Epidural)	10 mg/mL (25 mL)	465-10-1	475
D	125 mg bupivacaine	Injection (Epidural)	5 mg/mL (25 mL)	417-44-1	475

ASSAY METHOD: Ropivacaine and bupivacaine in plasma were determined by gas chromatography with a nitrogen-sensitive detector.
ASSAY SENSITIVITY: The limit of determination was 0.03 μmol/L (0.01 μg/mL).

ASSAY ACCURACY: The recovery was 99% (ropivacaine) and 97% (bupivacaine) and the inter-assay precision was 3.4% (ropivacaine 0.33 μg/mL) and 2.3% (bupivacaine 0.27 μg/mL).

BLOOD SAMPLING TIMES: Before, 5, 10, 15, 20 25, 30, 45, 60 minutes and 1.5, 2, 3, 4, 6, 9, 12, 20 ahd 24 hours after injection.

LABELING CLAIMS FROM STUDY: Of the 52 included patients had 41 results valid for a complete pharmacokinetic evaluation. The results were compatible with dose proportionality for C_{max} and AUC after single epidural administration of ropivacaine in doses up to 250 mg. There were no signs of systemic central nervous system effects of ropivacaine after epidural administration.

OBJECTIVE:

To evaluate dose-proportionality in pharmacokinetics after epidural administration of single doses of 125, 187.5, 250 mg of ropivacaine in female patients scheduled for abdominal hysterectomy. Bupivacaine 125 mg was used as an active control.

STUDY DESIGN:

The four parallel groups of female subjects received 25 mL of either 0.5% (125 mg), 0.75% (187.5 mg), 1.0% (250 mg) of ropivacaine, or 0.5% (125 mg) of bupivacaine epidurally over a period of 3 minutes. Pharmacokinetic evaluation was done by analyzing the plasma concentration data for the following parameters; C_{max}, t_{max}, $t_{1/2}$, AUC, and CL (assuming 100% bioavailability). Statistical analysis was performed to test the hypothesis of linear dose relations with zero intercepts for C_{max} and AUC and with the assumptions of no dose dependent differences of $t_{1/2}$, CL and t_{max}.

All tests of statistical hypothesis were made on the two-sided 5% level of significance.

RESULTS AND DISCUSSION:

C_{max} increased proportionally with the dose and C_{max}/dose also increased slightly with dose. The linear regression analysis of C_{max} vs dose resulted in an intercept not significantly different from zero. AUC and AUC/dose increased as the dose increased from mg but plateaued as the dose increased from mg complicating the intrepretation of dose proportionality of AUC with dose. However, AUC/dose at 125 mg and 250 mg doses were very close (0.047 and 0.044). Regression analysis of AUC against dose resulted in an intercept significantly different from zero intercept and with an r^2 value for the regression line of 0.28. The terminal half-life and clearance values were close between 125 and 250 mg doses of ropivacaine while those of 187.5 mg ropivacaine differed somewhat.

Since this study has only female subjects, gender analysis is not feasible in this study. In study 12, 9 male subjects were given an epidural injection of 150 mg, and the pharmacokinetic parameter values obtained were a t1/2 of 4.2 hours, a clearance of 363 mL/minute, C_{max}/dose of 0.0072, and AUC/dose of 0.043. These values compare very well with results of 125 mg ropivacaine

in this study (250 mg ropivacaine was also similar), t1/2 of 4.74 hours, CL of 344 mL/minute, C_{max}/dose of 0.006, and AUC/dose of 0.047. Although, a rigorous statistical analysis was not done examining the gender differences, the preliminary analysis performed here does not seem to indicate any gender differences.

CONCLUSIONS:

The sponsors claim from this study of C_{max} and AUC being compatible with dose proportional behaviour is valid for C_{max} only. AUC was not dose proportional in a strict sense although the 125 mg and 250 mg doses seemed to indicate a dose proportional tendency. Preliminary analysis indicates no gender diffences in ropivacaine's pharmacokinetics.

COMMENTS:

1 The cause for the unusual behavior of the 187.5 mg group of ropivacaine is unknown. From reading the report, it was not readily obvious if these subjects were treated any differently from the others. They seemed to have same demographic characteristics (e.g., age and weight) and have received same kinds of medications (e.g., midazolam and fentanyl). Analytical methodology did not seem to be a problem. The extrapolated AUC comprised less than 10% of total AUC. If the longer surgeries accompanied by loss of blood, infusion of electrolyte solutions, concomitant administration of other drugs contributed to the results seen is unknown.

Table 1. Pharmacokinetic parameter values (mean (% CV)) of ropivacaine after the epidural administration of single doses of 125, 187.5, and 250 mg ropivacaine in female patients scheduled for abdominal hysterectomy.

Pharmacokinetic parameters	125 mg ropivacaine[a]	187.5 mg ropivacaine[b]	250 mg ropivacaine[c]
C_{max}, mg/liter	0.75 (32)	1.2 (30)	1.77 (35)
C_{max}/dose	0.006 (32)	0.0064 (30)	0.0071 (35)
T_{max}, hours	0.65 (63)	0.99 (34)	0.51 (35)
AUC, mg hour/liter	5.82 (34)	11.37 (37)	10.98 (34)
AUC/dose	0.047 (34)	0.061 (37)	0.044 (34)
$t_{1/2}$, hours	4.74 (21)	6.53 (52)	4.07 (45)
CL, mL/minute	344 (27)	283 (45)	367 (27)

[a]n=11, [b]n=9-11, [c]n=11

STUDY 14

STUDY TYPE: PHARMACOKINETICS AND DOSE-PROPORTIONALITY AFTER RECTAL ADMINISTRATION **STUDY:** 14 91Ro42 (part II)

STUDY TITLE: Bioavailability and tolerability of ropivacaine dose and volume response after single rectal doses to volunteers.

NDA: 20-533 **SUBMISSION DATE:** March 29, 1995 **VOLUME:** 1.40

CLINICAL INVESTIGATOR:

ANALYTICAL INVESTIGATOR: T.Arvidsson, Ph.D.
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STUDY DESIGN:
Single Dose: Yes **Washout Period:** Yes
Cross-over: Yes **Other Design:** Four-way crossover with placebo as reference
Fasted: Yes **If fasted, how long (hours)?** 8 hours

SUBJECT BREAKDOWN:
Normal: Yes **Young** Yes **Number=** 20 **Male=** 12 **Female=** 8

Subject Type Male			Subject Type Female		
Weight;	Mean 82	Range	Weight;	Mean 64	Range
Age;	Mean 33	Range	Age;	Mean 35	Range

FORMULATION:

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
Normal	50 mg ropivacaine	Gel (Rectal)	2.54 mg/g (20 mL)	1068-1-1	47 (40 g) 88 (90 g)
Normal	100 mg ropivacaine	Gel (Rectal)	2.54 mg/g (40 mL)	1068-1-1	47 (40 g) 88 (90 g)
Normal	200 mg ropivacaine	Gel (Rectal)	2.54 mg/g (80 mL)	1068-1-1	47 (40 g) 88 (90 g)
Normal	Placebo (hydroxy-methyl-propyl gel)	Gel (Rectal)	(20 mL)	106-3-1	83

PLASMA SAMPLING TIMES: Prior to dosing, 5, 10, 20, 25, 30, 45, 60, 75, 90 minutes, 2, 3, 4, 6, 8, 10 and 12 hours after dosing

URINE SAMPLING TIMES: Collected in intervals 0-2, 2-4, 4-6, 6-8, 8-12 hours a.d.

ASSAY METHOD: Ropivacaine in plasma, gas chromatography with nitrogen-sensitive detection. Urine: Ropivacaine and 3-OH-ropivacaine by liquid chromatography with UV-detection.

ASSAY SENSITIVITY: Plasma: 0.03 µmol/liter (10 µg/liter). Urine: ropivacaine 0.5 µmol/liter, 3-OH-ropivacaine 1 µmol/liter.
ASSAY ACCURACY: Plasma: The recovery was 100% and the inter-assay precision 5.3% (2 µmol/liter). Urine: The recovery was 94% (ropivacaine 15 µmol/liter) and 98% (3-OH-ropivacaine 179 µmol/liter) and the inter-assay precision 2.3% (ropivacaine) and 1.9% (3-OH-ropivacaine).

LABELING CLAIMS FROM STUDY: Of the 20 included subjects 16 had valid results for a complete pharmacokinetic evaluation C_{max} and AUC increased proportionally with dose. The volume of gel did not affect the results. Ropivacaine was extensively metabolized with about 1% excreted unchanged and 3-OH-ropivacaine as the major metabolite. The ropivacaine gel was well tolerated both locally and systemically.

OBJECTIVES

To investigate the tolerability and dose proportionality in absorption after rectal administration of single doses of 50, 100, and 200 mg ropivacaine.

Hyperactive local nervous reflexes seem to be of pathogenic importance in distal ulcerative colitis/proctitis. Blockade of enteric nerves by ropivacaine may reduce the inflammatory response and result in symptomatic relief. This study was undertaken to find out (1) if there is dose proportionality in the systemic absorption of ropivacaine (2) the effect of the volume of the rectal formulation of ropivacaine on the bioavailability in that systemic absorption depends on the site of drug administration in the human rectum and the potential avoidance of presystemic elimination if given close to the anus, and (3) if ropivacaine is tolerated well locally where it is applied.

STUDY DESIGN

Subjects were encouraged to have a defecation in the morning before rectal administration of ropivacaine gel and were recumbent during and the first hour after administration. C_{max}, t_{max}, AUC, $t_{1/2}$ and f_e were the pharmacokinetic parameters that were evaluated.

In order to assess the local tolerability, inspection of the rectal mucosa and anal canal was performed 1-2 days before and within 22-26 hours after each drug administration.

RESULTS AND DISCUSSION

The mean plasma concentration-time profiles after the three rectal doses of 50, 100, and 200 mg ropivacaine showed that the absorption was relatively slow (Figure 1) with similar mean t_{max}'s over the dose range (2.77 - 3.35 hours). Mean C_{max} at the highest dose of 200 mg ropivacaine was 0.88 mg/liter (Table 1). C_{max} exhibted dose proportionality over the dose range with the equation describing the mean regression line being Cmax = 0.004*dose. The hypothesis of zero intercept was not rejected at the 5% level. AUC was also proportional to the dose with the hypothesis of zero intercept not being rejected. The mean regression line was given by the regression equation AUC = 0.027*doseThe mean terminal half-lives were consistent at the three doses and were 2.7, 2.6, and 2.4 hours respectively. The variability between individuals was approximately 3 and 2.5 times

higher than the intra-individual variability for AUC and C_{max} when evaluating the dose normalized parameters. The interindividual variability for AUC was statistically significantly greater than the intraindividual variability. The results obtained in this study were consistent with those of part 2 of study 91Ro42. Between the two parts the intercepts and slopes of the individually fitted regression lines (C_{max} and AUC) did not show any significant differences. Thus the volume of the rectal formulation did nor deem to have an effect on the absorption. Also, carry over or period effects were not significant. The fraction of ropivacaine excreted unchanged (f_e) up to 12 hours was less than 1% at the three doses. However, there was very high variability in the f_e values obtained. Examination of the rectal mucosa and anal canal through rectoscopy did not reveal any changes of clinical significance. There was no apparent correlation between either the observed C_{max} or AUC and the retention time of ropivacaine gel.

CONCLUSIONS

The results support the sponsors labelling claims from this study. Both AUC and C_{max} increased proportionally with dose. The volume of the gel does not seem to have an effect on the absorption.

COMMENTS

1 The sponsors made no reference to rectal administration of ropivacaine for pain relief of rectum in the label.

2 Study includes both male (nine) and female (seven) subjects and gender analysis could have been performed to isolate any such gender differences.

3 Clearance values could not be calculated because of the uncertainty of the total dose absorbed into the system.

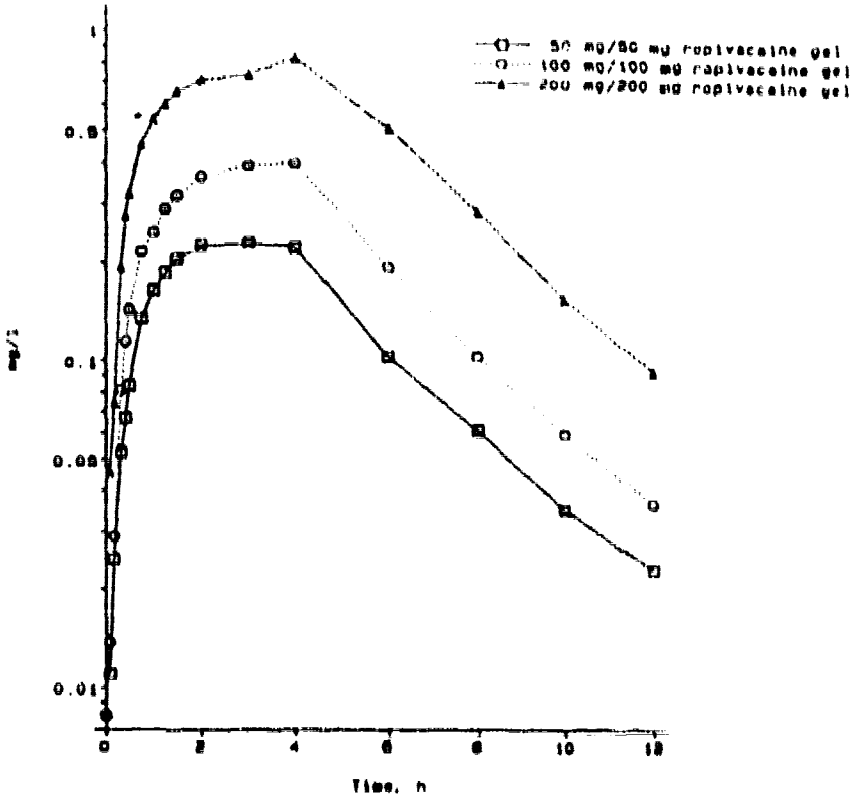

Figure 1. Mean plasma concentration-time profiles of 50, 100, and 200 mg of ropivacaine administered rectally in 20, 40, and 80 mL gel respectively in healthy subjects.

Table 1. Pharmacokinetic parameters of ropivacaine at 50, 100, and 200 mg doses administered rectally in healthy subjects (mean (% CV)).

Pharmacokinetic parameters	50 mg ropivacaine	100 mg ropivacaine	200 mg ropivacaine
C_{max}, mg/liter	0.26 (50)	0.44 (43)	0.88 (41)
t_{max}, hours	2.77 (40)	2.8 (35)	3.35 (37)
$t_{1/2}$, hours	2.69 (35)	2.64 (21)	2.43 (13)
AUC, mg hour/liter	1.47 (52)	2.52 (46)	5.48 (41)
f_e (0-12 hours)	0.34 (176)	0.25 (84)	0.47 (136)

STUDY 117

STUDY TYPE: PHARMACOKINETIC MONITORING AND EFFECT OF INJECTION VOLUME AFTER EPIDURAL INJECTION IN PATIENTS **STUDY:** 117 89Ro07

STUDY TITLE: A comparison of 0.5% and 1% ropivacaine and 0.5% bupivacaine in epidural anaesthesia in patients undergoing surgery for varicose veins or inguinal hernia - a pharmacokinetic evaluation

NDA: 20-533 **SUBMISSION DATE:** March 29, 1995 **VOLUME:** 1.52

CLINICAL INVESTIGATOR:

ANALYTICAL INVESTIGATOR: T.Arvidsson, Ph.D.
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STUDY DESIGN:
Single Dose: Yes **Washout Period:** No **Parallel:** Yes
Other Design: Double-blind (partial), randomized **Fasted:** Not specified

SUBJECT BREAKDOWN:
Patients Yes **Young** Yes **Elderly** Yes

Subject Type: Male				Number= 30	Male= 15		Female= 15
Weight;	Mean 78	Range	kg	Group A	N= 10	M= 4	F= 6
Age;	Mean 54	Range	yrs	Group B	N= 10	M= 5	F= 5
Subject Type: Female				Group C	N= 10	M= 6	F= 4
Weight;	Mean 67	Range	kg				
Age;	Mean 46	Range	yrs				

FORMULATION:

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
A	100 mg ropivacaine	Injection (Epidural)	5 mg/mL (20 mL)	471-9-1	467 (20 mL)
B	100 mg ropivacaine	Injection (Epidural)	10 mg/mL (10 mL)	465-12-1	167 (20 mL)
C	100 mg bupivacaine	Injection (Epidural)	5 mg/mL (20 mL)	417-35-1 *(417-44-1)	474 (20 mL) 475 (20 mL)

*)replacement

PLASMASAMPLING TIMES: Before administration and at 0, 10, 20, 30, 45, 60 and 90 minutes and 2, 4, 6, 8, 10, 24, 26, 28 and 48 hours after end of epidural injection.

ASSAY METHOD: Gas-chromatography with a nitrogen sensitive detector.

ASSAY SENSITIVITY: The limit of determination was set at 0.05 µmol/liter (15 ug/liter).

ASSAY ACCURACY: The recovery was 103% (ropivacaine, 0.5µg/mL) and 100% (bupivacaine 0.8 µmol/liter) and the inter-assay precision was 3.8% (ropivacaine) and 4.1% (bupivacaine).

LABELING CLAIMS FROM STUDY: The systemic kinetics of ropivacaine were not influenced by drug concentration and injected volume, but were significantly different to the kinetics of bupivacaine.

OBJECTIVES

To compare the pharmacokinetics of ropivacaine 5 and 10 mg/mL and bupivacaine 5 mg/mL after administration of standard epidural dose (100 mg) to patients undergoing surgery for varicose veins or inguinal hernia.

This study was done to assess the influence of drug concentration and injected volume of ropivacaine compared to that of bupivacaine. The treatment groups received 100 mg of ropivacaine in 20 mL or 10 mL volume or 100 mg of bupivacaine in 10 mL volume.

STUDY DESIGN

This was a randomized study in 30 patients with three parallel treatment groups. The administration of ropivacaine in 20 mL and bupivacaine 20 mL groups was performed double-blind. The administration of ropivacaine in 10 mL group was known to the investigator (single-blind). C_{max}, t_{max}, AUC, $t_{1/2}$, and CL (assuming 100% bioavailabilty) were the pharmacokinetic parameters evaluated in this study. Statistical analysis of the pharmackinetic parameters was done using the two-sided Wilcoxon rank sum test at 5% significance level.

RESULTS AND DISCUSSION

Mean plasma concentration-time profiles of ropivacaine in 10 mL and 20 mL groups and in bupivacaine 10 mL group is shown in Figure 1. Ropivacaine plasma profiles seem to be similar between the two treatments, with concentrations at most time points being very close. Plasma concentrations of bupivacaine were however lower initially and seemed to decline slower in the terminal phase. The t_{max} was the same between the three treatments, about 25 minutes. The C_{max} was similar between 5 mg/mL and 10 mg/mL ropivacaine but that of 5 mg/mL bupivacaine was significantly lower than that of ropivacaine at both concentrations. The mean $t_{1/2}$ was similar for ropivacaine at both concentrations (about 5 hours) which was shorter than that of bupivacaine (10.6 hours) and significantly different between the two drugs. Mean AUC was identical for the two concentrations of ropivacaine (345 mg minute/liter) while that of bupivacaine was slightly lower (333 mg minute/liter). Mean apparent CL was almost similar between the three treatments.

Ropivacaine undergoes absorption rate-limited elimination when given epidurally. Similar $t_{1/2}$'s between 100 mg ropivacaine given in 10 mL or 20 mL indicates similar absorption. This together with similar concentration-time profiles, C_{max}'s, and AUC's indicates the independency of ropivacaine pharmacokinetics of the injected volume/drug concentration. Significantly longer $t_{1/2}$ of bupivacaine over ropivacaine indicates relatively slower absorption which is consistent with the higher lipophilicity of bupivacaine (higher lipophilicity results in slower absorption from epidural space).

CONCLUSIONS

The results obtained support the sponsors labelling claims from this study. The results show that dose of 100 mg ropivacaine in 20 mL or 10 mL results in similar systemic kinetics. However the pharmacokinetics of ropivacaine were significantly different from those of bupivacaine.

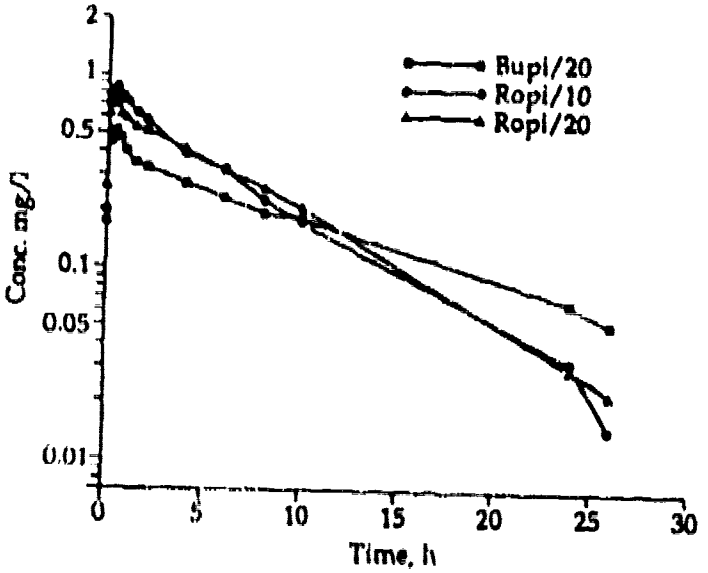

Figure 1. Mean total plasma concentration-time profiles of ropivacaine and bupivacaine after 100 mg dose given epidurally in patients.

Table 1. Pharmacokinetic parameters of ropivacaine (5 and 10 mg/mL) and bupivacaine 5 mg/mL after the administration of a standard dose of 100 mg epidurally in patients undergoing surgery for varicose veins or inguinal hernia (mean (% CV)).

Pharmacokinetic parameters	5 mg/mL ropivacaine	10 mg/mL ropivacaine	5 mg/mL bupivacaine
C_{max}, mg/liter	0.76 (32)	0.93 (32)	0.55 (20)
t_{max}, minute	27 (44)	24 (46)	26 (42)
AUC, mg minute/liter	345 (53)	346 (35)	333 (33)
$t_{1/2}$, hours	5.5 (15)	5.3 (51)	10.6 (41)
CL, mL/minute	314.0 (47)	282.0 (33)	301.0 (44)

STUDY 123

STUDY TYPE: PHARMACOKINETIC MONITORING DURING CONTINUOUS EPIDURAL INFUSION FOR PAIN RELIEF IN LABOR **STUDY:** I23 91RO45

STUDY TITLE: A pharmacokinetic study with continuous epidural infusion of ropivacaine and bupivacaine for pain relief in labour

NDA: 20-533 **SUBMISSION DATE:** March 29, 1995 **VOLUME:** 1.61

CLINICAL INVESTIGATOR:

ANALYTICAL INVESTIGATOR: T.Arvidsson, Ph.D.
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STUDY DESIGN:
Single Dose: No **Multiple Dose:** Continuous epidural infusion
Cross-Over: No **Parallel:** Yes **Other Design:** Double-blind, randomized
Fasted: Not specified

SUBJECT BREAKDOWN:
Normal Yes **Patients** Yes **Young** Yes **Number=** 30 **Male=none** **Female=** 30
Weight; **Mean** 74 **Range** kg **Group A** **Female=** 6
Age; **Mean** 28 **Range** yrs **Group B** **Female=** 12
Group C **Female=** 12

FORMULATION:

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
A	12.5 m 12.5 mg/hour ropivacaine	Injection (Epidural - bolus + infusion)	1.25 mg/mL	570-5-1 570-6-1	477 (20 mL) 356 (50 mL)
B	25+25 mg/hour ropivacaine	Injection (Epidural - bolus + infusion)	2.5 mg/mL	470-15-1 470-14-1	499 (20 mL) 1538 (50 mL)
C	25+25 mg/hour bupivacaine	Injection (Epidural - bolus + infusion)	2.5 mg/mL	416-55-1 416-54-1	708 (20 mL) 1314 (50 mL)

PLASMA SAMPLING TIMES: Before dose, 0, 10, 20, 30, 40 and 60 minutes after start of infusion + every second hour until delivery + at delivery + 2, 4, 6, 12 and 24 hours post infusion

ASSAY METHOD: The total plasma concentration of ropivacaine and bupivacaine were determined by gas-chromatography with a nitrogen sensitive detector. The free plasma levels of ropivacaine and bupivacaine were determined by coupled column liquid chromatography with UV-

detection.

ASSAY SENSITIVITY: The limit of determination was set at 0.03 µmol/L (10 µg/mL) for both ropivacaine and bupivacaine. The limit of determination of free ropivacaine and bupivacaine was set at 0.01 µmol/mL (3 µg/mL) for both.

ASSAY ACCURACY: Total concentration: The recovery was 104% (ropivacaine) and 100% (bupivacaine) and the inter-assay precision was 2.9% (ropivacaine, at 0.8 µmol/mL) and 3.9% (bupivacaine, at 0.9 µmol/mL). Free concentration: The recovery of aqueous controls was 101% (ropivacaine and bupivacaine at 0.7 µmol/mL). The inter-assay precision of plasma ultrafiltrate was 7.2 % (ropivacaine at 0.24 µmol/mL) and 5.6% (bupivacaine at 0.16 µmol/mL).

LABELING CLAIMS FROM STUDY: 12.5 mg/h gave poor analgesia. With 25 mg/hour ropivacaine vs bupivacaine: Total C_{max} (maternal, umbilical) were higher, $t_{1/2}$, was shorter and CL lower after ropivacaine. Mode of delivery was not different. (Apgar, NACS, acid-base status from umbilical cord) did not indicate any obvious negative effect in either group.

OBJECTIVES

To evaluate and compare the drug disposition in mother and new-born (umbilical cord) following continuous epidural infusion of ropivacaine and bupivacaine for pain relief after labor.

Along with the increased volume of distribution associated with pregnancy, there is an engorgement of the vertebral veins and a hyperkinetic circulation which may affect absorption of ropivacaine from the epidural space. Ropivacaine is lipophilic and therefore equilibrates rapidly across the placenta. Also, the α_1-acid glycoprotein levels are low in neonates and there is a possibility of free levels of ropivacaine being high in them during pregnancy. This study was conducted to evaluate ropivacaine plasma levels in the mother and in the umbilical cord when it is administered for pain relief during labor.

STUDY DESIGN

In a parallel study, 30 pregnant women were administered a continuous lumbar epidural infusion of ropivacaine 12.5 mg/hour, 25 mg/hour or bupivacaine 25 mg/hour until delivery. 12.5 mg/hour ropivacaine group of patients were dropped from the study due to insufficient analgesia and consequently only ropivacaine 25 mg/hour and bupivacaine 25 mg/hour groups were evaluated in this study. C_{max}, t_{max}, AUC, $t_{1/2}$, Cl_{total}, Cl_u, and f_u were the pharmacokinetic parameters evaluated. The umbilical vein/maternal vein (UV/MV) and umbilical artery/vein (UA/UV) ropivacaine and bupivacaine ratios were also determined. Differences between the ropivacaine and bupivacaine groups were analyzed using the two-sided Wilcoxon rank sum test.

RESULTS AND DISCUSSION

The mean duration of infusions were 6.2 hours and 8.2 hours, corresponding to mean doses of 180 mg and 227 mg of ropivacaine and bupivacaine respectively. The mean C_{max}'s were 1.05 and 0.8 mg/liter for ropivacaine and bupivacaine (Table 1). The mean $t_{1/2}$ was shorter after ropivacaine than after bupivacaine, 5.1 vs. 8.6 hours, and the total plasma clearance was lower, 223 vs. 299 mL/minute. The umbilical venous unbound plasma concentration was higher after ropivacaine than after bupivacaine (0.05 vs. 0.03 mg/liter). The mean umbilical venous unbound fraction was 0.17 with ropivacaine and 0.12 with bupivacaine and the unbound UV/MV ratios did

not seem to increase with the duration of the infusion indicating rapid equilibrium. The umbilical total plasma concentrations of the two drugs were similar in both venous and arterial plasma. The umbilical unbound venous plasma concentration was higher after ropivacaine than after bupivacaine. Evaluation of the new-borns using criteria such as Apgar scores, NACS, acid-base status from umbilical cord did not indicate any obvious detrimental effect of ropivacaine and bupivacaine on the behavior.

COMMENTS

The results support the sponsors labelling claims from this study. With 25 mg/hour ropivacaine vs bupivacaine: Total C_{max} (maternal, umbilical) were higher, $t_{1/2}$, was shorter and CL lower after ropivacaine. Evaluations of the new-born using criteria such as Apgar scores, NACS, acid-base status from umbilical cord did not indicate any obvious negative effect in either group (ropivacaine and bupivacaine).

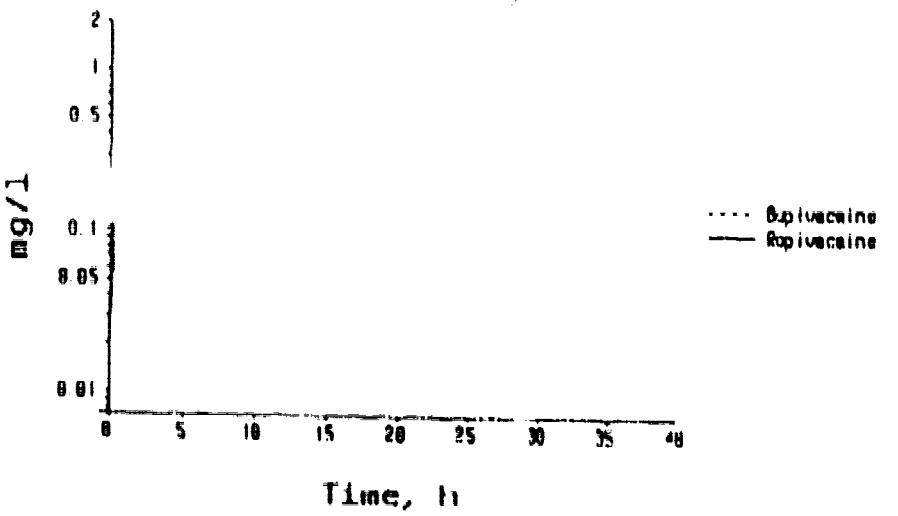

Figure 1. Plasma concentration-time profiles (individual subjects) of ropivacaine and bupivacaine after the continuous epidural infusion of 25 mg/hour dose until delivery.

Table 1. Pharmacokinetic parameters after the continuous epidural infusion of 25 mg/hour ropivacaine and bupivacaine during labour (mean (% CV)).

Pharmacokinetic parameters	Ropivacaine	Bupivacaine
Dose administered, mg	179.2 (24)	226.7 (38)
C_{max}, mg/liter	1.05 (27)	0.8 (28)
Time to delivery, hours	6.26 (27)	8.17 (42)
AUC, mg hour/liter	12.4 (29)	12.3 (45)
$t_{1/2}$, hours	5.1 (35)	8.6 (38)
Cl_{tot}, mL/minute	223 (27)	299 (31)
Cl_u, liter/minute	3.35 ± 41	6.4 ± 39
f_u	0.07 ± 29	0.05 ± 20

STUDY 118

STUDY TYPE: PHARMACOKINETICS AFTER EPIDURAL INJECTION FOR CESAREAN SECTION

STUDY TITLE: A double-blind comparative study between ropivacaine and bupivacaine in epidural anesthesia for Caesarean section. **STUDY:** 118 90Ro33

NDA: 20-533 **SUBMISSION DATE:** March 29, 1995 **VOLUME:** 1.53

CLINICALS INVESTIGATOR:

ANALYTICAL INVESTIGATOR: T.Arvidsson, Ph.D.
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STUDY DESIGN:
Single Dose Yes **Parallel:** Yes **Other Design:** Part I: Open. Part II: Double-blind, randomized.
Fasted: Not specified

SUBJECT BREAKDOWN:
Normal Yes **Patients** Yes **Young** Yes **Subject Type** Female

Weight: Mean 74 Range kg
Age: Mean 32 Range yrs

Group Part I N= 5 F= 5
Group Part II N= 60 F= 60
Group A N= 29 F= 29
Group B N= 31 F= 31

FORMULATION:

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
Part I	150 mg ropivacaine	Injection (Epidural)	5 mg/mL	0863111613	2425
A	150 mg ropivacaine	Injection (Epidural)	5 mg/mL	0863111613	2425
B	150 mg bupivacaine	Injection (Epidural)	5 mg/mL	1033105128	30880

PLASMA SAMPLING TIMES: Part I: Before, 30 minutes after injection and at time of delivery. Part II: Before, end of injection (0), 5, 10, 20, 30 and 60 minutes and 2, 4, 6, 8 12 and 24 hours after end of injection.

ASSAY METHOD: Total concentration of ropivacaine and bupivacaine in plasma was determined using gas-chromatography with a nitrogen sensitive detector. Free concentration of both ropivacaine and bupivacaine was determined using coupled column liquid chromatography with UV-detection.

ASSAY SENSITIVITY: The limit of determination for the total conc was set at 0.03 µmol/L (10

μg/mL) for both ropivacaine and bupivacaine and for the free conc at 0.01 μmol/L (3 ng/mL).

ASSAY ACCURACY: Total concentration: The recovery of control samples was 98% and 97% for ropivacaine and bupivacaine (at 1.3 μmol/mL). The inter-assay precision was 2.4% and 4.8% (ropivacaine, bupivacaine 1.3 μmol/mL). Free concentration: The recovery of aqueous control samples was 98% (ropivacaine) and 103% (bupivacaine) at 0.3 μmol/mL. The inter-assay precision of plasma ultrafiltrate was 8% for both compounds.

LABELING CLAIMS FROM STUDY: Maximum concentration of ropivacaine and bupivacaine was 1.3 and 1.0 mg/mL respectively. The free concentration of ropivacaine in mother and baby at delivery was 0.1 and 0.07 mg/mL respectively, and twice as high as for bupivacaine.

OBJECTIVES

To estimate the plasma concentrations of ropivacaine (part A) and ropivacaine and bupivacaine (part B) in both mother and child.

STUDY DESIGN

This study consisted of two parts, A and B. Part A was a pilot study for the more definitive part B study.

Part A: Five patients received 30 mL of 0.5% ropivacaine (150 mg) and 5 mL blood was sampled prior to drug administration, 30 minutes after injection and at the time of delivery for determination of total and free drug and α_1-acid glycoprotein concentrations (umbilical artery and vein blood were also sampled at delivery time).

Part B: This study was a randomized, double-blind, comparative, parallel group study with 60 patients. Of these 60 patients, 29 received 30 mL of 0.5% ropivacaine (150 mg) and the remaining 30 received 30 mL of 0.5% bupivacaine (150 mg). From 10 patients in each group receiving ropivacaine or bupivacaine, blood was sampled at before drug administration, at end of injection, 5, 10, 20, 30, 60 minutes and 2, 4, 6, 8, 12, and 24 hours after injection and also at the time of delivery. In all the 60 patients, blood was sampled at delivery from both mother vein and umbilical vein and arteries for the determination of total and free drug and α_1-acid glycoprotein concentrations. C_{max}, t_{max}, AUC, CL (assuming 100% bioavailability), free fractions and the ratios of umbilical artery to vein concentrations (UA/UV), and umbilical vein to mother vein concentrations (UV/MV) were were evaluated. Population analysis was also performed on the data.

RESULTS AND DISCUSSION

At the time of delivery, both total and unbound concentrations of ropivacaine and bupivacaine in the mother were higher than in the neonate. The mean total concentration was 1.25 mg/liter in the mother and 0.37 mg/liter in the neonate. The corresponding unbound concentrations were 0.089 mg/liters and 0.06 mg/liters. The mean ratio of unbound concentrations in umbilical vein/maternal vein at the time of delivery was 0.74. The mean unbound fraction was 0.07 in maternal and 0.18 in fetal plasma. Total C_{max} in maternal plasma was similar after both drugs, as was total plasma clearance but the terminal half-life was shorter after ropivacaine (Table 1). The mean unbound plasma clearance of ropivacaine was lower, 2.8 liter/minute, compared to

liter/minute. The unbound concentrations of ropivacaine were twice as high as the unbound concentrations of bupivacaine. The mean unbound fraction of ropivacaine in maternal plasma, 0.09, was also higher than for bupivacaine, 0.06 (Table 2). the unbound fraction of both drugs was higher in the umbilical vein, 0.25 vs 0.17. The maternal total drug concentration was higher than in the neonate for both ropivacaine and bupivacaine. The total umbilical vein concentration was also somewhat higher than the arterial concentration. The unbound concentration of the two drugs in the neonate was about 70-75 % of the unbound concentration in the mother, and the unbound concentrations in the umbilical vein and umbilical artery were almost the same. The umbilical vein/maternal vein ratios as well as the umbilical artery/umbilical vein ratios were similar after ropivacaine and bupivacaine for both the total and unbound drug at the time of delivery, indicating a similar transplacental passage of the drugs (Table 3). The umbilical vein/maternal vein ratio (UV/MV) of both the total and unbound drug as well as the umbilical artery/umbilical vein ratio (UA/UV) did not seem to be related to the time from drug administration to delivery.

NONMEM ANALYSIS;

Data sets were not provided along with this study report and no attempt was made by this reviewer to reanalyze the data. In this analysis, information was obtained regarding the absorption of ropivacaine given epidurally along with ropivacaine's plasma protein binding parameters (Kd and N). In an earlier study, absorption of ropivacaine was characterized thoroughly using Deconvolution techniques (Study I2). The protein binding parameters obtained in the NONMEM analysis were associated with very poor precision. Since, the NONMEM analysis did not contribute significant information or reliable estimates, no further effort was made to reanalyze the data and instead results of the NONMEM analysis were reviewed.

The pharmacokinetic submodel used to describe the data was a one-compartment model with two parallel first-order absorption rates and a first order disposition constant. This corresponds with the biphasic absorptive process as characterized in study I2. By using the unbound and total concentration obtained at the same time points, a covariate submodel for the protein binding was produced. For both ropivacaine and bupivacaine, a significant relationship was found between the unbound, total, and α_1-acid glycoprotein concentrations. In the case of ropivacaine a saturable relationship best described the data, whereas for bupivacaine, a linear relationship was adequate. These models were then combined in order to use all the maternal vein data relating the total concentrations to the unbound concentrations via the protein binding models. The absorption half-lives were estimated to be 7.7 minutes and 6.5 hours for bupivacaine and the fraction of drug absorbed by the slow route was estimated to be 80%. The disposition half-life was 41 minutes. The absorption half-lives for bupivacaine were estimated to be 5.3 minutes and 10.3 hours with the slow absorption phase estimated to comprise 86% of absorption. The unbound clearances were 3.3 and 4.2 liters/minute and the unbound volume of distribution was 192 and 212 liters respectively for ropivacaine and bupivacaine. The dissociation constant (Kd) for the binding of ropivacaine to α_1-acid glycoprotein was estimated to be 0.29 mg/liter and the number of binding sites 1. However, the precision regarding these estimates was poor, with large standard errors (30-40%).

Comparing the results of ropivacaine obtained in this analysis with those of study I2, the slow absorptive process comprised only 50% in study I2. This difference could be reflected in

inadequate and sub-optimum sampling points during the absorptive phase and also to the different subject composition in the present study (pregnant subjects as opposed to healthy males in study I2).

Table 1. Pharmacokinetic parameters of ropivacaine and bupivacaine after the epidural administration of 140 mg dose for patients undergoing cesarian section (mean (% CV)).

Pharmacokinetic parameters	Ropivacaine	Bupivacaine
C_{max}, mg/liters	1.3 (22)	1.1 (29)
t_{max}, hours	0.71 (37)	0.43 (38)
AUC, mg hour/liter	9.8 (40)	8.4 (32)
$t_{1/2}$, hours	5.2 (37)	10.9 (31)
CL, mL/minute	256 (36)	286 (25)
CL_u, liters/minute	2.8 (100)	4.8 (106)

Table 2. Plasma concentrations and free fractions of ropivacaine and bupivacaine at the time of delivery in maternal (MV), umbilical vein (UV), and umbilical artery (UA). The difference in concentrations between ropivacaine and bupivacaine groups was tested with Wilcoxon signed rank test (mean (% CV)).

Parameter	Ropivacaine	Bupivacaine
C_{MV}	1.1 (21)	0.85 (28)
C_{UV}	0.32 (50)	0.26 (38)
C_{UA}	0.22 (40)	0.19 (53)
Cu_{MV}	0.099 (26)	0.055 (25)
Cu_{UV}	0.072 (22)	0.041 (27)
Cu_{UA}	0.073 (22)	0.038 (32)
$f_{u,MV}$	0.092 (25)	0.067 (33)
$f_{u,UV}$	0.25 (28)	0.17 (26)
$f_{u,UA}$	0.3 (26)	0.15 (24)

Table 3. Umbilical vein/maternal vein (UV/MV) and umbilical artery/vein (UA/UV) ratios (mean (% CV)) for ropivacaine and bupivacaine (total and free concentrations).

Parameter	Ropivacaine	Bupivacaine
UV/MV (total)	0.29 (41)	0.32 (44)
UV/MV (free)	0.72 (18)	0.76 (21)
UA/UV (total)	0.72 (104)	0.70 (19)
UA/UV (free)	0.92 (8)	0.89 (16)

STUDY 124

STUDY TYPE: PHARMACOKINETICS AFTER BRACHIAL PLEXUS BLOCK IN PATIENTS.

STUDY TITLE: Plasma concentrations of ropivacaine given with or without epinephrine for brachial plexus block.

NDA: 20-533 **SUBMISSION DATE:** March 29, 1995 **VOLUME:** 1.62 **STUDY:** I24 87Ro11-01

CLINICAL INVESTIGATOR:

ANALYTICAL INVESTIGATOR: T.Arvidsson, Ph.D. Bioanalysis Astra Pain Control AB S-151 85 Södertälje, Sweden

STUDY DESIGN:
Single Dose: Yes **Parallel:** Yes **Other Design:** Open non-randomized, part in multi-center
Fasted: Not specified

SUBJECT BREAKDOWN:
Patients Yes **Young** Yes **Elderly** Yes **Number=** 17 **Male=** 17 **Female=**none
Weight; **Mean** 73 **Range** kg **Group A** N= 9 M= 9
Age; **Mean** 47 **Range** yrs **Group B** N= 8 M= 8

FORMULATION:

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
A	190 mg ropivacaine + epinephrine 5µg/mL	Injection (Brachial plexus)	5 mg/mL	483-4-1	411 (20 mL)
B	190 mg ropivacaine	Injection (Brachial plexus)	5 mg/mL	471-7-1	375 (20 mL)

PLASMA SAMPLING TIMES: 0, 5, 10, 15, 20, 25, 30, 45, 60 and 90 minutes and 2, 3, 4, 6, 9 and 12 hours after end of the injection.

ASSAY METHOD: Capillary gas chromatography with nitrogen phosphorus detection.

ASSAY SENSITIVITY: Limit of determination was set at 0.1 µmol/liter (30 µg/liter).

ASSAY ACCURACY: The recovery of the method was 102% and the inter-assay precision 7.9% at 1.1 µmol/liter.

LABELING CLAIMS FROM STUDY: No differences of C_{max}, t_{max}, and AUC between the two treatment groups. Indication of slow systemic µptake was associated with the duration of the block.

Some unexpected high individual plasma levels in four patients 23 mg/L (without) and 21 mg/L (with epinephrine) as the highest observed C_{max}. No signs of systemic toxicity.

OBJECTIVES

To assess the pharmacokinetics of 0.5% ropivacaine with or without epinephrine when used for brachial plexus anesthesia in patients undergoing orthopedic surgery.

Epinephrine injected locally in conjunction with a local anesthetic constricts blood vessels and enhances their activity by decreasing their systemic absorption. This study was conducted to determine whether epinephrine produces the same effect with ropivacaine i.e, to monitor plasma concentrations and find out if in the presence of epinephrine the plasma levels are lowered.

STUDY DESIGN

The patients received a single injection of 33 mL of 0.5% ropivacaine with or without 5 μg/mL epinephrine. C_{max}, t_{max}, AUC_{0-12} hours, and $t_{1/2}$ were the pharmacokinetic parameters estimated. For statistical analysis, the two groups were compared by the use of a two-sided Wilcoxon rank sum test with $p<0.05$ considered statistically significant using the Hodges-Lehman estimate.

RESULTS AND DISCUSSION

On a mean basis, the parameter values of C_{max}, t_{max}, $AUC_{0-12\ hours}$ and $t_{1/2}$ were similar between ropivacaine administered for brachial plexus block with and without epinephrine (Table 1). There was no statistical difference in any of the pharmacokinetic parameters indicating that presence of epinephrine did not produce any effect on the pharmacokinetics of ropivacaine (Table 2). Very high C_{max}'s of 10 to 23 mg/mL were seen in four patients (Figure 1). Inspite of these very high C_{max}'s, no adverse events were reported by these patients. However, midalozam was one of the concurrently administered drugs and it could have potentially blocked the CNS side effects that ropivacaine causes at toxic concentrations. The sponsors claim that these high C_{max}'s could have been an artifact (samples were re-analyzed but came out the same) as results from a similar study at another center in 17 patients gave small mean C_{max}'s (study I25 Ro11-02). The mean C_{max}'s with and without epinephrine were 1.59 ± 40 and 1.26 ± 33 mg/liter respectively with a maximum C_{max} of 2.91 mg/liter in this latter study (Table1).

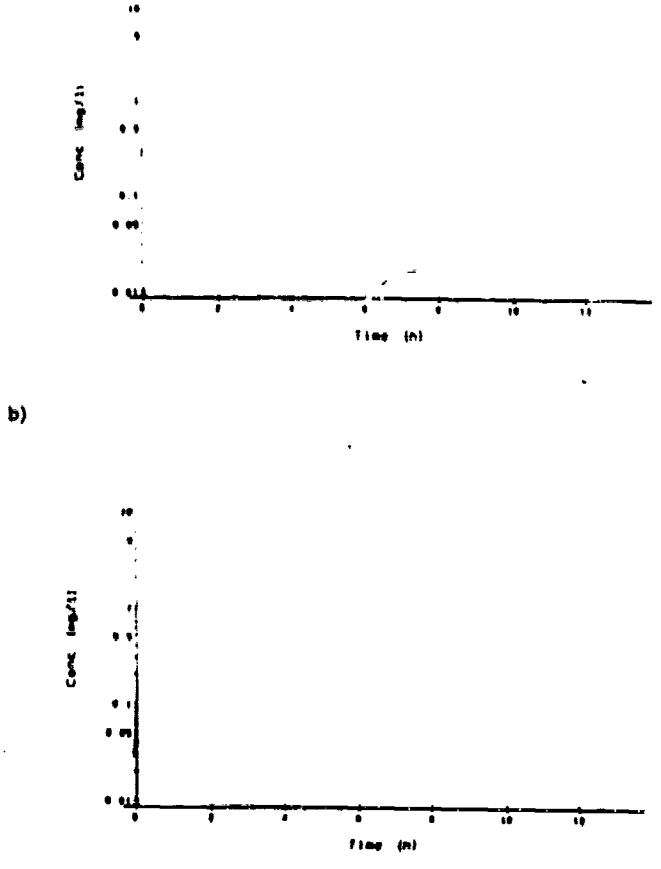
The $t_{1/2}$ of ropivacaine obtained in this study (6 hours) was longer than after iv infusion (2 hours) indicating that ropivacaine is undergoing absorption dependent elimination, absorption being very slow. Comparing the effect of epinephrine on ropivacaine obtained in this study with that on bupivacaine, lower peak concentrations resulted in the presence of epinephrine for bupivacaine. Earlier reports showed that ropivacaine increases vascular smooth muscle activity and decreases blood flow at the site of injection. Since, blood flow is already reduced, presence of epinephrine did not change the pharmacokinetics of ropivacaine. On the other hand presence of epinephrine reduced the blood flow resulting in lower plasma levels for bupivacaine.

CONCLUSIONS

The study supports the sponsors labelling claims from this study. No statistical differences were found between mean C_{max}'s and $AUC_{0\text{-}12\ hours}$ of ropivacaine administered for brachial plexus block with and without epinephrine. Systemic uptake was slow from the injection site. Four patients had very high C_{max}'s of 23.05, 20.69, 14.38, and 10.48 mg/liter respectively. Inspite of these high C_{max}'s no toxicity symptoms were noticed in any of the patients.

COMMENTS

1 Blood was sampled for only 12 hours after ropivacaine administration. In light of the slow absorption of ropivacaine after brachial plexus block, this sampling period was not adequate to perform a thorough pharmacokinetic analysis and as such the calculated $t_{1/2}$ should be treated with caution.



b)

Figure 1. Plasma concentrations of ropivacaine after single administration of 190 mg ropivacaine in (a) individual patients without epinephrine (b) individual patients with epinephrine.

Table 1. Pharmacokinetic parameter values after the administration of 190 mg ropivacaine with or without epinephrine for brachial plexus anesthesia.

Pharmacokinetic parameters	This study		Study I25 87Ro11-02	
	With epinephrine	Without epinephrine	With epinephrine	Without epinephrine
C_{max}, mg/liter				
mean	5.82	5.81	1.59	1.26
CV	109	143	40	33
maximum	20.7	23.05	2.91	1.98
minimum	1.04	0.71	0.82	0.85
t_{max}, hours				
mean	0.54	0.5	0.8	0.79
CV	109	130	53	36
maximum	2.0	2.0	1.5	1.0
minimum	0.08	0.08	0.42	0.42
$AUC_{0-12\ hours}$, mg liter/hour				
mean	8.69	11.55	7.66	6.95
CV	43	98	47	49
maximum	14.93	32.51	13.26	12.64
minimum	4.4	2.78	3.11	3.95
$t_{1/2}$, hours				
mean	6.78	5.74	5.8	8.0
CV	72	47	52	49
maximum	18.58	10.82	11.1	13.8
minimum	3.05	2.15	2.8	4.3

Table 2. 95% confidence intervals (based on Wilcoxon rank sum test) for difference in pharmacokinetic parameters derived from plasma concentrations after the administration of 190 mg ropivacaine with and without epinephrine.

Pharmacokinetic parameters	[redacted]	Lower limit	Upper limit
C_{max}	1.03	-3.9	5.7
t_{max}	0.00	0.34	0.42
AUC_{0-12}	0.17	-15.4	4.89
$t_{1/2}$	0.19	-2.79	2.98

STUDY 110

STUDY TYPE: PHARMACOKINETICS AFTER INTERCOSTAL BLOCK

STUDY TITLE: Pharmacokinetics of ropivacaine and bupivacaine when used for intercostal block in healthy male volunteers

NDA: 20-533 **SUBMISSION DATE:** March 29, 1995 **VOLUME:** 1.48 **STUDY:** 110 91Ro52

CLINICAL INVESTIGATOR:

ANALYTICAL INVESTIGATOR: T.Arvidsson, Ph.D. Bioanalysis Astra Pain Control AB S-151 85 Södertälje, Sweden

STUDY DESIGN:
Single Dose: Yes **Parallel:** Yes **Other Design:** Double-blind, randomized
FASTED: Yes **If fasted, how long (hours)?** From midnight prior the study day and until 3 hours after the administration.

SUBJECT BREAKDOWN:
Normal Yes **Young** Yes **Group** Normal **Number=** 14 **Male=** 14 **Female=** none
Weight; **Mean** 76 **Range** kg **Group** A **N=** 7 **M=**7
Age; **Mean** 32 **Range** yrs **Group** B **N=** 7 **M=** 7

FORMULATION:

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
A	140 mg ropivacaine	Injection (Intercostal)	2.5 mg/mL (56 mL)	0858111612	2640
B	140 mg bupivacaine	Injection (Intercostal)	2.5 mg/mL (56 mL)	109094	30215

PLASMA SAMPLING TIMES: Before, 0, 2.5, 5, 10, 15, 20, 30, 45 and 60 minutes and 2, 3, 4, 6, 8, 10, 12, 16, 20, 22 and 24 hours after end of drug injection.

ASSAY METHOD: Gas-chromatography with nitrogen-sensitive detector was used for determination of total conc of both ropivacaine and bupivacaine. A coupled-column liquid chromatography technique with UV-detection was used for determination of free concentration of both compounds.

ASSAY SENSITIVITY: The limit of determination of total concentration was set at 0.03 µmol/liter (11 µg/liter) for both ropivacaine and bupivacaine. The limit of determination of both free ropivacaine and free bupivacaine was set at 0.01 µmol/liter (3 µg/liter).

ASSAY ACCURACY: Total concentration: The recovery was 100% (ropivacaine) and 98%

(bupivacaine) and the inter-assay precision was 6% (ropivacaine) and 4% (bupivacaine) at 0.2 μg/mL (ropivacaine) and 0.7 μmol/liter (bupivacaine). Free concentration: The recovery of aqueous controls was 99% for both ropivacaine (0.16 μg/mL) and bupivacaine (0.4 μmol/liter). The inter-assay precision of plasma ultrafiltrate was 5.2% (ropivacaine 0.026 μg/mL) and 3.9% (bupivacaine 0.05 μmol/liter).

LABELING CLAIMS FROM STUDY: Ropivacaine and bupivacaine gave similar maximum total plasma concentrations of about 1 mg/liter and occurred at about 25-35 minutes (medians). The terminal $t_{\frac{1}{2}}$ of ropivacaine and bupivacaine were 2.3 and 4.6 hours respectively.

OBJECTIVES

To study the systemic plasma concentrations of ropivacaine compared to those of bupivacaine when administered for bilateral intercostal nerve block in healthy volunteers.

Intercostal block is used for acute and chronic pain control and for providing analgesia after upper abdominal and thoracic surgery. Vascular absorption of local anesthetics occurs more rapidly after intercostal injections than after other commonly used regional techniques, resulting in the highest plasma concentrations and risk of systemic toxicity. This study was performed to study the pharmacokinetics of ropivacaine and compare it with that of bupivacaine after an intercostal nerve block.

STUDY DESIGN

Skin infiltration over each of the 14 block sites was accomplished by making skin wheal over the site using 40 mg lidocaine without adrenaline. The total dose of 140 mg ropivacaine and bupivacaine was divided in 14 intercostal injections in each subject. The blockade was made in the region of the posterior axillary line with the subject in the prone position. The subjects were recumbent during the first three hours following the drug administration. C_{max}, t_{max}, AUC, $t_{1/2}$, CL (assuming 100% bioavailabilty), and free fraction were estimated from the plasma concentration-time data. For statistical analysis, the two groups were compared by the use of a two-sided Wilcoxon rank sum test with $p<0.05$ considered statistically significant.

RESULTS AND DISCUSSION

The mean plasma concentration-time profiles after the intercostal administration of 140 mg ropivacaine and bupivacaine in two different healthy groups show that both ropivacaine and bupivacaine were absorbed quite rapidly followed by a relatively short terminal elimination phase for ropivacaine and a relatively longer elimination phase for bupivacaine (Figure 1). Although the mean C_{max} was slightly higher for ropivacaine over bupivacaine (1.06 mg/liter vs. 0.92 mg/liter), they were statistically insignificant (Table 1). The mean t_{max} calculation for ropivacaine was complicated by the presence of secondary peaks in three of the 7 subjects. Inclusion of the secondary peak in subject gave a mean value of 53 ± 160(CV) minutes while inclusion of the first peak in the same subject, the t_{max} was 21 ± 43(CV) minutes. The t_{max} for bupivacaine was 30 minutes. The $t_{1/2}$ of ropivacaine was 2.3 hours and was considerably shorter than that of bupivacaine of 4.6 hours. The CL value (425 mL/minute) was slightly lower for ropivacaine when compared with that of bupivacaine (549 mL/minute). Comparing the $t_{1/2}$ and CL values of ropivacaine obtained in this

study after intercostal block with those obtained after iv infusion, the CL was slightly lower and the $t_{1/2}$ was similar.

The plasma concentrations of lidocaine (used for making skin wheals) reached maximum levels with a wide range mg/liter) within minutes. Since 14 skin wheals had to be performed, this means plasma levels of lidocaine are substantial and should be considered from a toxicity standpoint in the overall evaluation of systemic plasma concentrations of ropivacaine after intercostal administration. However there were no adverse effects that were related to the high plasma concentrations of ropivacaine and lidocaine in this study.

CONCLUSIONS

The results support the sponsors labelling claims from this study. Ropivacaine and bupivacaine gave similar mean maximum plasma concentrations of about 1 mg/liter with t_{max}'s of 25-30 minutes. The terminal $t_{1/2}$'s were 2.3 and 4.6 hours for ropivacaine and bupivacaine respectively.

COMMENTS

1 This study was completed in healthy volunteers and is the only study submitted in support of this indication. As such, there is no information regarding the pharmacokinetics of ropivacaine in patients where there is a possibility of existence of several complicating factors such as surgery, concurrent administration of other drugs etc.

2 It is apparent that lidocaine concentrations will be substantially higher after interostal block because of the mode of administration with a possibility of pharmacokinetic interaction between ropivacaine and lidocaine. Because of the lack of control group in this study, an evaluation of such an interaction was not feasible.

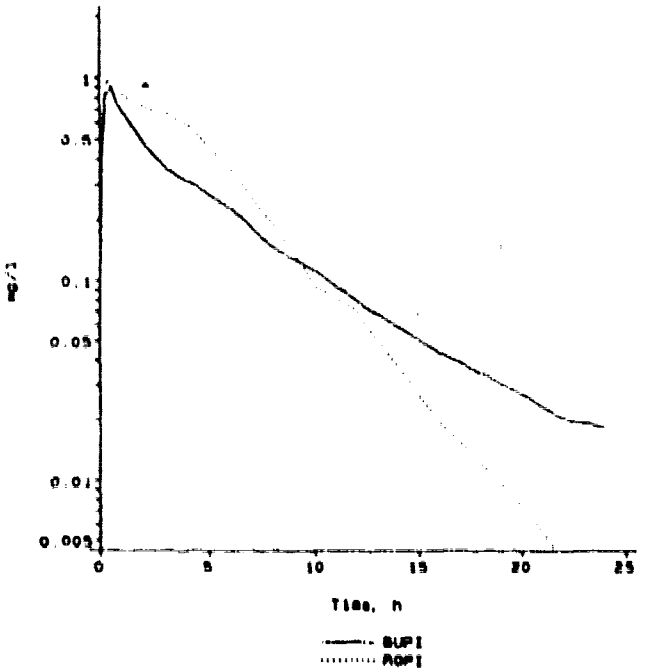


Figure 1. Mean total plasma concentration-time profiles of ropivacaine (n=7) and bupivacaine (n=7) after intercostal administration of 140 mg.

Table 1. Pharmacokinetic parameters after the intercostal administration of 140 mg each of ropivacaine and bupivacaine in healthy subjects (mean (CV)).

Pharmacokinetic parameter	140 mg ropivacaine (intercostal)	140 mg bupivacaine (intercostal)
C_{max}, mg/liter	1.06 (34)	0.92 (24)
T_{max}, minutes	53 (160)	30 (27)
AUC, mg minute/liter	306 (25)	243 (28)
$t_{1/2}$, hours	2.3 (35)	4.6 (57)
CL, mL/minute	425 (24)	549 (30)

STUDY I29

STUDY TYPE: PLASMA MONITORING AND DOSE PROPORTIONALITY OF INFILTRATION ROPIVACAINE FOR POST-SURGERY PAIN RELIEF.

STUDY TITLE: A double-blind, placebo-controlled comparison between 0.125%, 0.25% and 0.5% ropivacaine when used for postoperative infiltration in outpatients herniorraphies: A dose-response study - a pharmacokinetic evaluation.

NDA:20-533 **SUBMISSION DATE:**March 29, 1995 **VOLUME:**1.66 **STUDY:**I29 90Ro19

CLINICAL INVESTIGATOR:

ANALYTICAL INVESTIGATOR: T.Arvidsson, Ph.D. Bioanalysis Astra Pain Control S-151 85 Södertälje, Sweden

STUDY DESIGN:
Single Dose: Yes **Parallel:** Yes **Other Design:** Double-blind, randomized
Fasted: Not specified

SUBJECT BREAKDOWN:

Patients	**Yes**	**Young** Yes	**Elderly** Yes	**Number=** 38	**Male=38** **Female=**none
Weight;	**Mean** 82	**Range**	kg	**Groups** A, B	N= 10
Age;	**Mean** 56	**Range**	yrs	**Groups** C, D	N= 10

FORMULATION:

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot size Size
A	37.5 mg ropivacaine	Injection (Infiltration)	1.25 mg/mL (30 mL)	570-5-1	477
B	75 mg ropivacaine	Injection (Infiltration)	2.5 mg/mL (30 mL)	470-15-1	499
C	150 mg ropivacaine	Injection (Infiltration)	5 mg/mL (30 mL)	471-17-1	1399
D	Sodium chloride	Injection (Infiltration)	9 mg/mL (30 mL)	400-57-1	949

PLASMA SAMPLING TIMES: Before (0), 15, 30, 45, 60, 90 and 120 minutes after wound infiltration

ASSAY METHOD: Gas-chromatography with a nitrogen-sensitive detector.

ASSAY SENSITIVITY: The limit of determination was set at 0.03 µmol/liter (10 µg/liter).

ASSAY ACCURACY: The recovery was 100% and the inter-assay precision was 4.8% (1.5 µmol/liter).

LABELING CLAIMS FROM STUDY: The absorption of ropivacaine was slow. The increase in C_{max} and AUC_{0-2h} were proportional to the dose, with maximum plasma levels of 0.4-0.6 mg/liter after 150 mg.

OBJECTIVES

To estimate the maximum plasma concentration (C_{max}) and the time to reach C_{max} after three doses of ropivacaine given by wound infiltration postoperatively.

Postoperative infiltration of surgical wounds by ropivacaine has the potential of decreasing postoperative pain and the demand for narcotic analgesics after surgery. This study focusses on the absorption of ropivacaine into the systemic circulation from the view point of toxicity.

STUDY DESIGN

The study was a randomized, double-blind, multi-centre trial with four parallel treatment groups consisting of 32 male patients. The patients received postoperative wound infiltration during wound closure 37.5 mg ropivacaine (1.25 mg/mL), 75 mg ropivacaine (2.5 mg/mL), 150 mg ropivacaine (5 mg/mL) or physiological saline (for efficacy measurements). The surgery for elective inguinal herniorraphy was performed under spinal lidocaine injection. Blood was sampled at pre-infiltration and at 15, 30, 45, 60, 90 and 120 minutes after wound infiltration (total blood sampled was about 40 mL). The pharmacokinetic parameters calculated to evaluate the treatments were C_{max} and AUC_{0-2} (AUC from 0 to 2 hours).

RESULTS AND DISCUSSION

After post-operative wound infiltration the mean plasma concentration-time profiles of ropivacaine at 37.5, 75, and 150 mg doses rise to plateau concentrations around 45 minutes and remained at the plateau level for the remainder of the sampling period (75 minutes). Incomplete sampling period did not permit the observation of a declining phase and its associated terminal half-life at any of the three doses (Figure 1). The C_{max}'s and AUC_{0-2}'s of ropivacaine increased with increasing doses (Table 1). The mean C_{max} at the highest dose of 150 mg was 0.46 mg/liter, which is very much smaller than 1.92 mg/liter through iv infusion (80 mg dose), 1.09 mg/liter through epidural infusion (150 mg dose), and 1.1 mg/liter after intercostal administration (140 mg dose). A linear regression model with an intercept fitted the C_{max} (r^2=0.962) and AUC (r^2=0.958) data well with the intercept not significantly different from zero. This indicates dose-proportional behaviour of ropivacaine in the dose range of mg when administered by local wound infiltration.

CONCLUSIONS

The C_{max} after the highest dose of 150 mg used for infiltration was very much lower than the corresponding C_{max}'s after the highest doses administered through intravenous, epidural and intercostal modes of administration. Dose proportionality was demonstrated for both C_{max} and AUC_{0-2} in the dose range of mg ropivacaine and supports the sponsor's labelling claims

COMMENTS

1 Although the maximum dose used in this study was 150 mg, it is lower than the maximum recommended dose of 200 mg for post-operative pain management through infiltration (in study 128, dose proportionality was demonstrated upto a dose of 175 mg with a corresponding C_{max} of 1.3 mg/liter) and there is no data available for dose proportionality from 175-200 mg.

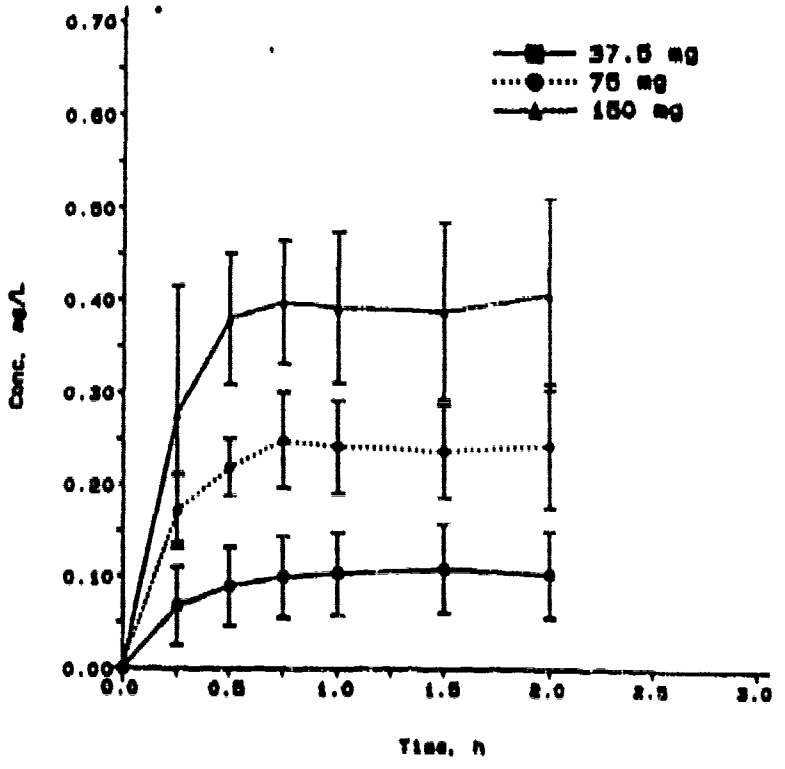


Figure 1. Mean plasma concentration-time profiles of ropivacaine base over the first two hours after post-surgery wound infiltration with 37.5, 75, and 150 mg.

Table 1. Pharmacokinetic parameter values (mean (CV)) after post-surgery wound infiltration with 37.5, 75, and 150 mg ropivacaine given in 30 mL over 2 minutes.

Pharmacokinetic Parameter	37.5 mg ropivacaine	75 mg ropivacaine	150 mg ropivacaine
C_{max}, mg/liter	0.11 (45)	0.27 (15)	0.46 (17)
T_{max}, minutes	81 (52)	63 (57)	70 (63)
AUC_{0-1}, mg minute/liter	10.7 (45)	26.9 (18)	42.8 (19)

10.0. APPENDIX II

10.1. DRUG FORMULATION DEVELOPMENT:

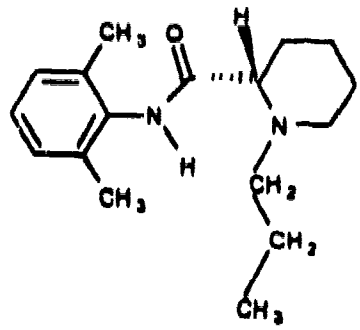
Chemistry And Nomenclature:

Chemical name;

(S)-(-)-1-Propyl-2',6'-pipecoloxylidide hydrochloride monohydrate.

According to IUPAC rules, the name is (S)-(-)-1-Propyl-piperidine-2-carboxylic acid (2,6-dimethyl-phenyl)-amide hydrochloride monohydrate.

Structural formula:



Molecularformula: $C_{17}H_{26}N_2O \times HCl \times H_2O$

Molecular weight: 328.89 (as hydrochloride monohydrate), 274.43 (as base)

Generic name: Ropivacaine hydrochloride monohydrate

Laboratory code name:

Chemical And Physical Properties:

Ropivacaine is a white crystalline powder with a melting range of 269.5-270.6° C. The pK_a value is 8.07 at 25° C. The pH of a 1 % solution (w/v) of the compound is about 5. The solubility in water at 25° C is 0.164 mol/liter (53.8 mg/mL). The solubility in physiological sodium chloride solution at 20°C and at different pH values is tabulated below [IIC1].

The distribution ratio ($D=C_{oct}/C_{aq}$) at 25 C° between n-octanol and phosphate buffer at pH 7.4 is 141 (log D = 2.15) [IIC1].

Ropivacaine is clearly less lipid soluble than bupivacaine. Its uptake into human epidural and human subcutaneous fat in vitro was intermediate between that of bupivacaine and lidocaine [X40].

Table 1. Solubility of ropivacaine in physiological sodium chloride solution at 20°C and at different pH values.

pH	Solubility mol/lx10^{-3}	mg/mL
3.1	98	32
4.0	93	31
5.3	97	32
5.8	82	27
7.0	5.6	1.8
8.0	0.79	0.26
8.5	0.47	0.15

Drug Formulation:

In a tolerability study with a simultaneous crossover design, 10 volunteers were given intradermal injections (0.1 mL) of ropivacaine in 4 different formulations using 7 test sites on the volar side of the lower arms [J5]. Injection of bupivacaine (Marcain®, Astra 5 mg/ml), physiological saline and needle insertion without subsequent injection were used as controls. The ropivacaine test solutions all contained 5 mg/mL in NaCl 8 mg/mL, NaCl 6 mg/mL, $CaCl_2$ 12 mg/mL, or Ringer solution. The bupivacaine solution contained 5 mg/mL and NaCl 8 mg/mL. The solutions were isotonic with the exception of the ropivacaine solution containing NaCl 6 mg/mL. Pain perception after needle insertion and, after recession of this pain, intradermal injection, and immediate vascular or other local effects and those observed after 24 hours were recorded.

There was a large variability of the pain perceived upon needle insertion. An even wider variability in the pain response was observed in connection with the injection of the test solutions. With the exception of saline, the 5 mg/mL ropivacaine in Ringer solution had a lower mean pain score than the other test solutions. The bupivacaine solution induced a higher pain score than saline. All test solutions induced local reactions, pallor or redness, in the injected areas. The lowest frequency of such reactions was observed after injection of saline, the highest after bupivacaine. The pain caused by the injected solutions was considered to be a local irritation caused by a combination of the vehicle, the local anesthetic, and a physical distension effect.

It was concluded that ropivacaine 5 mg/mL, in a vehicle made isotonic with sodium chloride 8 mg/mL, is suitable for infiltration, as it was not found to induce a higher frequency of initial pain in this study than that of the physiological saline solution. A formulation of ropivacaine made isotonic with sodium chloride has been used throughout the clinical program.

10.2. ANALYTICAL TECHNIQUES FOR BIOLOGICAL FLUIDS:

In all body fluids, concentrations are reported as ropivacaine base or bupivacaine base. Ropivacaine (base) 1 µmol/liter = 0.274 mg/liter.

Precision is defined as a measure of random error (repeatability) and is expressed as its coefficient of variation (CV).

Accuracy is defined as a measure of systematic error and expressed as percentage recovery.

TOTAL CONCENTRATION OF ROPIVACAINE IN PLASMA AND URINE:

Ropivacaine Determined By Gas Chromatography;

A specific GC method was used, comprising a capillary column with a cross-linked methyl-silicone phase and with helium as carrier gas. Splitless injection and detection with a nitrogen-sensitive (NP) detector were carried out.

Plasma and urine: After addition of the internal standard (1-pentyl-2',6'-pipecoloxylidide) the sample is made alkaline and ropivacaine is extracted into a mixture of n-hexane or n-heptane and methylene chloride (4:1,v/v). The organic layer is evaporated to dryness, the residue dissolved in a mixture of n-hexane or n-heptane and ethanol (9:1,v/v) and the solution is injected into the gas chromatograph.

Using 1 mL of plasma or urine, dissolving the evaporation residue in 200 to 250 μL and injection of 1 to 5 μL into the gas chromatograph, allows the determination of concentrations as low as about 0.02 μmol/liter in plasma and urine (CV = 5-14 % - inter-assay precision; the lower figure obtained after optimization of the GC column and the temperature program).

The accuracy of the method is close to 100 %. A plot of the peak height ratios of ropivacaine to the internal standard against concentration of ropivacaine is linear at least up to 5 μmol/liter when 1 mL of plasma or urine is used for analysis.

Plasma determinations of total concentrations of lidocaine and bupivacaine (used in comparative studies) were made according to the same principles as for ropivacaine. For lidocaine, however, the internal standard is 2-diethylamino-2',4',6'-trimethylacetate anilide. The sensitivity and linearity of standard curves are similar to those of ropivacaine. The inter-assay precision (CV) is about 6 % for bupivacaine (0.07 μmol/liter) and about 10 % for lidocaine (0.04 μmol/liter) when 1 mL of sample is used for analysis.

Ropivacaine And [$^2H_3$]-Ropivacaine Determined By Gas Chromatography/Mass Spectrometry;

The total amount of ropivacaine and [$^2H_3$]-ropivacaine was determined by gas chromatography/mass spectrometry using chemical ionization. The compounds were extracted employing a procedure similar to that described above for ropivacaine in plasma and urine. The internal standard is [$^2H_7$]-ropivacaine. The evaporation residue is dissolved in toluene (9:1,v/v). Separation is effectuated on a capillary column with cross-linked methyl silicone.

The selected ions, m/z, are 275, 278, and 282. The limit of determination is set at 0.03 μmol/l, the accuracy of the method is close to 100 %, and the inter-assay precision is about 10 % (CV) for ropivacaine and about 13 % (CV) for [$^2H_3$]-ropivacaine in plasma at about 0.15 μmol/l. The precision is somewhat higher in urine for both compounds.

A standard curve for the peak height ratios of ropivacaine and [$^2H_3$]-ropivacaine to the internal standard was plotted each time an analysis was carried out. As the curve is not linear over the whole concentration range, it was divided into two sections. The whole concentration range is from

μmol/liter.

Unbound Concentrations in Plasma;

Unbound (free) concentrations of ropivacaine and bupivacaine have been determined in human plasma.

About 1.5 mL of plasma is held at 37°C and the pH adjusted to 7.4 by bubbling CO_2 through it. A 1-ml aliquot is then ultrafiltered at 37°C with centrifugation at 2,000 rpm for 15 minutes. To avoid adsorption of the drug, parts of the ultrafilter device are washed with RBS solution, rinsed with water, and dried before use.

The concentration of the drug in the plasma ultrafiltrate is determined by liquid chromatography with UV detection at 210 nm after direct injection.

Two coupled systems are used. Due to low unbound concentrations of the drugs, larger volumes of ultrafiltrate have to be injected, which increases the risk of interfering peaks. The first system consists of a reversed-phase column and a mixture of pH 3 phosphate buffer and acetonitrile as the eluent. The second system uses a strong cation exchange column and a mixture of acetonitrile and phosphate buffer (pH 2.6) with a higher ionic strength than the first system. The ultrafiltrate is injected into the first system and the eluate is passed through a 1-ml loop of the second system. When ropivacaine appears in the loop, it is injected on the cation exchange column using the eluent from the first system. Ropivacaine is enriched at the top of the column and then eluated with the eluent for the second system.

Concentration of unknown samples are calculated by means of external standardization using a single plotted point calibration or from a standard curve from standards dissolved in pH 7.4 phosphate buffer. The concentrations of the standard solutions are chosen to be similar to those of the samples. At least 6 standard solutions are analyzed.

For determinations in human plasma, linearity has been verified between 0.01 and about 0.5 μmol/l. The limit of determination is 0.01-0.03 μmol/liter with a precision of about 5 % (CV). At a concentration of 0.1 μmol/liter the precision is 1.5 % (CV).

Control samples from spiked blank plasma are used to determine the overall precision of the analytical procedure. In human plasma the coefficient of variation is about 6 % at a unbound concentration of 0.2 μmol/liter.

The accuracy of the overall procedure, determined from aqueous control standards, is over 90 %. Due to the high degree of protein binding, the effect on the unbound fraction, caused by adsorption of the drug to the ultrafiltration device, can be regarded as negligible.

All these parameters which may influence the protein binding equilibrium, such as pH, temperature, and degree of adsorption, have been carefully studied and are well controlled.

α_1-Acid Glycoprotein in Human Plasma:

α_1-acid glycoprotein (AAG) is determined using an immunodiffusion technique. A commercially available kit (NOR-Partigen® acid-α_1-glycoprotein) from Behring is used and the diameters of the precipitation zones are measured. For each plate, a standard curve is plotted from three or four dilutions of a standard human serum and is used to quantify the concentration of AAG in the plasma samples. A control plasma sample is always run in parallel. The square of the diameter of the precipitation zones is plotted versus the concentrations of AAG in the standards. A linear range of up to about 20 μmol/liter is used. The limit of determination is set at 2 μmol/liter. The accuracy of the method is close to 100 % and the precision (CV) is 5-10 % at a concentration of 20 μmol/liter.

Racemization of Ropivacaine in Urine Samples from Man;

The urine samples are made alkaline, extracted with n-heptane and centrifuged and the organic phase is evaporated to dryness at 40°C. The residue is dissolved in 200 μL of pH 6 phosphate buffer and an aliquot (100 μL) of the solution is injected in a chromatographic system consisting of a chiral-AGP column. The two enantiomers are easily separated on this column, especially at 50°C.
Urine standards are prepared at two concentration levels and treated in the same way as the samples. They contain 0-6 % R-form calculated on the basis of the S-form.
The accuracy of the method is over 90 % and the limit of determination is 0.2 %.

Metabolites in Human Plasma and Urine

Metabolites of ropivacaine which were measured in human plasma and urine are 3-hydroxy-2,6-pipecoloxylidide, 2,6-pipecoloxylidide,
3-hydroxy-1-propyl-2,6-pipecoloxylidide (3-hydroxy-ropivacaine) and
4-hydroxy-1-propyl-2,6-pipecoloxylidide (4-hydroxy-ropivacaine). In addition , 2,6-dimethylaniline (2,6-xylidine) was determined in plasma. The internal standards used in the method are the ethyl- and isopropyl analogues of ropivacaine and 1-ethyl-3-hydroxy-2,6-pipecoloxylidide.
The sample is first hydrolyzed with hydrochloric acid to determine the total amounts of conjugated and unconjugated hydroxyl-metabolites, then extracted on a solid-phase column (cation exchange) and finally the metabolites are determined by step-gradient reversed-phase chromatography and detection by UV at 210 nm. The gradient systems include 5-15 mmol/liter of sodium octanesulfonic acid in mixtures of acetonitrile and pH 2 phosphate buffer. In most cases unmetabolized ropivacaine in the samples is determined by the same method.
In plasma, unconjugated metabolites are determined separately as well, i.e. hydrolysis of the samples is omitted while the total amounts of conjugated and unconjugated metabolites can only be determined after hydrolysis of ultrafiltered plasma. Direct injection of such ultrafiltered plasma can be sufficient to determine the possible presence of 2,6-dimethylaniline.
The limits of determination are about μmol/liter for ropivacaine and μmol/l for all metabolites except 2,6-dimethylaniline, where μmol/liter can be measured. The limits are somewhat lower in plasma than in urine.
The accuracy of the methods is close to 100 % for all metabolites. Curves plotted from up to seven standards are used for quantification . In urine, linearity has been proved for the major metabolite (3-hydroxy-ropivacaine) between μmol/liter while the range for the other metabolites is μmol/liter. In plasma, linear ranges between μmol/liter are used for quantification.
The inter-assay precision at concentrations close to the limit of determination is about 10 % (CV) for ropivacaine and 2,6-pipecoloxy-lidide and somewhat higher (CV= about 5 %) for the other metabolites.
3-Hydroxy-ropivacaine, the major metabolite in human urine, was also analyzed together with ropivacaine in a separate study. A somewhat simpler method was used, comprising hydrolysis, solid-phase extraction on a cation exchange column, and a simple reversed-phase chromatographic separation with UV detection at 210 nm. Linearity is tested between μmol/liter for ropivacaine and μmol/liter for the metabolite. The limits of determination are μmol/l for

ropivacaine and μmol/liter for the metabolite, with a precision of about 9 % (CV) for ropivacaine and about 5 % (CV at 18 μmol/liter) for the metabolite.

Validation;

All analytical test procedures were carefully validated before continuous use and then during use in clinical studies.

Validation data for all clinical studies where samples have been analyzed at Analytical Chemistry, Astra Pain Control, are documented as of 1991 in Validation Reports for each study. These reports include linearity of standard curves, precision, accuracy, limit of determination selectivity, records of reanalyzed samples (including the reason for reanalysis), and storage of raw data.
The absence of metabolic racemization of ropivacaine (the S-(-)-form) was verified in separate studies in man and in the dog, rat, and sheep using a chiral separation system. Thus, the use of achiral separation systems for quantification of ropivacaine in body fluids was considered sufficient.

Stability in Biological Fluids;

The stability of ropivacaine, including the unbound concentration as well as the metabolites 3-hydroxy-ropivacaine, 4-hydroxy-ropivacaine, PPX and 3-hydroxy-PPX has been tested in spiked plasma and urine samples. No sign of degradation was observed in plasma when ropivacaine was tested at -20° C for 6 months [IIQ3, IIQ19] and the metabolites for 5 months [IIQ26]. Ropivacaine showed no degradation in the urine when tested at -4° C for 4 months [IIQ10]; neither did the metabolites when tested in urine for one year [IIQ26].

10.3. PHARMACOKINETIC ANALYSIS:

The area under the plasma concentration-time curve (AUC) was calculated using the trapezoidal rule or log-trapezoidal rule and extrapolated to infinity (AUC_∞ or total AUC) using estimates of the log-linear terminal slope, β. $AUC_\infty = AUC_{0-n} + C_n/\beta$, where C_n is the last measurable plasma concentration. Plasma clearance (CL) was estimated from the ratio of dose (ropivacaine base) and AUC_∞. Estimates of unbound clearance (CL_u) were made as the ratio of CL and f_u, where f_u is the unbound fraction in plasma. Renal clearance was calculated as the product of plasma clearance and f_e, the fraction of the dose excreted unchanged. The distribution volume at steady state (V_{ss}) was calculated as [(infused dose*AUMC)/$(AUC_\infty)^2$] -[(infused dose*infusion time)/2*AUC_∞], where AUMC is the area under the first moment curve calculated by the linear trapezoidal rule up to C_n and the residual area estimated by integration. The bioavailability of ropivacaine following epidural administration, as compared to a simultaneous intravenous reference dose of [$^2H_3$]-ropivacaine, was derived from the ratio of dose-adjusted estimates of AUC_∞ and by deconvolution.

In most instances pharmacokinetic calculations were done using the pharmacokinetic computer program PHA [X66] written in the BS/1 command language

Release 6.08 of the SAS® system under VMS™ has also been used in the analysis and presentation of pharmacokinetic parameters (SAS Institute, 1989, 1990). The computer

program PCNONLIN (SCI Software, Lexington, KY, USA) was used for compartmental analysis. A deconvolution procedure written in PC DOS according to [X67] was used in calculations of the ropivacaine absorption process after epidural administration. Population analysis using the NONMEM program was performed at the University of Uppsala, Uppsala, Sweden.

10.4. STATISTICAL METHODS:

Primarily, robust nonparametric methods have been used. For tests of hypotheses between two groups of data, paired and unpaired, the one- and two-sample Wilcoxon tests, confidence intervals and associated Hodges-Lehmann estimates have been used. For more complex designs, i.e. higher order crossover designs, analysis of variance models have been used, utilizing the within-subject variation and correcting for possible period and carry-over effects. Data have been presented graphically by means of box plots with boxes between the 25th and 75th percentiles and with the median in between. In the report text, the data has been summarized as means (standard deviations). The p-values given are for two-sided tests.

To describe the difference in magnitude (shift in location) between two groups, the Hodges-Lehmann (HL) estimate has sometimes been used. The HL estimate in an unpaired situation is calculated as the median of all possible differences between an observation in one group and an observation in the other group. The HL estimate is an alternative to the difference in means or medians for estimating the difference in magnitude between two groups. It is more robust when it comes to single gross outliers than the difference in means. In some cases, this HL estimate and corresponding confidence interval are calculated for log-transformed data, and then back-transformed to the original scale in order to get a nonparametric estimate and confidence interval for the ratio of the two group medians.

In this summary, the relationship between certain pharmacokinetic response variables (AUC, C_{max}, clearance, and terminal half-life) and some predictors (age, sex, weight, BMI, pregnancy, and dose) have been studied using stepwise regression methods (SAS proc reg with the option selection=stepwise and the significance level 0.10 for entry and for staying in the model). Some of these response variables have also been analyzed in log-scale because of the skewness of the data. A brief description of the outcome of such an analysis is sometimes given in the text in connection with a certain response variable and a certain predictor variable. This is done by specifying the selection order of the predictor among the selected predictors as well as the R^2 value using all the selected predictors. Other predictor variables considered were study, surgical procedure, and type of regional block, which are closely related. These categorical variables were considered one at a time using an analysis of covariance model (SAS proc glm) where the variable was added to the model previously selected by the stepwise procedure.

Date: October 25, 1994

CONTENTS OF APPLICATION FOR ROPIVACAINE

ITEMS 13 AND 14

PATENT INFORMATION AND CERTIFICATION

Ropivacaine is claimed in US Patent Number 4,870,086 "Optically Pure Compound and a Process for Its Preparation," expiration date September 26, 2006 and US Patent Number 4,695,576 "L-N-n-propylpipecolic acid-2,6-xylidide," expiration date September 22, 2004. The owner of these patents, ASTRA LAKEMEDEL AKTIEBOLAG (Sweden), is an affiliate of the applicant.
21 USC 355(b)(2)

In the opinion of the applicant and to the best of its knowledge, there are no other US patents which claim the drug named in this application nor which claim use of the drug for which the applicant seeks approval.
21 USC 355(b)(2)

NDA 20-533
NAROPIN™
(ropivacaine HCl monohydrate)

CERTIFICATION STATEMENT (21 U.S.C. 355a)

Astra USA, Inc., hereby certifies that, to the best of its knowledge, it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Federal Food, Drug, and Cosmetic Act, in connection with this application.

Signed Gillian Black-Noller Date 11/16/94

Gillian Black-Noller, MD.
Associate Director
Clinical Research
Hospital Division

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DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-533 Trade (generic) names Nexium (Esomeprazole IV)

Check any of the following that apply and explain, as necessary, on the next page:

___ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

✓ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. ~~The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).~~ BP

✓ a. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
✓ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: See attached correspondence from Sponsor regarding Commitment to perform pediatric studies

Sponsor has committed to do pediatric studies, per this letter dated March 21, 1996. We have had discussions regarding the proposed studies but have not seen final protocols.

Signature of Preparer

March 13, 1996
Date

Mar 13, 1996

cc: Orig NDA
HFD-170/Div File
NDA Action Package

ROPIVACAINE IN CHILDREN

Introduction

Ropivacaine is a new long-acting local anesthetic that is chemically homologous to amide local anesthetics in present clinical use, e.g. bupivacaine and mepivacaine. Ropivacaine has pharmacodynamic and pharmacokinetic properties resembling those of bupivacaine in animals. However, ropivacaine is less toxic regarding central nervous and cardiovascular systems than bupivacaine in animals and man.

Ropivacaine was developed for use in epidural anesthesia for surgery and for postoperative pain management, local infiltration, and peripheral nerve blocks. Ropivacaine and bupivacaine have comparable potency for sensory block regarding the onset, degree, and duration of sensory block. However, the degree of motor block with ropivacaine has been found to be lower and the duration shorter.

Experience from the use of bupivacaine is available in all age groups but so far the use of ropivacaine has not been documented in children.

A major advance in pediatric anesthesia and postoperative pain management during the past 10 years has been the widespread application of regional anesthesia both as a supplement to general anesthesia intraoperatively and for postoperative use (1). The long duration of action of bupivacaine permits children to emerge from general anesthesia comfortable and without opioid side effects. Caudal epidural blocks and peripheral nerve blocks are therefore commonly used in pediatric ambulatory surgery. In most of these children regional blockade is performed under sedation or general anesthesia. Only for minor procedures and in older children, local anesthesia can be used without supplementation with a sedating agent. In some patient groups (muscular diseases, obstructive lung disorders or neonates with a history of apnea) local anesthesia with sedation may be preferred before general anesthesia (2).

PHARMACOLOGIC CONSIDERATIONS

The pharmacology of local anesthetics is basically the same in children as in adults. There are, however, clinically significant differences that are readily evident in the neonate and the young infant during the first year of life (3).

All the clinically used local anesthetics can be metabolized by children (including neonates), but the capacity may be reduced. The mean terminal half-life of local anesthetics is increased in neonates. However, the maximum peak blood concentration with a comparable dose is lower than in adults. This is in part due to an increased volume of distribution. A lower plasma binding in infants probably contributes to these findings, making a greater proportion of the drug in plasma available for tissue uptake (4). Amide local anesthetics are mainly bound to alpha-1 acid glycoprotein but also to alb umin. The levels of these proteins are low at birth and reach adult levels between 6 and 12 months of age. Due to the prolonged half-life, there are significant risks of accumulation with multiple injections in neonates and small infants (1). However, infants (including neonates) are not more apt to react with systemic toxicity than older children.

In children as well as adults the onset of local anesthesia is more rapid after lidocaine than bupivacaine (5). The duration of anesthesia for local infiltration is about 30-60 min for lidocaine and 90-180 min for bupivacaine. For epidural blocks the duration for lidocaine is approximately 45-90 and for bupivacaine 120-360 min. Long durations are more common in neonates.

The concentration of the drug is of importance for the extent of sensory and motor blocks. In children the myelination of the nerve fibers in the peripheral nerves are not complete until at about 4 years of age. Therefore the same concentration of a local anesthetic may give different effects on motor fibers depending on age (6). Since myelin is a lipidic substance, large myelinated fibers may entrap significant amounts of local anesthetic due to their lipid solubility. Another age-related difference is the reduced amount of epidural fat in infants. This may also be of importance for the availability of the local anesthetic.

An interesting difference when comparing adults and children below the age of 5-8 years, is the hemodynamic effects after central blocks (7). Both after spinal and epidural blocks blood pressure changes are minimal in comparison to those found in adults. The reason for this difference is not clear but the practical consequence is that fluid loading and vasoactive drugs are not required prior to epidural anesthesia in children. Another difference is that micturition problems after epidural blocks are less common in children than in adults.

SAFETY AND DOSAGE

Safe administration guidelines for single doses of local anesthetics have been developed on the basis of pharmacokinetic studies of infants and children receiving wound infiltration, peripheral nerve blocks, or epidural and

interpleural analgesia. The dosage varies with the weight of the child. Peak plasma concentrations occur within 5 to 25 min depending on the route of administration (8). Recommended doses for bupivacaine are 2.0-2.5 mg/kg depending on site of application (1). It must be remembered that local anesthetics can produce toxic symptoms by inadvertent direct administration into veins and arteries, albeit the given dose otherwise is considered to be safe.

When calculating the dose of a local anesthetic, the volume and the concentration of the drug must be considered. For example when performing an epidural caudal block in children about 0.5 ml/kg of the anesthetic solution is needed in order to produce a lumbosacral block (9). The concentration of the drug in the injected solution is then important for the degree and duration of the block. Lower concentrations of the drug may be sufficient in infants and neonates as their nerves are thinner and myelination is incomplete.

Judged from experience in adults equal doses of ropivacaine and bupivacaine in mg could be expected to be effective and safe also in children. Since the potency of these two drugs is comparable, dosage can be based on experience from the use of bupivacaine, i.e. a dose of 2.0-2.5 mg/kg depending on the area of application. Since ropivacaine is less toxic than bupivacaine, such a dosage regimen should be less likely to be associated with toxicity.

Suggested further studies

The aim of the suggested studies is to obtain more information about the local anesthetic effects of ropivacaine in children down to two years of age. Safety aspects such as signs and symptoms of toxicity have to be carefully monitored. Caudal block in children is an easy and safe technique suitable for a wide range of surgery (9). If a long-acting local anesthetic is used, the block will often extend well into the postoperative period, and the technique can be used for day surgery. In these studies other techniques will also be considered, e.g. wound infiltration or ilioinguinal and iliohypogastric nerve blocks that are commonly used for postoperative analgesia after inguinal surgery.

AGE GROUP 8-16 YEARS

In children over the age of 8 years there are no important differences in pharmacokinetics, safety and efficacy for currently available local anesthetics. Therefore results from studies in adults can be used as a basis for the use of ropivacaine in this age group.

AGE GROUP 2-8 YEARS

In the age-group 2-8 years two studies in different centers could be planned. The primary objectives of the studies will be to evaluate safety, pharmacokinetics and postoperative analgetic effect of ropivacaine (2 mg/ml) either as open-label or placebo-controlled studies. The duration of analgesia will be evaluated with techniques suitable for the age of the patients. One study could be in patients receiving epidural caudal blocks in combination with general anesthesia. The volume of the anesthetic solution could be 0.5-1.0 ml/kg, sufficient for an analgetic effect for e.g. circumcision and inguinal hernia operation. In the second study wound infiltration or ilioinguinal and iliohypogastric nerve blocks after inguinal surgery could be evaluated. Also in this study the volume of the anesthetic solution could be 0.5-1.0 ml/kg.

For study reasons the children can be divided into two groups, one mainly with patients aged 2-4 years and one mainly with patients aged 6-8 years. There are several reasons for this division, e.g. different myelinisation of nerve fibers, different techniques for evaluation of pain and different methods for the induction of anesthesia being of importance for the postoperative period.

Conclusion

Ropivacaine is a new long-acting local anesthetic that is closely related to bupivacaine and mepivacaine. Ropivacaine and bupivacaine have comparable potency for sensory block regarding the onset, degree, and duration of sensory block. However, ropivacaine has a lower potential for central nervous system and cardiotoxic effects than bupivacaine in animals and man.

In children aged between 8 and 16 years current dosage regimens for bupivacaine can be applied also for the use of ropivacaine for epidural

anesthesia, local infiltration, and peripheral nerve blocks. Recommended doses for ropivacaine (just as for bupivacaine) could be 2.0-2.5 mg/kg depending on site of application.

In the age group between 2 and 8 years, further studies are planned mainly focusing on safety, postoperative analgesia and pharmacokinetics.

Södertälje, July 25, 1995

ASTRA PAIN CONTROL AB
Clinical R&D

Jan-Robert Jansson, M.D.
Vice President

Lars Larsson, M.D., Ph.D.
Assoc. Prof. in Pediatric Anesthesiology
Medical Advisor

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NDA #: 20-533
NAME: NAROPIN (Ropivacaine)
REVIEWER: C. Philip Larson Jr., M.D.
REVIEW DATE: August 1994
RESUME: Local Anesthetic and Circulatory Effects of Bilateral Ulnar Nerve Blockade with Ropivacaine in Volunteers

1. RESUME

Background

This study was designed to evaluate the effects of ropivacaine 0.25, 0.5, 0.75 and 1% without and with epinephrine 5 ug/ml when injected into a peripheral nerve to produce sensory and motor blockade. Prior studies in animals suggest that ropivacaine is as potent as bupivacaine in producing a peripheral nerve block. No studies of local neurotoxic effects of ropivacaine in man have been reported so this was evaluated as well.

Clinical Study

Investigators: Hans Nolte, M.D., Klinikum Minden, Minden, West Germany
Heinrich Fruhstorfer, M.D., Marburg, West Germany

Study Plan. Forty healthy volunteers were divided randomly into four groups of ten each. Each volunteer received a bilateral ulnar nerve block, with one of four concentrations (0.25, 0.5, 0.75 and 1%) with one side containing plain solution and the other epinephrine 5 ug/ml. One investigator performed all of the blocks (HN) and he was blinded to which study drug was being injected. The ulnar nerve was located with a nerve stimulator, and 2 ml of study drug was injected. During the onset of blockade, loss of sensory, motor and sympathetic function was tested every one minute. Three hours after completion of the block or upon first signs of recovery of nerve function, whichever occurred first, the block was tested in the same manner every hour until first evidence of recovery was found, after which the block was tested every 15 min. Sensory function was tested by the use of heat (42.5°), cold (17.5°) and pinprick over the hypothenar eminence. The volunteer could switch off the stimulus if it was felt, and when the volunteer no longer terminated the stimulus it was concluded that the block was complete. Motor function was tested by having the volunteer abduct the 5th finger and compress a water-filled balloon for 1 sec. A decrease of 50% in abduction force was used as the standard test of motor block. Sympathetic function was tested by measuring skin blood flow over the 5th metacarpal bone using a laser Doppler flowmeter, by measuring skin temperature of the 5th finger and by comparing it to the temperature of the 2nd finger of the same hand. Volunteers were evaluated 1, 7, 30 and 90 days after the study to determine any adverse effects of the blocks.

Efficacy Assessment. The study groups were comparable in age, weight and height. There were deviations in protocol in that three groups (.25, .5, .75% plain) had only nine evaluations, and one group (.25% with epi) had only eight evaluations.

1) Onset Time: The onset of sensory blockade varied from 4 to 28 min but there were no significant differences among the four concentrations used or the presence of epinephrine. The onset time to 50% decrease in abduction force (motor block) varied from 8 to 27 min. for all solutions except 1% with epi where the onset time was 4 min., which was significantly shorter ($p=0.05$) than all other solutions. The onset of sympathetic blockade varied from 6 to 21 min with no significant differences among the concentrations used or the presence of epi with one exception. At 1% solution with epi, the time to 50% temperature difference between the 2nd and 5th digits averaged 4 min, which was significantly shorter than all other times.

2) Duration of block: With the addition of epi, the duration of sensory block varied from 384 to 602 min with no significant differences among the concentrations used. Without epi, the duration of sensory block varied from 365 to 575 min with the times being significantly prolonged at the higher concentrations. With epi, the duration of motor block varied from 373 to 589 min, with none of the times being statistically significantly different. Without epi, the duration varied from 409 to 556 min, with significant prolongation at the higher concentrations. With epi, the duration of sympathetic block varied from 476 to 640 min with no significant differences among the four concentrations used. Without epi, the sympathetic block varied from 421 to 591 min, and the higher concentrations produced a significantly longer block.

Safety Assessment. There were several complications reported by the volunteers. Six reported slight edema at the injection site on day one or seven, two of whom received plain solution and one epi. Three volunteers had bilateral edema. Twenty one volunteers reported pain at the site of injection: in 6 it was bilateral, and in one it was severe, primarily when flexing or extending the elbow or with pressure at the injection site. Ten volunteers reported paraesthesias in the forearm or hand one 5 weeks after the block. Two volunteers had necrosis of the skin over the medial condyle thought to be due to sustained pressure during anesthesia. All adverse events had resolved by 3 months after the blocks. The investigators speculate that the adverse events were due either to trauma to the ulnar nerve at the time of injection from stimulating the nerve electrically through an uninsulated needle, or from hematoma formation, but not to the local anesthetic. They state that subsequent studies (data not provided) show a much lower incidence of those adverse events when an insulated needle is used.

2. CONCLUSIONS

This study demonstrates that ropivacaine is effective in producing a long acting peripheral nerve block. The onset time of sensory, motor or sympathetic block did not vary with the anesthetic concentration in the absence of epi and averaged about 6 to 19 min with no apparent differences among the three modalities evaluated. With the addition of epi, the motor and sympathetic onsets were significantly shortened to 4 min at 1% concentration, and had a larger number of patient been studied, it is likely that the sensory onset would have been significantly shorter as well at the 1% concentration. From this we can conclude that the use of 1% with epi shortens the onset time by about 50% as compared to the other three

concentrations with our without epi. In terms of duration of block, use of the highest concentration without epi produces a longer block, while the addition of epi does not prolong the block appreciably. While adverse events were common in this study, the investigators believe that they were not due to a local toxic effect of ropivacaine, but rather to the use of an uninsulated needle to identify the ulnar nerve using electrical stimulation. They support this conclusion by the fact that the adverse events were not dose related, and when they converted to an insulated needle, the incidence of adverse events markedly decreased. However, no data were provided to support this conclusion.

3. RECOMMENDATIONS REGARDING LABELING:

a) Page 5, lines 192-194: Based on this study the sponsor is able to give specific time for the average onset and duration of peripheral nerve block instead of just saying that it is rapid and long-lasting, which isn't very meaningful to the clinician. Whether the data should appear here or on pages 6-7 can be adjudicated with the sponsor, but clearly the data are different from brachial plexus block and should be so noted.

b) Page 6, lines 243-244 and page 7, lines 245-255: From this study it is clear that the onset time is shorter if the drug is deposited directly on a peripheral nerve, and this should be stated and the average times noted. The fact that the onset time can be nearly halved by the use of epinephrine should also be mentioned. Finally, it should be noted here that the duration of block is greater with the higher concentrations of ropivacaine (with average times given), but the epi does not prolong the block.

c) Pages 6-7: It would be useful to the clinician if the sponsor would refer to the table on page 21 when discussing the data from the clinical trials, since this is where the data were derived.

d) Pages 14-17: Reading through this section I could not find any specific mention of the fairly high incidence of adverse events associated with peripheral nerve block (pain and paraesthesias). I would think that this should be mentioned either more specifically on page 14, lines 18-19 or page 17, lines 146-170.

C. Philip Larson, M.D.
Reviewer

NDA #	20-533
NAME:	NAROPIN (Ropivacaine)
REVIEWER	C Philip Larson Jr., M.D.
REVIEW DATE	August 1994
RESUME	Local Anesthetic and Circulatory Effects of Bilateral Ulnar Nerve Block with Ropivacaine 0.5% and Bupivacaine 0.25% with Epinephrine in Volunteers

1. RESUME

Background

This study was designed to compare the effects of ropivacaine 0.5% with bupivacaine 0.25% both with epinephrine when injected into a peripheral nerve to produce sensory and motor blockade. This concentration of ropivacaine was apparently chosen because it would appear from a prior study that the duration of action is about the same as for bupivacaine 0.25%. The investigators also wanted to evaluate the incidence of adverse events when an insulated needle was used to identify the nerve prior to injection.

Clinical Study

Investigators Hans Nolte, M.D., Klinikum Minden, Minden, West Germany
Heinrich Fruhstorfer, M.D., Marburg, West Germany

Study Plan. Fifteen healthy volunteers were selected to receive a bilateral ulnar nerve block, one side being injected with ropivacaine 0.5% and the other side with bupivacaine 0.25%, both containing epinephrine 5 ug/ml (or 10 ug total dose). One investigator performed all of the blocks (HN) and he was blinded to which study drug was being injected on which side. The ulnar nerve was located with an insulated nerve stimulator, and 2 ml of study drug was injected. During the onset of blockade, loss of sensory, motor and sympathetic function were tested every one minute. Three hours after completion of the block or upon first signs of recovery of nerve function, whichever occurred first, the block was tested in the same manner every hour until first evidence of recovery was found, after which the block was tested every 15 min. Sensory function was tested by the use of heat (42.5°), cold (17.5°) and pinprick over the hypothenar eminence. The volunteer could switch off the stimulus if it was felt, and when the volunteer no longer terminated the stimulus it was concluded that the block was complete. Motor function was tested by having the volunteer abduct the 5th finger and compress a water-filled balloon for 1 sec. A decrease of 50% in abduction force was used as the standard test of motor block. Sympathetic function was tested by measuring skin blood flow over the 5th metacarpal bone using a laser Doppler flowmeter, by measuring skin temperature of the 5th finger and by comparing it to the temperature of the 2nd finger of the same hand. Volunteers were evaluated 1, 7, 30 and 90 days after the study to determine any adverse effects of the t

Efficacy Assessment The study groups were comparable in age, weight and height. There were deviations in protocol in that only 8 to 12 comparative evaluations were made, rather than the 15 as planned The reasons for these deviations are not stated.

1) Onset Time The onset times for all variables varied from 6 to 9 min for ropivacaine, and from 9 to 21 min for bupivacaine. These differences were significantly different for all variables except thermal sensation of warmth, analgesia to pin prick and motor block. However, the average times were always lower for ropivacaine, so had additional patients been studied, it is possible that all variables would have been statistically different.

2) Duration of block The duration of the block varied from 453 to 604 min and was not significantly different for the two agents except for analgesia which averaged 59 min shorter for ropivacaine

Safety Assessment. There were several complications reported by the volunteers. One volunteer given ropivacaine and four given bupivacaine reported slight or moderate pain at the site of injection on the 1st day. One volunteer given ropivacaine also noted hypesthesia in the forearm and hand on day 7 No side effects were noted at 3 months.

2 CONCLUSIONS

This study demonstrates that ropivacaine 0.5% with epinephrine is effective in producing a long acting peripheral nerve block, with a shorter onset time and equivalent duration to bupivacaine 0.25% also with epi. Transient pain and paraesthesias occurred but they were without long-term sequelae.

3. RECOMMENDATIONS REGARDING LABELING:

C. Philip Larson, M.D.
Reviewer

NDA #	20 533
NAME:	NAROPIN (Ropivacaine)
REVIEWER:	C. Philip Larson Jr., M.D.
REVIEW DATE	August 1994
RESUME	Uteroplacental and Fetal Hemodynamics during Extradural Anesthesia with Ropivacaine and Bupivacaine for Cesarean Section

1. RESUME

Background:

This study was designed to compare the effects of ropivacaine with bupivacaine administered epidurally for cesarean section on:

1) blood flow in maternal uterine and placental arcuate arteries
2) blood flow in fetal umbilical, renal and middle cerebral arteries
3) fetal myocardial function
4) free and bound plasma concentrations in mother and fetus
5) spread of sensory and degree of motor block
6) effects on neonatal neurobehavioral tests

Prior studies in animals and man have produced conflicting results concerning the effects bupivacaine on the placental circulation. In one study in vitro, bupivacaine was observed to contract umbilical vascular smooth muscle. In vivo studies suggest either no change or an increase in uteroplacental and fetal circulations with bupivacaine. Similar studies with ropivacaine have not been done.

Clinical Study

Investigators: Arno I Hollmen, M.D., Ph.D., Oulu University Central Hospital

Study Plan. Lumbar epidural anesthesia was administered at L3-4 for cesarean section in 10 healthy patients given bupivacaine and 11 healthy patients given ropivacaine both at a dose of 115 mg (23 ml of 0.5% solution). The cesarean section was done for pelvic disproportion or placenta previa. The investigators were blind to which local anesthetic they were administering. If a sensory level to T4-6 was not achieved in 20 min another 25 mg (5 ml of 0.5% solution) was administered. Five of 11 ropivacaine and 3 of 10 bupivacaine patients received the additional 5 ml dose. Maternal blood samples (5 ml) were drawn prior to and at 0, 5, 10, 20, 30, 40, 50, 60 min, at delivery, and 2, 4, 6, 8, 12 and 24 hrs after delivery for measurement of the total concentration of the local anesthetic. Blood samples were also taken at delivery from the umbilical vein and artery for drug concentration and acid-base status. Maternal heart rate and blood pressure were monitored and recorded every two minutes until delivery, and fetal heart rate was monitored continuously with a cardiotachometer. Maternal and fetal hemodynamic variables were assessed prior to injection, 5 min after injection and when the sensory level reached T4-6 (30-60 min) using a color Doppler ultrasound. Specifically, pulsatility indices were derived by measuring the difference between peak-

systolic and end-diastolic waveforms divided by the averaged maximum flow velocity. An increase in blood velocity waveform index indicates an increase in vascular resistance distal to the point of measurement. Simultaneously, fetal myocardial function was evaluated by M-mode echocardiography. Sensory analgesia using the pin prick test and motor blockade (leg motion) were evaluated at 10, 20, 30 and 60 min prior to delivery and the quality of analgesia was assessed at delivery by the attending anesthesiologist. Apgar scores were recorded at 1, 5 and 15 min after delivery, and neurological and adaptive capacity scores (NACS) were made at 15 min, 2 and 24 hrs post delivery. The blood samples were analyzed for local anesthetic using gas chromatography, and the free fraction by liquid chromatography.

Efficacy Assessment: I could not determine if the two groups were similar in age, weight and height since the only criteria were 18-40 years of age, less than 100 kg in weight, and more than 155 cm in height. There were minor protocol deviations but they did not affect the results.

1) Hemodynamic variables. The only significant differences in blood velocity waveform indices when a level of T4-6 was achieved was an increase in the nonplacental artery after ropivacaine and an increase in the maternal placental and nonplacental artery after bupivacaine. There were no significant differences in fetal blood velocity waveforms with either drug when T4-6 was blocked. Neither drug had any effects on fetal echocardiographic function except for a significant decrease in circumferential shortening of the right ventricle after ropivacaine.

2) Analgesia. The quality of analgesia was judged as satisfactory in all patients. The motor block was variable among the patients, and not appreciably different between the two drugs.

3) Neonatal assessment. The Apgar scores were 8 or greater in all infants 1 min after birth. Two infants in the ropivacaine group had low NACS scores; one at birth most likely due to a low birth weight (2440 g), and the other 2 hrs after delivery, probably due to hypoglycemia. Both infants had normal NACS scores on followup exams.

4) Maternal blood-gas variables: The umbilical artery and venous blood gas variables at delivery were sometimes slightly deviant from the reference values.

5) The Cmax and tmax values for both drugs were similar (1.18 v. 1.21 mg/L and 31 v. 29 min). The maternal free plasma concentration at delivery was almost twice as high for ropivacaine (0.06 v. 0.03 ml/L) so the calculated mean free fraction was also higher for ropivacaine (9 v. 4%). The umbilical arterial and venous free fractions were also higher after ropivacaine compared to bupivacaine (22 v. 12%). The total plasma clearance (CLtot) was not different between the two drugs (248 v. 328 ml/min), but the free plasma clearance (CLu) was significantly higher for bupivacaine (7382 v. 3344 ml/min). The terminal half life (t1/2) was significantly shorter for ropivacaine (5.9 v. 8.8 hr) than for bupivacaine. .The AAG levels were normal in both groups.

Safety Assessment: Maternal blood pressures were satisfactory in all patients but one given bupivacaine who developed hypotension that needed treatment. Maternal heart rates were

satisfactory except for one patient who received ropivacaine who developed a transient tachycardia to 123 beats/min that resolved spontaneously in a few minutes. Fetal bradycardia to a rate of 58 beats/min occurred in the patient who developed hypotension following bupivacaine. Fetal bradycardia to 50 beats/min occurred in one patient given ropivacaine who developed a nodal bradycardia to 44 48 beats/min without hypotension.

2. CONCLUSIONS

This study demonstrates that ropivacaine administered for epidural anesthesia for cesarean section does not have adverse effects on uteroplacental or fetal circulations or on fetal myocardial function. The Cmax and tmax values were the same for both local anesthetics, but the maternal and umbilical free plasma concentrations of ropivacaine were significantly greater than for bupivacaine. The higher free fractions of ropivacaine were not associated with any adverse effects in the fetus.

3. RECOMMENDATIONS REGARDING LABELING:

I didn't find that this study was utilized in the preparation of the labeling. This study did not show a biphasic absorption from the epidural space with two half lives of 14 min and 4 hrs (page 2, lines 63-67). From this study I could not document the statement that "The degree of plasma protein binding in the fetus is less than in the mother resulting in lower total plasma concentrations in the fetus than in the mother" (page 3, lines 85-87). I believe that the comparisons are too few to draw conclusions that are statistically significant.

C. Philip Larson, M.D.
Reviewer

NDA #	20 533
NAME:	NAROPIN (Ropivacaine)
REVIEWER:	C. Philip Larson Jr., M.D.
REVIEW DATE	August 1994
RESUME	Pharmacokinetics of Ropivacaine and Bupivacaine when used for intercostal block in healthy male volunteers

1. RESUME

Background

This study was designed to compare the pharmacokinetics of ropivacaine with bupivacaine when the drugs are injected into the intercostal space to produce an intercostal nerve block. The reason for doing this study was to evaluate the pharmacokinetics of ropivacaine when it is injected into a highly vascular area. It is well known that the vascular absorption of local anesthetics is more rapid after intercostal injection than after other kinds of regional blocks, resulting in the highest plasma concentrations, and hence having the highest risk of systemic toxicity

Clinical Study

Investigators. Gale Thompson, M.D., Virginia Mason Clinic

Study Plan. Bilateral intercostal nerve blocks from T5-11 were performed in 14 healthy male volunteers ranging in age from 29-42 years. The volunteers randomly received injections of either ropivacaine 4 ml (2.5 mg/ml) or bupivacaine 4 ml (2.5 mg/ml) into seven intercostal spaces (T5-11) on each side, for a total dose of 140 mg (56 ml). The injections were completed within four minutes by two anesthesiologists. A skin weal was made at each site using lidocaine before the start of the intercostal blocks. Blood samples (10 ml) were drawn prior to, immediately after, and at 2.5, 5, 10, 15, 20, 30, 45 and 60 min, and 2, 3, 4, 6, 8, 10, 12, 16, 20, 22 and 24 hrs after the end of injection. The blood samples were frozen and sent to Sweden for the analysis of ropivacaine and bupivacaine using gas chromatography. The 5 and 30 min and the 6 and 12 hr samples were also analyzed for free concentrations of both drugs using liquid chromatography. Finally, the blood sample obtained before injection was assayed for alpha-1-acid glycoprotein (AAG) using a radial immunodiffusion technique. Presence of a sensory block was evaluated every 2 hr until the block had disappeared using pin prick, perception of temperature change, and pinching with an Allis clamp.

Efficacy Assessment The study groups were similar in age, weight and height. There were minor protocol deviations but they did not affect the results. The Cmax and tmax values for both drugs were similar (1.06 v. 0.92 mg/L and 21 v. 30 min) if one excludes the data from one patient given ropivacaine who had a second peak at 244 min. This second peak at such a late time is highly likely to be an error in analysis, which is possible because the samples were not analyzed for over six months after procurement. The terminal half life (t1/2) was

significantly shorter for ropivacaine (2.3 hr) than for bupivacaine (4.6 hr). The mean clearance was not significantly different for the two drugs (425 v. 549 ml/min). The free plasma concentration was twice as high for ropivacaine (0.06-0.19 ml/L) compared to bupivacaine (0.03-0.08 mg/L), so the calculated mean free fraction was also higher for ropivacaine (7.1 v. 5.2%). The AAG levels were normal in both groups. The duration of objective sensory block was 6 hrs with ropivacaine and 9 hrs with bupivacaine, but the subjective sensory block was the same (9 hrs) in both groups.

Safety Assessment There were no important complications in either group. Both groups had patients with minor adverse events such as flushing, rash, headache, and bradycardia with injection of the skin weals

2. CONCLUSIONS

This study demonstrates that ropivacaine is both effective and safe for intercostal nerve block when administered to healthy adults in a total dose of 140 mg. The Cmax and tmax values were the same for both local anesthetics, but the duration of anesthesia was shorter for ropivacaine than bupivacaine The free fraction of ropivacaine was greater than for bupivacaine

3. RECOMMENDATIONS REGARDING LABELING:

The t1/2 was somewhat longer in this study (2.3 hr) than that noted in the proposed labeling (1.8 hr) (page 3, line 94). The 94% protein binding agrees with the 7% free fraction noted in this study

C. Philip Larson, M.D.
Reviewer

September 21, 1995

TO: David Morgan
Fax - (301) 443-7068

FROM: Robert Merin, M.D.

SUBJ: Cardiovascular Toxicity Review of Naropin (Ropivacaine HCL)

My apologies for the tardiness in producing this report. The month of August was much hectic than I anticipated and I am afraid the ropivacaine data was at the bottom of my pile! I hope this is what you need. If it is not, please fax me immediately. I also request as much advance notice as possible for the actual NDA day at the end of November?

Thank you.

Robert Merin MD

Report on NDA 20-533
Naropin (Ropivacaine HCL monohydrate)

Subject: Cardiovascular effects and toxicity of ropivacaine

It is of some interest that there is essentially no new data presented on the cardiovascular effects and toxicity of ropivacaine since the previous pre NDA review in 1992(?) The most important work about this topic are the articles by Nancarrow et al (1), Rutten et al (2), Scott et al (3), Feldman et al (4-5), Reiz et al (6), and Moller and Covino (7). All of these publications in various models from guinea pig Purkinje fibers (7) through human volunteers (3) show that ropivacaine is definitely less cardiotoxic than bupivacaine. However, in all instances where bupivacaine and ropivacaine have been compared with lidocaine, there is almost a qualitative difference between these two drugs and lidocaine. In other words the basic pharmacologic effects of ropivacaine on the cardiovascular system are much more similar to those of bupivacaine than of lidocaine. Although I am not aware of studies on this aspect of the pharmacology of these local anesthetic drugs, I suspect that as is the case with bupivacaine, ropivacaine, should it be investigated, will prove not to be a useful antiarrhymic drug, in contrast to lidocaine. This highlights the pharmacologic differences between the three local anesthetics.

Generally speaking, the review by Ericson and Henriksson (documented as F38; Report 802-550-LF-0227-01 in the materials supplied to the FDA by ASTRA) dated August 10, 1994 appears to be generally correct. I would highlight several points in their report:

Page 6, last 2 lines over on to Page 7: "Not all hearts could be evaluated due to the occurrence of arrythmias." In this report which I have reviewed, there is no information as to the incidence of arrythmias between the two local anesthetics. Also of note is: "At the highest concentration AV block II and III and ventricular extra systolic beats were found in four of five treated with bupivacaine and four of six treated with ropivacaine." Obviously no difference between bupivacaine and ropivacaine. Further on down on Page 7: "No statistically significant differences were seen between the effects of ropivacaine and bupivacaine in this study because of the loss of hearts due to arrhythmias." Again, I point out that the incidence of these arrhythmias was never reported.

Page 13, Section 5.1.2: This is a report on the study of Reiz et al (6). Of note is that in fact there were very little differences between the hemodynamic and ECG effects of ropivacaine and bupivacaine after intracoronary injection in pigs.

Page 15, bottom Section 5.1.5: There is no indication as to the mode of death in these LD_{50} studies.

Page 16, Section 5.1.7: This is a report of the article by Rutten et al (2) in which it is noted that there is again no statistically significant differences between the two compounds as far as mortality is concerned.

Page 17, Section 5.2: Title "Treatment of the Acute Toxicity". This is a major failing in the submission. I noted in the preliminary NDA review that the lack of significant differences on the treatment of the acute toxicity between bupivacaine and ropivacaine was a factor that should be investigated further. From the appearance of this NDA submission, there have been no further investigations since my suggestion on that preliminary NDA date. The report in this section of the Ericson and Henriksson document refers only to the Feldman, et al study (5). "There was no difference in the cardiovascular or respiratory effects or arterial blood concentrations between the groups"; and over on page 18 "the difference between mortality between the two groups were not significant". This was in spite of the fact that all dogs in the two times convulsive dose of ropivacaine were resuscitated where as 2 of 6 of the bupivacaine dogs could not be resuscitated. Obviously, repeat experiments with the greater n are necessary. This is particularly true in view of the fact that the Pedigo, et al study which is reported only as an IARS abstract (Anes Anag 67:S166, 1988) in which resuscitation studies on anesthetized dogs showed no difference between recovery of cardiovascular toxicity between bupivacaine and ropivacaine.

In line with these comments, I also would like to point out some areas in the official NDA submission synopsis of which might be discussed.

Proposed text of labeling - annotated page 6, line 184-186. As indicated above, there is no statical differences between resuscitative measures when ropivacaine is compared bupivacaine in the reported studies.

Page 53 (section on non clinical Pharmacology & Toxicology summary) and over on to 54: "in most studies comparison were also made with lidocaine. In general these results have not been included; however, all were consistent with the observation with that a given dose of lidocaine was less toxic than the same dose of ropivacaine and bupivacaine" Not only was a given dose less toxic but as I pointed out before it would appear that the qualitative effects of lidocaine are different from ropivacaine and bupivacaine. I believe this should be included somewhere in the labeling.

Page 57, first complete paragraph the last sentence: "ropivacaine appears to be intermittent between lidocaine and bupivacaine" is not acceptable. This is based on the data which show "Na channels blocked by lidocaine recovered in 0.3 seconds while those blocked with ropivacaine and bupivacaine recovered in 2.05 and 3.56 seconds respectively". I would again argue that ropivacaine is much closer to bupivacaine than to lidocaine. This statement suggests that it is half-way between.

Page 11, second complete paragraph: The study reported here on the difference between progesterone treated rabbit hearts when bupivacaine or ropivacaine was added is a 7 year old abstract. I would suggest that if this report has not been published than there is something wrong with it.

Page 71: Section on "Superiority in pharmacodynamic differences from available long-acting local anesthetics are evident in five major areas."
3. "The reversibility of cardiac arrest is better with a ropivacaine overdose than if bupivacaine is used". As indicated, the data is not there to support this statement.

Summary: In general, I believe the data supports the contention that ropivacaine is less cardiotoxic than bupivacaine in most preparation studied, particularly intact animals. The data for improved treatment response to overdose simply is inadequate. Finally, there can be little doubt that ropivacaine is much closer chemically and pharmacologically to bupivacaine than to lidocaine and this should be included in the practice guidelines.

References:

1. Nancarrow, et al. Myocardial and cerebral drug concentrations in the mechanisms of death after fatal intravenous doses of lidocaine, bupivacaine and ropivacaine in the sheep. Anes Analg 69:276-83, 1989.

2. Rutten, et al. Hemodynamic and central nervous systems effect of intravenous bolus doses of lidocaine, bupivacaine and ropivacaine in sheep. Anes Analg 69:291-9, 1989.

3. Scott, et al. Acute toxicity of ropivacaine compared with that of bupivacaine. Anes Analg 69:563-9, 1989.

4. Feldman, et al. Comparative systemic toxicity of convulsant and supraconvulsant doses of intravenous ropivacaine, bupivacaine and lidocaine in the conscious dog. Anes Analg 69:794-801, 1989.

5. Feldman, et al. Treatment of the acute systemic toxicity after the rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Anes Analg 73:373-84, 1991.

6. Reiz, et al. Cardiotoxicity of ropivacaine - a new amide local anesthetic agent. Acta Anaesthesiol Scand 33:93-98, 1989.

7. Moller and Covino. Cardiac electrophysiologic properties of bupivacaine and lidocaine compared with those of ropivacaine, a new amide local anesthetic. Anesthesiology 73:322-329, 1990.

August 24, 1995

Introductory comments to Studies L-1 through L-14 which are parts of NDA Number 20-533 for Naropin (ropivacaine HCL monohydrate):

These studies include dose-ranging studies, studies comparing ropivacaine with bupivacaine, and studies to determine the effects of ropivacaine with and without epinephrine. The object of the studies is to determine the efficacy and safety of ropivacaine. It appears that the sponsor has called on what must be a vast experience in testing local anesthetic drugs by applying techniques and protocols the sponsor has standardized for assessing neural blockade from local anesthetics. As a result, the methods described in studies L-1 through L-14 were similar and had variations so minor, in my view, as to be inconsequential. I have not repeated a description of methods in each review.

The assessments of efficacy, that is detemining the characteristics of the drug in producing the desired sensory and motor blockade included the following:

1. Sensory blockade (analgesia)
   Assessments by pin prick method were performed 2, 5, 10, 15, 20, 25, and 30 minutes after injection of study drug and then every 30 minutes until return of normal sensation. Tests were made bilaterally in most instances and from the S-5 dermatome cephalad to as high as the block existed. In some studies fewer dermatomes were tested but the full range of blockade was still examined. In this way the onset, extent and duration of the analgesia were studied.

2. Motor blockade (muscle relaxation) -- two methods were used Modified Bromage Scale, that is:
   0 = no motor blockade
   Degree 1 = inability to raise extended legs (just able to move knees
   Degree 2 = inability to flex knees (able to move feet only)
   Degree 3 = inability to flex ankle joints (unable to move feet or knees)
   Degree 4 = motor paralysis (unable to move feet, knees or toes) This degree was not mentioned in all studies.

In two studies a RAM test (Rectus Abdominus Muscle test) was applied which is intended to assess the degree of abdominal wall muscle relaxation. In includes:
100% = able to rise a from supine to sitting position with hands behind head
80% = can sit up only with arms extended forwards
60% = can only lift head and scapulae off bed surface
40% = can only lift shoulders off bed surface
20% = an increase in abdominal muscle tension can be felt during effort, with no other response

These tests were usually applied at 5, 10, 15, 20, 25, 30, and 45 minutes after administration of the study drug. They were usually discontinued during surgery and resumed following surgery until full recovery of motor function existed.

3. Quality of surgical anesthesia. The overall quality of anesthesia was judged by the surgeon and investigator following the operation. They decided whether the analgesia and muscle relaxation relevant to the procedure being done were satisfactory, satisfactory until a specified time, or unsatisfactory. In instances when additional anesthesia was required, the inadequacy of the blockade was obvious.

Assessments of <u>safety</u> included circulatory changes and occurrence of adverse events.

1. Cardiovascular changes were analyzed by measuring systolic, diastolic and mean systemic arterial pressures and heart rate and calculation of rate pressure product before injection of the study drug and 5, 10, 20, 25, 30 minutes after the injection and then each 30 minutes for three hours.

2. Adverse events were recorded during performance of the block, during anesthesia, before discharge from the recovery room, daily during hospitalization, and at least once between the 14-21 day after surgery.

3. Other indications of adverse events included records of concomitant medications used during anesthesia care.

W C Stevens

Wendell C. Stevens, MD
Concultant reviewer, Studies L-1 through L-14

Following are some conclusions and impressions from review of studies L-1 through L-14 on epidural anesthesia with ropivacaine. The concentrations of ropivacaine which were tested were 0.5%, 0.75%, and 1.0%. In one study the total volume injected was 10 ml of 1.0% solution. In the other studies the volumes were either 20 or 25 ml of the various concentrations.

1. Epinephrine, 5 ug/ml, has no significant effect on the sensory or motor block of ropivacaine.

2. The extent of epidural block is greater with higher concentrations of ropivacaine.

3. The duration of sensory block is greater with higher concentrations of ropivacaine.

4. In comparing ropivacine and bupivacaine

   a. The sensory block produced by equal concentrations of these drugs is quite similar.

   b. If equal concentrations of these drugs are used, the motor block of bupivacaine is slightly greater than that with ropivacaine and it lasts longer.

   c. The period of time over which continued spread of analgesia occurs is quite long with both agents.

5. Patchiness of block may be a characteristic of epidural anesthesia and is not related to the drug which is used.

6. The circulatory events and adverse events during ropivacaine epidural anesthesia are the same as those occurring with epidural anesthesia with any local anesthetic drug.

Wendell C. Stevens, MD
Consultant
8/29/95

MEDICAL OFFICER REVIEW

IND#: 20-533 Study L-1

NAME: A multicenter open study of 0.5%, 0.75% and 1.0% ropivacaine with epinephrine (5ug/ml) in epidural anesthesia in patients undergoing urological surgery

SPONSOR: Astra
PO Box 4500
Westborough, MA 101581-4500
Phone (508) 366-1100, Fax (508) 366-7460

SUBMISSION DATE: March 29, 1995

REVIEWER: Wendell C. Stevens, MD

REVIEW DATE: August 10, 1995

SUBMISSION TYPE: Commercial IND

1. RESUME:

BACKGROUND

Ropivacaine is a long-acting local anesthetic which has undergone extensive evaluation both in North America and in Europe. It is believed to be less cardiotoxic or neurotoxic than bupivacaine and to offer as effective and longlasting sensory blockade as bupivacaine with less motor blockade. This is a dose-ranging study performed in support of the sponsor's NDA.

CLINICAL STUDY

Investigators: Kehlet, Hvidovre, Denmark; Gielen, Nijmegen, The Netherlands; Axelsson, Orebro, Sweden

Treatment Plan: 46 ASA I or II patients, (45 males and 1 female), who underwent urological surgery on the bladder, prostate or external genitalia participated in this open, non-randomizeed study. The study was conducted simultaneously at the 3 institutions. Successive groups of 5 patients (there was one replacement patient resulting in 6 patients receiving 0.75% ropivacaine at one institution) in each study received 20 ml 0.5%, 0.75% and 1.0% ropivacaine with epinephrine (5 ug/ml) epidurally. A test dose of 3-4 ml 1-2% lidocaine with 5 ug/ml epinephrine preceded administration of the study drug. All drugs were given in 5 ml doses each 60 seconds via a lumbar epidural catheter. Assessments of sensory and motor block were performed bilaterally 2, 5, 10, 15, 20, 25 and 30 minutes after the study drug was given and every 15-30 minutes until return of normal sensation and motor function. Motor block was measured using the three degree Bromage scale (no block and 1,2,3 degrees, 3=unable to move feet or knees). Heart rate and blood pressure were recorded before premedication

was given and then 2, 5, 10, 15, 20, 25, and 30 minutes after injection of the study drug and then every 30 minutes for 3 hours. Adverse events such as convulsions, headache, or shivering were to be recorded during anesthesia, on the first postoperative day and once between 6 and 14 days after anesthesia.

This pattern or plan of sensory, motor, circulatory and adverse events assessment was essentially the same in all of these Astra supported studies, numbers L-1 through L-14.

The patients were of similar ages (mean 58+13 yrs), heights and weights at all institutions. The one female had a bladder operation. Lack of adequate anesthesia was termed a technical failure and this led to loss of the patient from efficacay assessment and the addition of another patient to that center's group as noted above. There were protocol deviations in 19 patients but they were not crucial to their efficacy assessments--overweightedness, greater preexisting medical illness, an interspace lower than planned for injection.

Efficacy Assessment: There were 45 evaluable patients. The sponsors summary statements describe the results accurately and satisfactorily.

1). Onset of anesthesia: Onset of analgesia at T12 occurred at 5 min with each dose. For the T11 and below dermatomes relevant for surgery, the times varied between 6 and 15 minutes. The 1.0% drug gave a significantly faster onset at S5 than 0.75% drug. Maximum cephalad spread was T4 or T5 with each agent.

2) Motor block: 1.0% ropivacaine produced significantly more 3-degree block than 0.5%. 10/15 of the 1.0%, 7/15 of the 0.75%, and 3/15 of the 0.5% patients had 3-degree blocks. Lesser degree blocks occurred with similar incidence with all doses. It took an average of 53 minutes to achieve the 3-degree block with 1.0% ropivacaine.

3) Adequacy of anesthesia: Analgesia for surgery was unsatisfactory in 5 paitents, 2 in the 0.5% group, 2 in the 0.75% group, and 1 in the 1.0% group. Three patients received general anesthesia and 1 received a different epidural drug as supplementl anesthesia. Two of the patients in the 0.5% group and 1 in the 1.0% group were judged to have inadequate muscle relaxation although in many instances muscle relaxation was not necessary to accomplish surgery. Thus, analgesia rather than muscle relaxation may be a more important factor in adequacy of anesthesia for this specific type surgery.

4) Duration of anesthesia: Duration of anesthesia at T12 or below, the levels relevant for this surgery, were median durations at T12 of 3.1, 3.9 and 4.4 hours for the 0.5%, 0.75%, and 1.0% groups, respectively. 0.75% and 1.0% ropivacaine produced

significantly longer anesthesia at L5, L2 and T10 levels than 0.5% ropivacaine.

Safety Assessment: The most common adverse reaction was hypotension whether measured as systolic, diastolic or mean pressure. Statistical differences existed at various times soon after injection of the study drug but there were no consistent, dose related effects. Furthermore, the significance of any changes are diluted by having data from three institutions, each contributing a small number of cases. Other adverse events included shivering, mild difficulty breathing, bradycardia, headache, nausea, ventricular ectopic beats, all occurring as single incidents in almost every instance.

2. CONCLUSIONS:

All of the concentrations of ropivacaine produced anesthesia which was effective for elective urological surgery done in the bladder, urethra, or external genitalia in this predominantly male cohort. Onset of anesthesia at the lowest dermatome, S5,was signigicantly faster with the highest concentration of ropivacaine. The cephalad spread was not different among the concentrations but the duration of effect increased with increasing dose.

3. RECOMMENDATIONS REGARDING LABELING:

This study supports the labeling indicating the speed of onset of sensory and motor block and the durations of blockade. Intensity and duration of motor block tended to be (and with 1.0% ropivacaine was statistically so) more profound at higher concentrations of drug which fits with the labeling statements.

The most common adverse reaction, hypotension, occurred as described in the labeling materials.

Wendell C. Stevens MD
Consultant

Pharmacologist Review

Pilot Drug Evaluation Staff
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

NDA: 20-533

Submission: NDA Dated: March 25, 1995
Received by CDR: March 31, 1995
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Review Completed: October 30, 1995
Reviewers: M. Anwar Goheer, Ph.D. & Almon W. Coulter, Ph.D.

Sponsor: Astra Pharmaceutical Products, Inc.
50 Otis Street
Westborough, MA 01581

Information to be conveyed to the sponsor: Yes

Drug: Ropivacaine HCl monohydrate, LEA-103

Category: Local Anesthetics

Indications: Surgical Anesthesia: epidural block for surgery including caesarean section, major nerve block; local infiltration.
Acute Pain Management: epidural continuous infusion or intermittent bolus e.g., postoperative or labor; local infiltration.

Related NDAs: NDA 16-964 Bupivacaine (Marcaine, Sensorcaine)
NDA 17-751 Etidocaine (Duranest)

Names:

Chemical name: (S)-(-)-1-Propyl-2', 6'-pipecoloxylidide HCl H_2O

IUPAC name: (S)-(-)-1-Propyl-piperidine-2-carboxylic acid (2, 6-dimethyl-phenyl)-amide hydrochloride monohydrate

Generic name: Ropivacaine hydrochloride monohydrate

CAS number: 132112-35-7

Trade name: NAROPIN™

Laboratory code name: LEA-103

Physical and Chemical characteristics:

Appearance: A white, crystalline powder

NDA 20-533

(2) Secondary Effects

1. Effects on the cardiovascular system

a) In vivo studies
Intravenous administration -
anesthetized pig-
conscious rat - with and without adrenaline
conscious dog
Intracoronary administration - anesthetized pig
Effects of Pretreatment with atropine - conscious rat

b) In vitro studies

Effects on the isolated heart - rat
Effects on sodium and calcium conductance in the papillary muscle - guinea-pig
Effects on conductance in Purkinje fibers ventricular muscle cells - rabbit
Effects on the portal vein - rat

2. Effects on the central nervous system

Intravenous administration
conscious rat (with and without adrenaline)
conscious dog
Effects of diazepam and thiopentone on LEA 103 induced CNS toxicity-conscious rat

(3) Interactions

Anticholinergic - Atropine
Tranquilizers - Diazepam
Analgesics - Morphine, Fentanyl
General Anesthetic Agents - Thiopentone, Enflurane
Muscle Relaxants - Pancuronium, Suxamethonium

II. ACUTE TOXICITY

III. SUBCHRONIC TOXICITY STUDIES

1. Dose range finding study of LEA 103 given subcutaneously to rats for 2 weeks
2. General toxicity of LEA 103 given subcutaneously to rats for one month
3. A dose range finding and MTD study of LEA 103 given subcutaneously to dogs for 3 days
4. General toxicity of LEA 103 given subcutaneously to dogs for one month

IV. SPECIAL TOXICITY STUDIES

1. Hemolysis and protein flocculation in human blood of LEA 103 studied in vitro
2. Vaso- and tissue irritation study in dogs of LEA 103 given intravenously and subcutaneously for 5 days
3. Local effects of LEA 103 given to dogs as a single subarachnoid or epidural injection
4. Effects of LEA 103 on peripheral nerve tissue following sciatic nerve block in guinea-pigs
5. Effects of LEA 103 on peripheral nerve tissue following sciatic nerve block in guinea-pigs: A complementary study

V. MUTAGENICITY STUDIES

1. Mutagenicity evaluation of LEA 103 in the Ames Salmonella/mammalian microsome mutagenicity test
2. Mutagenicity evaluation of LEA 103 in the L5178Y mouse lymphoma cell thymidine kinase locus mutagenicity test
3. Mouse micronucleus test of LEA 103

VI. PHARMACOKINETIC DATA

CONVERTING TABLE OF μmol INTO mg FOR LEA 103, BUPIVACAINE AND LIDOCAINE

μmol	mg		
	LEA 103	bupivacaine	Lidocaine
5	1.6	1.6	1.4
8	2.5	2.6	2.2
10	3.1	3.2	2.7
16	5.0	5.2	4.3
20	6.2	6.2	5.4
28	8.7	9.1	7.6
56	17.4	18.2	15.2
60	18.7	19.5	16.2
85	26.4	27.6	23.0

INDEX TO NONCLINICAL PHARMACOLOGY & TOXICOLOGY SECTION

I. PHARMACOLOGICAL ACTIONS

A. Therapeutic Indications [pp 19-30]

1. In Vivo

(1) F1 Astra Report 802-50 AF 15-1, 1986-02-12. On the local anesthetic effect and the acute toxicity of enantiomers and the racemate of 1-propyl-2',6' -pipecoloxylidide. Akerman B, Hellberg I-B, Trossvik C. [51/1.17]

(2) F2 Astra Report 802-50 AF 14-1, 1986-02-12. Effects of LEA 103 in spinal anaesthesia (mouse) and epidural anaesthesia (guinea pig). Akerman B, Trossvik C. [69/1.17]

(3) F3 Astra Report 802-50 AF 69-2, 1986-11-26. Sciatic nerve block in the rat: studies on LEA 101 and bupivacaine. Feldman HS. [83/1.17].

(4) Anesth Analg 1988;67:1047-52. Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. Feldman HS, Covino BG. [95/1.17].

(5) F4 Astra Report 802-550 LF-0055-02, 1994-03-28. Intrathecal injection of LEA 103 (ropivacaine) in rats twice daily for 14 days via an indwelling catheter: Local anaesthetic effect. Ask A-L, Alari L, Sjogren L, Stahlberg M. [101/1.17].

(6) F5 (F15) Astra Report 802-50 AF 13-1, 1986-01-12. Primary evaluation of the local anesthetic effect of LEA 103. Akerman B, Hellberg I-B, Sperber B, [165/1.17].

(7) Acta Anaesthesiol Scand 1988;32:571-78. Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). Akerman B, Hellberg IB, Trossvik C. [188/1.17].

(8) F6 Astra Report 802-550 LF-0228-01, 1994-04-30. Local anesthetic effects of 3-hydroxy- and 4-hydroxy ropivacaine in the guinea-pig. Akerman B, Hellberg I-B, Halldin M. [196/1.17]

(9) F7 Astra Report 802-50 AF 59-1, 1986-09-23. Brachial plexus block in the guinea pig with LEA 103, bupivacaine and lidocaine with and without adrenaline. Akerman B, Hellberg I-B. [207/1.17].

(10) F8 Astra Report 802-50 AF 63-1, 1986-09-22. A comparative study of LEA 103, AL 381 and bupivacaine in epidural anesthesia in the guinea pig. Akerman B, Trossvik C. [216/1.17]

(11) F9 Astra Report 802-50 AF 49-1, 1986-02-17. AL 381 - primary evaluation of efficacy as a spinal and epidural local anaesthetic agent. Feldman HS. [233/1.17].

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(13) F10 Astra Report 802-50 AF 70-2, 1986-12-01. Epidural anesthesia in the dog: A comparative efficacy study of LEA 103 and bupivacaine plain solutions and solutions containing epinephrine. Feldman HS. [256/1.17].

(14) Anesth Analg 1988;67:1047-52. Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. Feldman HS, Covino BG. [278/1.17].

(15) F12 Astra Report 802-550 LF-0167-01 Comparative local anesthetic efficacy of epidurally administered ropivacaine and bupivacaine in the dog. Feldman HS. [284/1.17].

(16) F13 Astra Report 802-550 LF-0229-01 Comparative efficacy of epidurally

administered ropivacaine and bupivacaine in the sheep. Evaluation of the local anesthetic effects. Feldman HS. 389/1.17].

(17) F14 Astra Report 802-550 LF-0202-01 Epidural anesthesia in the rhesus monkey with ropivacaine (LEA 103). Bridenbaugh PO, Denson DD. [461/1.17]

(18) Biopharmaceutics and Drug Disposition 1993; 14:773.1-10. Pharmacokinetics of intravenous and epidural ropivacaine in the rhesus monkey. Katz JA, Sehlhorst CS, Thompson GA, Denson DD, Coyle D, Bridenbaugh PO. [495/1.17].

2. In Vitro

(19) F15 (F5) Astra Report 802-50 AF 13-1, 1986-02-12. Primary evaluation of the local anesthetic effect of LEA 103. Akerman B, Hellberg I-B, Sperber B. [165/1.17].

(20) Acta Anaesthesiol Scand 1988;32:571-78. Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). Akerman B, Hellberg IB, Trossvik C. [188/1.17].

(21) F16 Astra Report 802-50 AF 74-1, 1986-11-28. Effects of LEA 103 and bupivacaine on action potential propagation in frog sciatic nerve in vitro. Ask A-L, Sperber B, Akerman B. [505/1.17].

B. Effects Related to Possible Adverse Reactions [pp 30-48]

1. In Vivo

(22) F18 Astra Report 802-50 AF 56-1, 1986-02-20. Effects on electrocardiogram and convulsive properties of LEA 103, bupivacaine and lidocaine in the conscious rat. Forsberg T. Nilsson S. Sperber B. Oberg E. [124/1.18].

(23) F39 Astra Report 802-550 LF-0186-01, 1994-01-26. Spinal cord blood flow after intrathecal injection of ropivacaine and other local anaesthetic agents to male rats. Post C, Freedman J. [168/1.18]

(24) F40 Astra Report 802-550 LF-0205-01, 1994-05-06. Spinal cord blood flow after intrathecal injection of ropivacaine, bupivacaine with or without epinephrine in rats. Kristensen JD, Karlsten R, Gordh T, Ask, A-L. [182/1.18].

(25) F41 Astra Report 802-550 LF 0008-01, 1992-01-16. Effects of subcutaneous injections of LEA 103 (ropivacaine hydrochloride monohydrate), lidocaine hydrochloride, lidocaine hydrochloride with adrenaline and adrenaline on local circulation in the hind paw in the rat. Forsberg T. Carlsson S. Ericson A-C. Akerman B. [204/1.18].

(26) F30 Astra Report 802-50 AF 118-1, 1992-09-02. Treatment of acute toxicity resulting from rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Feldman HS . [186/1.25].

(27) Anesth Analg 1991; 73:373-84 Treatment of acute systemic toxicity after the rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Feldman HS, Arthur GR, Pitkanen M, Hurley R, Doucette AM, Covino BG, [396/1.25]

(28) F11 (F32) Astra Report 802-50 AF 101-1, 1992-03-04. Hemodynamic effects of

epidural anesthesia in the dog with ropivacaine and bupivacaine. Feldman HS. [239/1.18].

(29) Reg Anesth 1991;16(6);303-8 The effects of epinephrine on the anesthetic and hemodynamic properties of ropivacaine and bupivacaine after epidural administration in the dog. Hurley RJ, Feldman HS, Latka C, Arthur GR, Covino BG. [321/1.18].

(30) F33 (G31) Astra Report 802-50 AF 48-1, 1986-02-19. Systemic hemodynamics and myocardial kinetics following intravenous administration of LEA 103, bupivacaine and lidocaine to pentobarbital anesthetized pigs. Reiz S, Haggmark S, Johansson G, Nath S. [327/1.18].

(31) F42 Astra Report 802-50 AF 102-1, 89-12-20. Effect of ropivacaine on cutaneous capillary blood flow in pigs. Kopacz DJ, Carpenter RL, Mackey DC . [1/1.9].

(32) Anesthesiology 1989;71:69-74. Effect of ropivacaine on cutaneous capillary blood flow in pigs. Kopacz DJ, Carpenter RL, Mackey DC. [21/1.19].

(33) F35 Astra Report 802-50 AF 103-1, 1989-12-15. Haemodynamic and central nervous system effects of intravenous bolus doses of ropivacaine (LEA 103) compared to lignocaine and bupivacaine in sheep. Mather LE, Rutten AJ. [124/1.26]

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(35) F36 Astra Report 802-50 AF-120-1, 1992-07-02. Systemic toxicity of ropivacaine in pregnant and nonpregnant ewes. Santos AC. [166/1.22].

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(37) F43 Astra Report 802-50 AF 124-1, 1992-07-02. Effects of ropivacaine, bupivacaine and epinephrine on uterine blood flow in pregnant sheep. Santos AC. [27/1.19]

(38) Anesth Analg 1992;74(1):62-7. Effect of ropivacaine and bupivacaine on uterine blood flow in pregnant ewes. Santos AC, Arthur GR, Roberts DJ, Wlody D, Pedersen H, Morishima HO, Finster M, Covino BG. [81/1.19]

2. In Vitro

(39) F44 Astra Report 802-550 LF-0184-01, 1994-01-18. Interaction of ropivacaine, bupivacaine and lidocaine with seven selected receptor recognition sites in the rat brain. Fowler CI, Brannstrom G. [87/1.19].

(40) F45 Astra Report 802-50 AF 57-1, 1986-03-17. Monoamine oxidase inhibitory effect of LEA 103. Ross S, Fagerwall I. [111/1.19]

(41) F46 Astra Report 802-50 AF 75-1, 1986-12-01. Effects of LEA 103, LEA 104 and bupivacaine on the portal vein in vitro. Forsberg T, Westman I. [116/1.19]

(42) Anaesthetist 1988;37:121. Difference in vasoactivity between ropivacaine and bupivacaine. Forsberg T, Westman I, Akerman B. [128/1.19].

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bupivacaine and adrenaline on the rat portal vein in vitro. Forsberg T, Holmstrom -Svensson M , Ericson A- C, Akerman B. [129/1.19].

(44) F48 Astra Report 802-50 AF 77-2, 1994-05-04. Effects of LEA 103, bupivacaine and lidocaine on the rat heart in vitro. Norrman S. [146/1.19].

(45) F49 Astra Report 802-50 AF 51-1, 1986-02-18. Actions of three local anesthetics: lidocaine, bupivacaine and LEA 103 on guinea-pig papillary muscle sodium channels. Arlock P. [225/1.19]

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(48) F51 Astra Report 802-50 AF 54-1, 1986-02-21. Comparative cardiac electrophysiological effects of lidocaine, bupivacaine and LEA 103. Moller RA, Covino B G. [271/1.19]

(49) Anesthesiology 1990;72:322-29. Cardiac electrophysiologic properties of bupivacaine and lidocaine compared with those of ropivacaine, a new amide local anesthetic. Moller RA, Covino BG. [307/1.19]

(50) F52 Astra Report 802-550 LF 0049-01, 1992-05-26. Effect of progesterone on the cardiac electrophysiological alterations produced by ropivacaine and bupivacaine. Moller RA, Covino BG. [315/1.19].

(51) Anesthesiology 1992;77(4):735-741. Effect of progesterone on the cardiac electrophysiologic alterations produced by ropivacaine and bupivacaine. Moller RA, Covino BG [339/1.19]

(52) F53 Astra Report 802-50 AF 119-1 Chronotropic and inotropic effects of lidocaine, bupivacaine and ropivacaine in the spontaneously beating and electrically paced isolated, perfused rabbit heart. Feldman HS. [1/1.20]

(53) Anesthesiology 1990;73 (Suppl 3A):A844. Effects of ropivacaine bupivacaine and lidocaine upon the isolated spontaneously beating rabbit heart (abstract). Feldman HS, Pitkanen M, Arthur GR, Manning T, Covino BG. [250/1.20]

(54) F54 Astra Report 802-550 LF-0166-01, 1993-11-11. Local anesthetics do not affect protein kinase C function in intact neuroblastoma cells. Martinsson T, Fowler CJ. [251/1.20]

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(56) F55 Astra Report 802-550 LF-0196-01 1994-03-17. Comparison of vascular effects of ropivacaine and lidocaine on isolated rings of human arteries. Gherardini G Samuelson U, Jernbeck J, Aberg B, Sjostrand N. [279/1.20].

C. Drug Interactions [pp 48-53]

(57) F22 Astra Report 802-50 AP 82-1, 1986-12-12. Cardiac effects of intravenous injection of LEA 103 in conscious rats premedicated with atropine. Nilsson S, Ogenstad S, Sperber B, Westman I . [1/1.21]

(58) F23 Astra Report 802-50 LF 0143-01, 1994-03-30. The effect of atropine on bradycardia produced by intravenous injection of ropivacaine, bupivacaine and lidocaine in conscious rats. Nilsson S, Sperber B, Westman I. [19/1.21].

(59) F24 Astra Report 802-50 AF 79-1, 1986-12-12. Effects of intravenous injection of LEA 103 in conscious rats premedicated with diazepam, morphine or atropine. Nilsson S, Westman I, Oberg E. [41/1.21].

(60) F25 Astra Report 802-550 LF-0144 02, 1994-06-28. Protective effects of midazolam and diazepam on convulsions induced by intravenous infusion of ropivacaine, bupivacaine and lidocaine in the rat. Nilsson S, Sperber B. [62/1.21].

(61) F26 Astra Report 802-50 AF 83-1, 1986-12-12. Inhibitory effects of diazepam and thiopentone sodium on convulsions induced by an intravenous injection of LEA 103 in the rat. Nilsson S, Sperber B, Westman I, Oberg E. [76/1.21].

(62) F27 Astra Report 802-550 LF-0145-02, 1994-06-28. Inhibitory effects of midazolam and diazepam on convulsions induced by intravenous infusion in ropivacaine, bupivacaine and lidocaine in the rat. Nilsson S, Sperber B. [93/1.21].

(63) F19 Astra Report 802-50 AF 80-1, 1986-12-12. Effects of fentanyl and morphine in conscious rats pretreated with subcutaneous injection of LEA 103, bupivacaine or lidocaine. Nilsson S, Sperber B. [107/1.21]

(64) F56 Astra Report 802-50 AF 81-1, 1986-12-12. Effect of thiopentone sodium, enflurane, pancuronium and suxamethonium in conscious rats pretreated with subcutaneous injection of LEA 103, bupivacaine or lidocaine. Nilsson S Sperber B, Westman I, Oberg E. [136/1.21].

(65) F57 Astra Report 802-550 LF 0146-02, 1994-06-28 Influence of the local anesthetics, ropivacaine, bupivacaine and lidocaine on the effects of the muscle relaxants pancuroniurn and suxamethonium in anaesthetized rats. Nilsson S, Sperber B. [170/1.21]

(66) F28 Astra Report 802-550 LF 0009-01, 1991-04- 25. Interactions of LEA-103 (ropivacaine hydrochloride monohydrate) with cardiovascular effects of acetylcholine, adrenaline, noradrenaline and carotid occlusion after intravenous injection in anaesthetized cats. Forsberg T, Carlsson S, Lindeberg A, Ericson A-C. [186/1.21].

II. TOXICOLOGICAL EFFECTS

A. Acute [pp 53-61]

(1) A2 Astra Report 802-50 T1731, 1994-04-18. Acute toxicity of LEA 103 in mice after single intravenous administration. Astra Toxicology Laboratories, Sodertalje, Sweden. [63/1.22]

(2) F17 Astra Report 802-550 LF 0224-01, 1994-04-27. Evaluation of the behavioral toxicity of ropivacaine and bupivacaine in male NMRI mice. Holm AC, Amkeus E, Lennmark M, Ogren SO. [80/1.22]

(3) A1 Astra Report 802-50 T1729, 1986-01-30. Acute toxicity of LEA 103 in mice after a single subcutaneous administration. Astra Toxicology Laboratories,

Sodertalje, Sweden. [93/1.22]

(4) F1 Astra Report 802-50 AF 15-1, 1986-02-12. On the local anesthetic effect and the acute toxicity of enantiomers and the racemate of 1-propyl-2',6'-pipecoloxylidide. Akerman B, Hellberg I-B, Trossvik C. [51/1.17]

(5) A4 Astra Report 802-50 T1730, 1986-01-30. Acute toxicity of LEA 103 in rats after single intravenous administration. Astra Toxicology Laboratories, Sodertalje, Sweden. [109/1.22].

(6) F21 Astra Report 802-50 AF 89-2, 1987-06-05. Acute toxicity of adrenaline containing solutions of LEA 103, bupivacaine and lidocaine after intravenous administration in conscious rats. Forsberg T, Westman I, Oberg E. [126/1.22].

(7) A3 Astra Report 802-50 T1728, 1986-01-30. Acute toxicity of LEA 103 in rats after single subcutaneous administration. Astra Toxicology Laboratories, Sodertalje, Sweden. [150/1.22]

(8) F30 Astra Report 802-50 AF 118-1, 1992-09-02. Treatment of acute toxicity resulting from rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Feldman HS. [186/1.25]

(9) Anesth Analg 1991;73:373-84. Treatment of acute systemic toxicity after the rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Feldman HS, Arthur GR, Pitkanen M, Hurley R, Doucette AM, Covino BG. [396/1.25]

(10) F36 Astra Report 802-50 AF 120-1, 1992-07-02. Systemic toxicity of ropivacaine in pregnant and non pregnant ewes. Santos AC, Arthur GR, Pedersen H, Morishima HO, Finster M, Covino BG. [166/1.22]

(11) Anesthesiology 1991;75;137-41. Systemic toxicity of ropivacaine during ovine pregnancy. Santos AC, Arthur GR, Pedersen H, Morishima HO, Finster M, Covino BG. [208/1.22]

(12) F35 Astra Report 802-50 AF 103-1, 1989-12-15. Haemodynamic and central nervous system effects of intravenous bolus doses of ropivacaine (LEA 103) compared to lignocaine and bupivacaine in sheep. Mather LE, Rutten AJ. [124.1,26]

(13) Anesth Analg 1989;69:291-9. Hemodynamic and central nervous system effects of intravenous bolus doses of lidocaine, bupivacaine, and ropivacaine in sheep. Rutten AJ, Nancarrow C, Mather LE, Ilsley AH, Runciman WB, Upton RN. [239/1.26].

B. Multidose [pp 61-69]

(14) B1 Astra Report 802-50 T1745, 1986-02-27. Dose range finding study of LEA 103 given subcutaneously to rats for two weeks. Astra Toxicology Laboratories, Sodertalje, Sweden. Appendix contains report G3 802-50 AF11-2, 1994-06-28. [1/1.23]

(15) B2 Astra Report 802-50 T1749, 1986-03-05. General toxicity of LEA 103 given subcutaneously to rats for one month. Astra Toxicology Laboratories, Sodertalje, Sweden. Appendix contains report G4 802-50 AF12-2, 1994-06-28 [38/1.23]

(16) B3 Astra Report 802-50 T1746, 1986-02-28. A dose range finding and MTD

study of LEA 103 given subcutaneously to dogs for 3 days. Astra Toxicology Laboratories, Sodertalje, Sweden. Appendix contains report G14 802-50AFI0-I, 1986-01-22. [182/1.23]

(17) B4 Astra Report 802-50 T1748, 1992-10-20. General toxicity of LEA 103 given subcutaneously to dogs for 1 month. Astra Toxicology Laboratories, Sodertalje, Sweden. Appendix contains report G15 802-50 AF 19-1, 1986-01-23 [278/1.23]

(18) B5 Astra Report 802-24 T2465, 1991-12-13. General toxicity study of ropivacaine (LEA 103) given subcutaneously and rectally to dogs for 6 months. Astra Safety Assessment, Sodertalje, Sweden. Appendix contains report G16 802-524 LF-0005-01 1991-11-12 [1/1.24]

C. Special [pp 69-86]

1. In Vivo

a. Cardiovascular/CNS Toxicity

(19) F20 Astra Report 802-50 AF 76-1, 1986-12-02. Cardiovascular effects and convulsive properties of adrenaline containing solutions of LEA 103 after intravenous administration in conscious rats. Forsberg T, Westman I, Sperber B, Oberg E. [30/1.25]

(20) F29 Astra Report AF 8534, 1986-02-11. Comparative overt central nervous system and cardiovascular system toxicities of lidocaine, bupivacaine and LEA 103 administered intravenously to unanesthetized, unsedated dog Feldman H S, Arthur G R, Covino B C. [69/1.25]

(21) Anesth Analg 1989;69:794.-801. Comparative systemic toxicity of convulsant and supraconvulsant doses of intravenous ropivacaine, bupivacaine, and lidocaine in the conscious dog. Feldman HS. Arthur GR. Covino BG. [178/1.25].

(22) F32 (F11) Astra Report 802-50 AF 101-1, 1992-03-04. Hemodynamic effects of epidural anesthesia in the dog with ropivacaine and bupivacaine. Feldman HS. [239/1.18].

(23) Reg Anesth 1991;16(6);303-8. The effects of epinephrine on the anesthetic and hemodynamic properties of ropivacaine and bupivacaine after epidural administration in the dog. Hurley RJ. Feldman HS. Latka C. Arthur GR. Covino BG. [321/1.18]

(24) F30 Astra Report 802-50 AF 118-1, 1992-09-02. Treatment of acute toxicity resulting from rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Feldman HS. [186/1.25]

(25) Anesth Analg 1991;73:373-84. Treatment of acute systemic toxicity after the rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Feldman HS, Arthur GR, et al. [396/1.25]

(26) F31 Astra Report 802-50 AF 104-1, 1994-06-22 Cardiovascular toxicity and

resuscitation studies with ropivacaine (LEA 103), bupivacaine and lidocaine in the anesthetized dog - a blinded comparison study. [1/1.26]

(27) F34 Astra Report 802-50 AF 67-1, 1987-01-08. Cardiotoxicity of LEA 101 - a new amide local anaesthetic agent. Reiz S, Haggmark S, Johansson G, Nath S. [92/1.26].

(28) Acta Anesthesiol Scand 1989;33:93-98. Cardiotoxicity of ropivacaine - a new amide local anaesthetic agent. Reiz S, Haggmark S, Johansson G, Nath S. [118/1.26]

(29) F35 Astra Report 802-50 AF 103-1, 1989-12-15. Haemodynamic and central nervous system effects of intravenous bolus doses of ropivacaine (LEA 103) compared to lignocaine and bupivacaine in sheep. Mather LE, Rutten AJ. [124/1.26].

(30) Anesth Analg 1989;69:291-299 Hemodynamic and central nervous system effects of intravenous bolus doses of lidocaine, bupivacaine and ropivacaine in sheep. Rutten AJ, Nancarrow C, Mather LE, Ilsley AH, Runciman WB, Upton RN. [239/1.26]

b. Potential for methemoglobinemia

(31) G41 Astra Report 802-50 AF 65-1, 1986 10-15. An investigation on the formation of methemoglobinemia after an intravenous infusion of 10 μmol/kg ropivacaine (LEA-103) in dog. Halldin M. Elofsson S. [1/1.27]

c. Local Irritation

(32) H10 Astra Report T2748, 1993-12-23. Effect on peripheral nerve tissue of ropivacaine (LEA 103) and bupivacaine (LEA 131) after single perineural and intraneural administration to rats. Astra Safety Assessment, Sodertalje, Sweden. [11/1.27]

(33) H11 Astra Report 802-50 T2621, 1993-03-17. Histopathology Report: Effects of LEA 103 (ropivacaine) on the spinal cord of the rat, following repeated intrathecal administration via an indwelling catheter for 14 days. Astra Safety Assessment, Sodertalje, Sweden. [74/1.27]

(34) H8 Astra Report 802-50 T1788, 1994-05-03. Effect of LEA 103 on peripheral nerve tissue following sciatic nerve block in guinea pigs. Astra Safety Assessment, Sodertalje, Sweden. [94/1.27]

(35) H9 Astra Report 802-50 T1789, 1994-05-03. Effect of LEA 103 on peripheral nerve tissue following sciatic nerve block in guinea pigs. Complementary study. Astra Safety Assessment, Sodertalje, Sweden. [116/1.27]

(36) H5 Scantox T2451, 1991-10-07. Primary skin irritation study in rabbits. [136/1.27]

(37) H6 Scantox T2452, 1991-10-21. Primary skin irritation study in rabbits with iontophoresis. [148/1.27]

(38) H7 Scantox T2501, 1992-02-10. Primary skin irritation study in rabbits with iontophoresis. [161/1.27]

(39) H2 Astra Report 802-50 T1733, 1994-04-22. Vaso- and tissue irritation study in

dogs of LEA 103 given intravenously and subcutaneously for 5 days. Astra Toxicology Laboratories, Sodertalje, Sweden. [175/1.27]

(40) H12 Astra Report 802-50 T1786, 1994-04-22. Local effects of LEA 103 given to dogs as a single subarachnoid or epidural injection. Astra Safety Assessment, Sodertalje, Sweden. [199/1.27]

(41) H13 Astra Report 802-50 T2724, 1993-10-25. Pilot/dose-range finding epidural (continuous infusion) tolerance study in the Beagle dog of ropivacaine (LEA 103) and bupivacaine (LEA 131). Astra Safety Assessment, Sodertalje, Sweden. [1/1.28]

(42) B5 Astra Report 802-24 T2465, 1991-12-13. General Toxicity Study of Ropivacaine (LEA 123) given subcutaneously and rectally to dogs for 6 months. Astra Safety Assessment, Sodertalje, Sweden. Appendix contains report G16 802-524 LF 0005-01, 1991-11-12. [1/1.24].

(43) H3 Astra Report 802-24 T2318, 1991-01-07. Dose finding and pilot irritation study in dogs of ropivacaine (LEA 103) given rectally for up to 5 days. Astra Safety Assessment, Sodertalje, Sweden. Appendix contains G18 report 802-24AF 1-1, 1990-06-18. [151/1.28].

(44) H4 Astra Report 802-24 T2324, 1991-01-21. Local tolerance study in dogs of ropivacaine given rectally for 1 month. Astra Safety Assessment, Sodertalje, Sweden. Appendix contains report GI9 802-24AF 3-1, 1990-08-31. [202/1.28]

2. In Vitro

(45) H1 Astra Report 802-50 T1740, 1986-02-06. Hemolysis and protein flocculation in human blood of LEA 103 studied in vitro. Astra Toxicology Laboratories, Sodertalje, Sweden. [298/1.28]

III. REPRODUCTION EFFECTS

A. Segment I [pp 86-89]

(1) C1 Astra Report 802-50 T2328, 1991-01-23. Multigeneration study in rats of LEA 103 given subcutaneously. Astra Safety Assessment, Sodertalje, Sweden. [1/1.29]

B. Segment II [pp 89-94]

(2) C2 Astra Report 802-50 T2047, 1988-10-25. Pharmacokinetic and dose range finding teratology study of LEA 103 given subcutaneously to pregnant rats. Astra Safety Assessment, Sodertalje, Sweden. Appendix contains report GS 802-SO-AF 90-2, 1988-09-26. [137/1.29].

(3) C3 Astra Report 802-50 T2049, 1988-10-28. Effect upon pregnancy in rats of LEA 103 given subcutaneously. Astra Safety Assessment, Sodertalje, Sweden.

[203/1.28].

(4) C4 Astra Report 802-50 T2048, 1988-10-25. Pharmacokinetic and dose range finding teratology study of LEA 103 given subcutaneously to pregnant rabbits. Astra Safety Assessment, Sodertalje, Sweden. Appendix contains report G9 802-50 AF 91-2 1988-09-26 and report G38 802-50 AF 92-2 1988-09-26 . [265/1.29]

(5) C5 Astra Report 802-50 T2052, 1988-11-09. Effects upon pregnancy in rabbits of LEA 103 given subcutaneously. Astra Safety Assessment, Sodertalje, Sweden. [361/1.29]

C. Segment III [pp 94-98]

(6) C6 Astra Report 802-50 T2249, 1990-06. Peri- and Postnatal study in rats of LEA 103 after subcutaneous administration during late pregnancy and lactation. Astra Safety Assessment, Sodertalje, Sweden. [1/1.30]

(7) Anesthesiology 1990;73(Suppl 3A) A927. Effects of ropivacaine on uterine blood flow in pregnant sheep [abstract]. Santos AC, Wlody DJ, Pedersen H, Morishima HO, Finster M. [45/1.30].

(8) G6 Astra Report 802-550 LF 0058-01, 1992-04-20. Effects of LEA 103 and LEA 131 given subcutaneously to pregnant rats from day 15 of pregnancy until day 3 post parturition - a dose finding study. Astra Pain Control AB. [46/1.30].

(9) C7 Astra Report 802-50 T2639, 1993-04-06. Comparative study of effects during the peri- and postnatal period in rats of ropivacaine (LEA 103) and bupivacaine (LEA 131) given subcutaneously. Astra Safety Assessment, Sodertalje, Sweden. Appendix contains report G7 802-550 LF 0068-01, 1993-04-01. [141/1.30]

D. MUTAGENICITY [pp 98-104]

1. In Vitro

(10) D1 Astra Report 802-50 T1671, 1985-06-11. Mutagenicity evaluation of LEA 103 in the Ames Salmonella/mammalian microsome mutagenicity test. Astra Toxicology Laboratories, Sodertalje, Sweden. [1/1.31]

(11) D2 Astra Report 802-50 T1894, 1994-02-28. Mutagenicity evaluation of LEA 103 in the L5178Y mouse lymphoma cell thymidine kinase locus mutagenicity test. Astra Safety Assessment, Sodertalje, Sweden. [21/1.31]

(12) D3 Astra Report 802-50 T1977, 1994-02-28. Mutagenicity evaluation of LEA 103 in the L5178Y mouse Lymphoma cell thymidine kinase locus mutagenicity test - repeat. Astra Safety Assessment, Sodertalje, Sweden. [46/1.31]

(13) D4 Astra Report 802-50 T2278, 1994-04-11. Genotoxicity evaluation of LEA 103 in the E.coli differential repair test in vitro. Astra Safety Assessment, Sodertalje, Sweden. [70/1.31].

(14) D5 Astra Report 802-50 T2020, 1988-06-23. Analysis of structural chromosome aberrations in human lymphocytes treated with LEA 103 in vitro. Astra Safety Assessment, Sodertalje, Sweden. [85/1.31]

2. In Vivo

(15) D6 Astra Report 802-50 T1893, 1987-06-09. Mouse micronucleus test of LEA103. Astra Safety Assessment, Sodertalje, Sweden. [103/1.31].
(16) D7 Astra Report 802-50 T2285, 1990-06-15. Genotoxicity evaluation of LEA 103 in the E.coli host mediated DNA repair test. Astra Safety Assessment, Sodertalje, Sweden. [125/1.31]
(17) D8 Astra Report 802-50 T2283, 1990-06-15. Somatic mutation and recombination test in Drosophila melanogaster of LEA 103. Astra Safety Assessment, Sodertalje, Sweden. [157/1.31].

IV. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION STUDIES

A. Absorption and Pharmacokinetics [pp 104-116]

(1) G1 Astra Report 802-550 LF 0002-01 Pharmacokinetics of ropivacaine after oral administration in male rats. Eloffson S. [58/1.32]
(2) G2 Astra Report 802-550 LF 0057-01, 1992-04-20. Pharmacokinetics of LEA 103 (ropivacaine) in male rats. Halldin M. [72/1.32].
(3) G8 Astra Report 802-550 LF 0056-01, 1993-03-18. Pharmacokinetic evaluation of LEA 103 (ropivacaine) after repeated intrathecal administration to male rats for 14 days. Lindstrom BE, Halldin M, Engman M. [112/1.32]
(4) G3 Astra Report 802-50 AF 11-2, 1994-06-28. Pharmacokinetic considerations of the study: Dose range finding study of LEA 103 given subcutaneously to rats for 2 weeks. Halldin M. Osterlof G. [133/1.32].
(5) G4 Astra Report 802-50 AF 12-2, 1994-06-28. Pharmacokinetic evaluation of the study: General toxicity of LEA 103 given subcutaneously to rats for 1 month. Halldin M, Osterlof G. [151/11.32].
(6) G5 Astra Report 802-50 AF 90-2, 1988-9-26. Placental transfer and pharmacokinetics of LEA 103 given subcutaneously to pregnant rats. Halldin M, Elofsson S, Danielson M, Osterlof G. [176/1.32].
(7) G7 Astra Report 802-550 LF 0068-01, 1993-04-01. Comparative study of effects during the peri- and postnatal period in rats of ropivacaine (LEA 103) and bupivacaine (LEA131) given subcutaneously: Evaluation of plasma concentration and protein binding. Lindstrom BE, Halldin M, Brunfelter K. [199/1.32].
(8) G9 Astra Report 802-50 AF 91-2, 1988-09-26. Placental transfer and pharmacokinetics of LEA 103 given subcutaneously to pregnant rabbits. Halldin

M, Elofsson S, Danielson M, Osterlof G. [229/1.32]

(9) G10 Astra Report 802-550 LF-0154-02, 1994-05-01. Pharmacokinetics of ropivacaine (LEA 103) in male dogs. Halldin M. [265/1.32].

(10) G11 Astra Report 802-50 AF 71-1, 1986-12-9. Pharmacokinetics of LEA 103 after intravenous and epidural administration in dogs. Arthur GR, Feldman HS, Covino BG. [300/1.32].

(11) Anesth Analg 1988;67:1053-1058 Comparative pharmacokinetics of bupivacaine and ropivacaine, a new amide local anesthetic. Arthur GR, Feldman HS, Covino BG. [321/1.32].

(12) G12 Astra Report 802-550 LF 0106-02, 1993-09-01. Pilot/Dose-finding epidural (continuous infusion) tolerance study in the beagle dog of LEA 103 and LEA 131: Evaluation of the plasma concentration data. Halldin M. [327/1.32].

(13) G13 Astra Report 802-550 LF-0182-01, 1994-02-17. Pharmacokinetics and excretion of LEA 103 (ropivacaine) in dogs after intravenous, subcutaneous and rectal administration. Ekstrom G, Lindstrom, Boo E, Brunfelter K. [347/1.32].

(14) G14 Astra Report 802-50 AF 10-1, 1986-01-22. Pharmacokinetic considerations of the study: a dose range finding study of LEA 103 and bupivacaine given subcutaneously to dogs for 3 days. Halldin M, Osterlof G, Lundin D. [396/1.32]

(15) G15 Astra Report 802-50 AF 19-1, 1986-01-23. Pharmacokinetic evaluation of the study: General toxicity of LEA 103 given subcutaneously to dogs for 1 month. Halldin M, Osterlof G, Lundin D. [1/1.33]

(16) G18 Astra Report 802-24 AF 1-1, 1990-06-18. Dose finding and pilot irritation study in dogs of ropivacaine given rectally for up to 5 days: Evaluation of plasma concentrations of ropivacaine. Halldin M, Boo E, Jonze M. [24/1.33].

(17) G19 Astra Report 802-24 AF 3-1, 1990-08-31. Local tolerance study in dogs of ropivacaine given rectally for 1 month: Evaluation of plasma concentration data. Halldin M, Boo E, Jonze M. [48/1.33]

(18) G16 Astra Report 802-524 LF 0005-01, 1991-11-12. General toxicity study of ropivacaine (LEA 103) given subcutaneously and rectally to dogs for six months: Evaluation of the plasma concentration. Halldin M. Boo E. Brunfelter K Arvidsson T. [111/1.33]

(19) G17 Astra Report 802-24 AF 2-1, 1990-06-18. Plasma concentrations of LEA 103 (ropivacaine) after rectal administration in dogs. Comparison of different gel vehicles. Halldin M, Boo E, Olsen Sundelin C, Jonze M. [176/1.33].

(20) G31 (F33) Astra Report 802-50 AF 48-1, 1986-02-19. Systemic hemodynamics and myocardial kinetics following intravenous administration of LEA 103, bupivacaine and lidocaine to pentobarbital anesthetized pigs. Reiz S, Haggmark S, Johansson G, Nath S. [188/1.33]

(21) G20 Astra Report 802-550 LF-0147-01, 1993-12-23. Pharmacokinetic evaluation of the study: Effects of ropivacaine on uterine blood flow in pregnant sheep. Halldin M, Arthur GR. [230/1.33].

(22) G21 Astra Report 802-50 AF 125-1, 1992-07-02. Pharmacokinetics and serum protein binding in pregnant, fetal and nonpregnant sheep: Systemic toxicity and pharmacokinetics of ropivacaine in pregnant and nonpregnant ewes. Arthur GR. [261/1.33].

(23) Anesth Analg. 1990;70:262-266. Pharmacokinetics of ropivacaine in nonpregnant

and pregnant ewes. Santos CA, Pederson H, Sallusto JA, Johnson HV, Morishima HO, Finster M, Arthur GR, Covino BG. [320/1.33].

(24) G22 Astra Report 802-550 LF-0175-01 Pharmacokinetics, protein binding and systemic toxicity of ropivacaine and bupivacaine in pregnant and nonpregnant ewes. A pharmacokinetic evaluation. Halldin M, Arthur GR. [1/1.34].

(25) G42 Astra Report 802-550 LF-0176-01 Pharmacokinetics, protein binding and systemic toxicity of ropivacaine and bupivacaine in pregnant and nonpregnant ewes. Biotransformation of ropivacaine. Halldin M, Askemark Y, Brunfelter K. [52/1.34].

(26) F37 Astra Report 802-550 LF-0219-01 Pharmacokinetics, protein binding and systemic toxicity of ropivacaine and bupivacaine in pregnant and non pregnant ewes; systemic toxicity evaluation. [96/1.34].

(27) G23 Astra Report 802-550 LF-0204-01. Comparative efficacy of epidurally administered ropivacaine and bupivacaine in the sheep. Evaluation of the pharmacokinetics. Halldin M. [145/1.34].

B. Protein binding [pp 116-118]

1. In Vivo

(28) G28 Astra Report. 802-550 AF 128-1, 1991-01-07. Plasma protein binding of LEA 132 (ropivacaine) and LEA 112 (bupivacaine) in rats after repeated subcutaneous administration . Halldin M. Boo E. Elofsson S. Eklund E. [192/1.34].

2. In Vitro

(29) G32 Astra Report 802-50 AF 20-2, 1996-02-28. Blood/plasma concentration ratio of ^{3}H-LEA 103 and binding to serum protein from man, dog and rat. Elofsson S, Jostell KG, Halldin M. [211/1.34].

(30) G33 Astra Report 802-50 AF 66-1, 1986-10-15. Effect of sex and pregnancy on the in vitro binding of ropivacaine (LEA 103) to human serum proteins. Halldin M, Elofsson S. [224/1.34].

C. Tissue distribution/accumulation [pp 118-120]

(31) G25 Astra Report 802-50 T1732, 1986-01-30. Whole-body autoradiographic study on the distribution of radioactivity in mice after single intravenous injection of LEA 103-^{3}H. Astra Toxicology Laboratories, Sodertalje, Sweden. [245/1.34].

(32) G24 Astra Report 802-50 AF 98-1, 1987-11-11. Retention of LEA 103 (Ropivacaine hydrochloride mono hydrate) in melanin containing tissues of pigmented mice after single subcutaneous administration. Halldin M, Elofsson S. [267/1.34].

(33) G26 Astra Report 802-550 LF 047-01, 1993-10-10. Tissue distribution of ropivacaine (LEA 103) after single intravenous administration to male rats. Elofsson S, Halldin M, Boo E, Neidenstrom P. [286/1.34].

(34) G29 Astra Report 802-550 LF-0151-01, 1994-02-04. Tissue distribution of

^{14}C-ropivacaine (LEA 103) after subcutaneous administration to male dogs. Halldin M. Elofsson S, Lindstrom Boo E. [322/1.34].

D. Metabolism Characteristics, Metabolites, and Excretion [pp 120-129]

1. In Vivo

(35) G34 Astra Report 802-50 AF 99-1, 1987-11-11. Biotransformation of LEA 103 (ropivacaine hydrochloride monohydrate) in pigmented mice after single subcutaneous administration. Halldin M. Elofsson S. [1/1.35]

(36) G35 Astra Report 802-550 LF-0165-01, 1994-02-20. Biotransformation and excretion of ^{14}C-ropivacaine (LEA 103) in male rats following single intravenous and subcutaneous administration. Elofsson S, Halldin M. [16/1.35].

(37) G36 Astra Report 802-50 AF 18-1, 1986-01-23. Biotransformation of LEA 103 in rats. Erixson E, Halldin M. [43/1.35]

(38) G27 Astra Report 802-550 LF-0178-01, 1994-05-01. Distribution of ^{14}C-ropivacaine to milk of lactating rats. Floby E, Elofsson S, Halldin M. [60/1.35].

(39) G38 Astra Report 802-50 AF 92-2, 1988-09-26. Biotransformation of LEA 103 given subcutaneously to pregnant rabbits Halldin M. Elofsson S, Danielson M, Osterlof G, Thorin H. [92/1.35].

(40) G39 Astra Report 802-550 LF-177-01, 1994-06-01. Biotransformation of ^{14}C-ropivacaine (LEA 103) in male and female dogs, following single intravenous, subcutaneous and rectal administration. Elofsson S, Lindstrom Boo E, Halldin M. [114/1.35]

(41) G40 Astra Report 802-50 AF 17-1, 1986-01-23. Biotransformation of LEA 103 in dogs. Elofsson S. Halldin M. Thorin H. [140/1.35].

(42) G37 Astra Report 802-550 LF-0212-01, 1994-03-01. Lack of metabolic racemization of ropivacaine in urine samples of man, dog, rat and sheep. Arvidsson T, Bredberg E, Forsmo Bruce H, Halldin M. [158/1.35].

2. In Vitro

(43) G43 Astra Report 802-550 LF 0117-01, 1993-08-13. In Vitro metabolism of LEA 103 (ropivacaine) in liver microsomes prepared from male animals and man. Ekstrom G, Gunnarsson U-B. [174/1.35]

(44) G44 Astra Report 802-550 LF-0118-01, 1993-12-02. In vitro metabolism of LEA 103 (ropivacaine) in liver microsomes prepared from female animals, including the pregnant rat and man. Ekstrom G, Gunnarsson U-B. [195/1.35].

(45) G45 Astra Report 802-550 LF-0183-01, 1994-02-17. In Vitro metabolism of LEA 103 (ropivacaine) in microsomes prepared from lung and kidney of male and female rats. Ekstrom G, Gunnarsson U-B . [217/1.35].

(46) G46 Astra Report 802-550 LF-0173-01, 1993-12-20. Evaluation of the contribution of cytochrome P4502D to the metabolism of LEA 103 (ropivacaine). Ekstrom G. [234/1.35].

(47) G47 Astra Report 802-550 LF-0172-01, 1993-12-06. Identification of a new metabolite formed from LEA 103 (ropivacaine) that is hydroxylated in the orto methyl group (LEA 166). Ekstrom G. 248/1.35].

Summary, Evaluation and Recommendations [pp 129-137]

Note - Portions of this review were excerpted directly from the sponsor's submission. Studies reviewed previously are summarized in the evaluation sections. The code names cited in studies for ropivacaine (Naropin) and its salts are LEA101, LEA103 and AL381.

Studies Reviewed:

I. PHARMACOLOGICAL ACTIONS

A. Therapeutic Indications

1. In Vivo

(1) F1 Astra Report 802-50 AF 15-1, 1986-02-12. On the local anesthetic effect and the acute toxicity of enantiomers and the racemate of 1-propyl-2',6' -pipecoloxylidide. Akerman B, Hellberg I-B, Trossvik C. [51/1.17]

Local anesthetic effects of LEA 100 (racemic anhydrous hydrochioride), LEA 103 [L-(-) hydrochloride monohydrate], and LEA 104 [D-(+) hydrochloride monohydrate of ropivacaine were compared in a) spinal (subarachnoid) anesthesia in mice, b) infiltration anesthesia in guinea pigs, and c) sciatic nerve block in guinea pigs. Solutions were prepared in 0.9% saline and blinded. The Mann-Whitney U-test was used for statistical evaluation. The acute iv and sc toxicities of the three compounds were determined in male NMRI mice and compared to that of bupivacaine. The study was done by Astra, Sweden in April-May 1985.

RESULTS

No differences were observed between LEA 100, LEA 103, and LEA 104 in time of onset for the spinal block. Dose-related increases occurred in duration of block with all three. At 0.75%, the duration of motor block was significantly longer for LEA 100 (11.4 min); at 1.0% the duration of block (12.0 min) was similar to that of LEA 103 (13.4 min). In the sciatic nerve block, the onset was similar with all compounds. LEA 103 gave longer durations (not significant) in the motor (83-152 min) and sensory block (58-134 min), but at 1.0% concentration, the block duration was decreased somewhat with all compounds. In the infiltration anesthesia, the duration of complete block was longer with LEA 103 at 0.25% and 0.50% concentrations. Duration for complete recovery was longest for LEA 103 and least for LEA 104. In the acute part of the study,

there was little difference between the 50% mortality level of the three forms of ropivacaine following iv administration (11.0 mg/Kg); for bupivacaine iv the value was 7.9 mg/Kg. Values following sq administration were LEA 100 = 135 mg/Kg, LEA 103 = 145 mg/Kg, LEA 104 = 101, and bupivacaine 64 mg/Kg. Unfortunately the cause of death was not investigated.

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(2) F2 Astra Report 802-50 AF 14-1, 1986-02-12. Effects of LEA 103 in spinal anaesthesia (mouse) and epidural anaesthesia (guinea pig). Akerman B, Trossvik C. [69/1.17]

LEA 103, lidocaine, and bupivacaine were compared in spinal (mouse) and epidural (guinea-pig) anesthesia. Each drug was prepared in 0.9% saline from their hydrochloride monohydrate. Concentrations evaluated were 0.25%-1.0% for LEA 103 and bupivacaine. Lidocaine concentrations were 2% and 4%. The study was conducted by Astra, Sweden in April-November 1985.

RESULTS

In the spinal anesthesia, the onset of motor blockage was slightly decreased with increasing concentrations (0.25% to 1.0%) of bupivacaine (15 to 8 sec) or LEA 103 (17 to 10). A dose related and significant increase ($p<0.001$) in the duration of blockage occurred with bupivacaine (4.4-18.9 min) with the above concentrations when compared to the same concentrations of LEA 103 (1.8-13.4 min). Both LEA 103 and bupivacaine produced longer durations of spinal block at lower concentrations than lidocaine.

Epidural anesthesia results showed the mean onset times to be similar for LEA 103 and bupivacaine at all concentrations (0.25%-1.0%). The duration of motor and sensory block was significantly longer with bupivacaine at concentrations of 0.25%-1.0% but the significance decreased with increasing concentrations. The durations were greater for LEA 103 at >0.5% concentrations than for lidocaine at 2% concentration. With drug solutions containing epinephrine (10 μg/ml), the mean onset times were somewhat less for LEA 103 than bupivacaine. Block duration between LEA 103 and bupivacaine was not always significant. Block duration was longer with LEA 103 and bupivacaine than with lidocaine, but not significantly.

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(3) F3 Astra Report 802-50 AF 69-2, 1986-11-26. Sciatic nerve block in the rat: studies on LEA 101 and bupivacaine. Feldman HS. [83/1.17].

LEA 101 (anhydrous HCl) solutions of 0.25, 0.50, 0.75, and 1.0 mg (0.25%-1.0%, 0.1 ml) were compared with bupivacaine (anhydrous HCl) 0.25, 0.50, and 0.75 mg (0.25%-0.75%, 0.1 ml) in sciatic nerve block in male SD rats, 200 to 400 g body weight. Injections were in the hind legs.

RESULTS

The time to onset of block and duration of the block were shorter for LEA 101 at 0.25-0.75 mg. Both parameters were dose dependent. The frequency of block increased from 90% at 0.25 mg to 100 % at 1.0 mg for LEA 101. The results were similar for bupivacaine. At 1.0 mg LEA 101, the time to onset of block was 4.4 ± 0.2 min compared to 5.1 ± 0.2 min for 0.75% bupivacaine - the durations of blocks were about equal. No signs of a prolonged block or adverse conditions were reported. No gross abnormalities were seen at the injection site of any animal. This study was done in the

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(4) Anesth Analg 1988;67:1047-52. Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. Feldman HS, Covino BG. [95/1.17].

These authors evaluated sciatic nerve blockade in rats and motor blockage of lumbar epidural or subarachnoid administration in dogs. Both LEA 103 and bupivacaine were evaluated.

Sciatic nerve block studies indicated 0.5% and 0.75% ropivacaine had a somewhat shorter time of onset (5.0 and 3.0 min respectively) compared to bupivacaine values of 7.9 and 5.1 min, respectively. The duration of block for ropivacaine was 147 min at 0.50% and 143 min at 0.75%; bupivacaine values were 161 min at 0.50% and 143 min at 0.75%.

Ropivacaine was less potent in the dog subarachnoid studies, having a shorter duration of motor block than bupivacaine at equal drug concentrations. The 1% solution of LEA 103 was similar in onset and duration to that of 0.75% bupivacaine. The addition of epinephrine (1:200,000) delayed the onset and increased the duration of motor block with 0.50%-1.0% ropivacaine, but neither were significar .

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(5) F4 Astra Report 802-550 LF-0055-02, 1994-03-28. Intrathecal injection of LEA 103 (ropivacaine) in rats twice daily for 14 days via an indwelling catheter: Local anaesthetic effect. Ask A-L, Alari L, Sjogren L, Stahlberg M. [101/1.17].

Compound: LEA 103, Batch N°. F3
Route: Intrathecal via an indwelling catheter
Number: 6/group, Group 7a contained 3 animals

Dosage: Group:	1	2	3	4	5	6a	6b	7a	7b
mg/day:	0.052	0.106	0.22	0.00	0.22	0.11	0.22	0.00	0.00
μmol/day:	0.160	0.320	0.64	0.00	0.64	0.32	0.64	0.00	0.00

Groups 1, 2, 3 ,4, 5, 6b, and 7b were treated in equally divided doses at 8 am and 4 pm. Groups 6a and 7a were single injections. The concentrations were calculated as LEA 101 (ropivacaine HCl, mol wt. = 310.89).

Volume of Injection: 10 μL bolus drug followed by 15 μL bolus saline flush. Controls were injected with 25 μL saline.
Species: Sprague-Dawley males, 300-350 g body weight, 60-75 days old
Control Treatment: Physiological saline
Study Site: Astra Pain Control AB, Sweden Date: August 1991 to March 1994
GLP/QAU Statements: Both present and signed.

The study was conducted to evaluate the local anesthetic effect of LEA 103 after repeated intrathecal injections via an indwelling catheter. Motor block duration was taken as the inability to walk normally on the hind limbs and recorded on Days 1, 2, 3, 4, 7, 8, 9, 10, 11, and 14. Weight gain was recorded on Days 1, 8, and 14. Groups 1-4 were used for histopathological evaluation of the spinal cord at Th:10 (cranial to the injection site), L:1 (region for the subarachnoidal injection), and at L:5 (caudal to the injection site). Groups 5-7 were used for PK data.

RESULTS

A dose related increase occurred in the duration of motor block. No motor block was observed at 0.16 μmol/day (Group 1). Day 1 block in Group 2 was 2.1 minutes and weak throughout the rest of the study. In Groups 3, 5, and 6b, block duration was relatively stable over the recorded time periods. Tachyphylaxis was not observed. Weight gain reduction was significant ($p<0.05$) for Groups 3, 5, and 6b on Day 8 and for Groups 5 and 6b on Day 14. A slight mononuclear meningeal reaction occurred in 2 or 3 animals of Groups 3 and 4 at Th:10. At L:1, a mononuclear meningeal reaction, focal granuloma, and microfocal axonal (nerve root) changes occurred in all four groups. At section 3 (L:5, caudal to injection site), a meningeal reaction was reported in Groups 1, 3, and 4 in 1 or 3 animals. There was also microfocal axonal (nerve root) changes in Groups 1,2, and 3. In conclusion, the histopathology reported no neurotoxicity. The duration of the motor block did not change over the study period. The PK data are shown in the following tables (from Tables 2, 3a, 3b, 5, and 6; pp. 159, 160, 161).

Mean Plasma Concentration of LEA 103 (nmol/L)

Time (h):	0.08	0.25	0.50	1	2	4	6
Single Injection: (Day 1)							
Group 6a	271.2	189.2	123.7	53.8	<40	<8	
Multiple Injections: (Day 14)							
Group 5	447.5	249.2	156.2	72.5	23.5*		
Group 6b							<8

*From two animals

Pharmacokinetic Parameters

Single Injection

C_{max} (nmol/L)	t_{max} (h)	$t_{½}$ (h)	MRT (h)	$AUC_{0-\infty}$ (nmol·h/L)	CL (mL/min Kg)	V_{ss} (L/Kg)	F (%)
271	0.09	0.41	0.61	167.77	61.96	2.27	71.5

Multiple Injection

C_{max} (nmol/L)	t_{max} (h)	$t_{½}$ (h)	MRT (h)	$AUC_{0-\infty}$ (nmol·h/L)	CL (mL/min Kg)	V_{ss} (L/Kg)	F (%)
447.8	0.11	0.42	0.60	233.99	61.96	2.21	101.5

Limit of detection = 0.008 to 0.08 μmol/L, depending on the sample volume.

These data show a rapid absorption after intrathecal administration, followed by a rapid elimination. The estimated systemic availability was 72% after a single intrathecal injection and 102% after multiple injections.

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(6) F5 (F15) Astra Report 802-50 AF 13-1, 1986-01-12. Primary evaluation of the local anesthetic effect of LEA 103. Akerman B, Hellberg I-B, Sperber B, [165/1.17].

This study evaluated the in vitro block of evoked action potential, sciatic nerve block , intracutaneous anesthesia, topical anesthetic effect, and local irritation of LEA 103. The results were compared to lidocaine HCl monohydrate and bupivacaine HCl monohydrate. This study was done by Astra, Sweden in March-December 1985.

RESULTS

The equilibrium blocks in sheathed sciatic nerves of the frog at three different concentrations of LEA 103 (30% at 10^{-5}M, 60% at $5x10^{-5}$M, 78% at 10^{-4} M) were similar to those of bupivacaine (27%, 46%, 67%) at the same molar concentrations.

The mean time of onset and mean duration of the motor block and sensory block in the sciatic nerve of the guinea pig were similar to bupivacaine at concentrations of 0.25% to 1.0%. However, the duration was significantly longer with bupivacaine at 0.25% (motor and sensory block) and at 0.5% (sensory block). Lidocaine at 2% was less potent than 1.0% LEA 103. The addition of 5 μg/mL of epinephrine prolonged the duration of the block. Maximum duration of the block was seen with a 0.75% solution of either drug, with or without added epinephrine.

LEA 103 and bupivacaine were unable to produce complete anesthesia in the intracutaneous wheal pin-prick test in the guinea pig at 0.125%. At 0.25-0.75%, LEA 103 was significantly longer acting than bupivacaine. The effectiveness of the three drugs improved with the addition of 5 μg/mL of epinephrine solution. LEA 103 was significantly more potent at the higher concentrations with epinephrine.

In the corneal anesthesia study, no significant differences were seen with 0.5%-1.0% concentrations in the duration or time of onset of the block with LEA 103 and bupivacaine.

Irritation scores for the rabbit ear dermal study were lower with LEA 103 at 0.75% and 1.0% concentrations than with bupivacaine. Slight hyperemia and edema that developed remained for 2-3 days. Scores for lidocaine were less than either LEA 103 or bupivacaine.

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(7) Acta Anaesthesiol Scand 1988;32:571-78. Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). Akerman B, Hellberg IB, Trossvik C. [188/1.17].

This publication reported on the block potential in isolated sheathed sciatic nerve of the frog and on the following in vitro studies: a) sciatic nerve block in male guinea pigs, b) brachial plexus block in male guinea pigs, c) epidural anesthesia in male guinea pigs, d) spinal (subarachnoid) anesthesia in male mice, e) infiltration anesthesia in male guinea pigs, local irritation in male rabbits, and f) acute toxicity (IV and SC) toxicity in male NMRI mice.

The IC_{50} value in the action potential of the frog nerve was 4 μmol/L for ropivacaine and 5 μmol/L for bupivacaine. In the sciatic nerve block, the duration was of the order: S (-) enantiomer > racemate > R (+) enantiomer. Differences between the three forms were significant at 0.5% concentration. In the intradermal wheal test (pin prick), the S (-) enantiomer was 3x more effective than the R (+) enantiomer, with the racemate falling between the S (-) and R (+) enantiomers. No significant differences were reported between ropivacaine and bupivacaine in duration and mean onset time in the sciatic nerve block. Epinephrine prolonged the duration of the sciatic block. Ropivacaine and bupivacaine were equally effective in the brachial plexus block. In epidural anesthesia, bupivacaine was significantly more effective in the mean duration and mean onset time to block. With the spinal and epidural block, ropivacaine was somewhat shorter lasting. No signs of necrosis were reported in the study. Recovery from the block was complete with no apparent effects, other than slight irritation.

There were no signs of any systemic toxicity. The cause of mortality was not determined. The 50% lethality values for ropivacaine, bupivacaine, and lidocaine were as follows:

	IV	SC
Ropivacaine (mg/Kg):	11.0 ± 0.2	144.8 ± 8.8
Bupivacaine (mg/Kg):	7.9 ± 0.4	64.5 ± 5.0
Lidocaine (mg/Kg):	18.8 ± 2.5	288.9 ± 22.7

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(8) F6 Astra Report 802-550 LF-0228-01, 1994-04-30. Local anesthetic effects of 3-hydroxy- and 4-hydroxy ropivacaine in the guinea-pig. Akerman B, Hellberg I-B, Halldin M. [196/1.17]

The local anesthetic effects were determined for 3'-hydroxy R,S-ropivacaine

(LEA-145), the major conjugated metabolite in urine in all species, and 4'-hydroxy R,S-ropivacaine (LEA-144), a minor metabolite in most species. The compounds (10 mg/mL) were injected (0.2 mL) into the space surrounding the sciatic nerve of male guinea pigs, 6/group (from Table 1, p. 206).

	Sciatic Nerve Block in Minutes			
	Motor Block		Sensory Block	
	Onset	Duration	Onset	Duration
3'-Hydroxy-	≤1	47.0 ± 2.7[a]	3.5 ± 0.6[a]	33.3 ± 3.1[a]
4'-Hydroxy-	≤1-3[b]	23.6 ± 1.0[a]	no block obtained	

[a] calculated for successful block
[b] range for successful block

Motor and sensory block were seen with the 3'-hydroxy compound. The 4'-hydroxy compound produced a motor block but sensory block was not observed. Block duration for both compounds was much shorter than that for ropivacaine. No adverse reactions or sequelae were reported. The study was done in February 1987 by Astra, Sweden.

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(9) F7 Astra Report 802-50 AF 59-1, 1986-09-23. Brachial plexus block in the guinea pig with LEA 103, bupivacaine and lidocaine with and without adrenaline. Akerman B, Hellberg I-B. [207/1.17].

The effects of brachial plexus block after injection of 0.2 mL of solutions (0.5% and 0.75% LEA 103 and bupivacaine), 2.0% lidocaine with and without adrenaline 5 μg/ml, produced similar results. Adrenaline addition resulted in an increase in the duration of both motor and sensory block. Only minor changes were seen between the low and high dose. One animal in each group convulsed (2-15 minutes) when injected with the 0.75% solution of either LEA 103 or bupivacaine. Recovery was completely reversible. These studies were conducted in June-October of 1986 by Astra, Sweden.

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(10) F8 Astra Report 802-50 AF 63-1, 1986-09-22. A comparative study of LEA 103, AL 381 and bupivacaine in epidural anesthesia in the guinea pig. Akerman B, Trossvik C. [216/1.17]

The time to onset of block and frequency of block were evaluated for LEA 103 (batch 465-4-1 or 472-3-1 without epinephrine and 484-3-1 with 5 μg/mL epinephrine), bupivacaine (Marcaine - hydrochloride monohydrate, without and with 5 μg/mL epinephrine), and AL 381 (the hydrochloride anhydride of LEA 103) without and with epinephrine 5 μg/mL in epidural anesthesia in the guinea pig. Coded solutions were used. Concentrations used were 0.75% and 1.0% at 0.1 mL. Previous results were confirmed in this study. Slightly shorter durations were produced with LEA 103 at equal % concentrations. The duration of the block was prolonged with the addition of adrenaline in the three compounds. Astra, Sweden did the study in June-July 1986.

(11) F9 Astra Report 802-50 AF 49-1, 1986-02-17. AL 381 - primary evaluation of efficacy as a spinal and epidural local anaesthetic agent. Feldman HS. [233/1.17].

The study was done in mongrel dogs to evaluate AL 381 (LEA 101) as a spinal and epidural local anesthetic. In the spinal anesthesia (subarachnoid), 1.0 mL of 0.75% or 1.0% AL 381 was injected, followed by 0.5 mL flush with sterile dextrose solution. In the epidural anesthesia, 3.0 mL of 0.75% bupivacaine or 1.0% Al 381 was injected, followed by a 0.5 mL flush with sterile saline. Lidocaine (5%) was also evaluated. Comparison was made to the firm's data base on lidocaine, bupivacaine, and tetracaine. The study was done by Astra, Sweden in November-May 1984.

RESULTS

Al 381 (1%) was comparable with that of 5.0% lidocaine, 1.0% tetracaine, or 0.75% bupivacaine regarding the onset of motor and sensory block in the intrathecal studies. In the epidural anesthesia block, 1.0% AL 381 had a longer time (29%) to onset of motor block, a shorter duration of block (26%), and a shorter time (25%) to complete recovery. The results were said to be not significant (Student's t-test). The animals recovered with no apparent motor or sensory deficit or apparent adverse reactions. The study stated the relative potency of AL 381 is slightly less than bupivacaine (1.0% AL 381 vs 0.75% bupivacaine), but no substantial clinical difference occurred.

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(12) Anesth Analg 1988;67:1047-52. Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. Feldman HS, Covino BG. [250/1.17]

Ropivacaine and bupivacaine were compared as local anesthetic agents for sciatic nerve block in the rat. At concentrations of 0.5% and 0.75% ropivacaine, a significant ($p < 0.05$) mean onset of 5.0 min and 3.0 min to block was seen, respectively. Bupivacaine values for these concentrations were 7.9 minutes and 5.1 minutes, respectively. The duration of the block was significantly shorter for ropivacaine. No signs of adverse reactions or irreversible blocks were reported. In the subarachnoid and epidural block in the dog, no significant difference was reported for the onset at 0.75%, but the duration of block was about 37% shorter for ropivacaine. No adverse reactions were reported.

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(13) F10 Astra Report 802-50 AF 70-2, 1986-12-01. Epidural anesthesia in the dog: A comparative efficacy study of LEA 103 and bupivacaine plain solutions and solutions containing epinephrine. Feldman HS. [256/1.17].

LEA 103 and bupivacaine were evaluated in the onset of motor block and time to complete recovery in epidural administration (3.0 mL) in dogs. LEA 103 was less potent in frequency of block compared to bupivacaine at ≥ 0.5 % concentration. The treatment also included drug administration with epinephrine (1:200,000). No block duration or

frequency of block was seen at 0.25% with either drug in the presence or absence of epinephrine. The time to complete recovery was less with LEA 103 than with bupivacaine at all concentrations with or without epinephrine. No significant differences were seen in these experiments. No adverse reactions or prolonged blocks were reported in any animal in the study. These tests were done by the

Blood samples were taken for pharmacokinetic evaluations. These results are contained in (10) G11 (Report No. 802-50 AF 71-1) in the ADME section.

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(14) Anesth Analg 1988;67:1047-52. Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. Feldman HS, Covino BG. [278/1.17].

This publication was submitted along with (11) F9. The data and results of the study are contained above in (12).

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(15) F12 Astra Report 802-550 LF-0167-01 Comparative local anesthetic efficacy of epidurally administered ropivacaine and bupivacaine in the dog. Feldman HS. [284/1.17].

This was a comparative potency study in dogs with LEA 103 and bupivacaine as a local anesthetic after epidural injection. The drugs were injected into the lumbar epidural space through an indwelling catheter. The volume injected was 3.0 mL of 5.0 mg/mL or 7.5 mg/mL solutions, followed by 0.3 mL saline flush. Blood was also taken for determining serum concentrations of the drugs and serum protein binding. QAU and GLP statements are present and signed. The study was performed at

RESULTS

- findings were similar to what was reported in earlier studies-
- ropivacaine had a shorter duration of motor block than bupivacaine at equal concentration; significance was seen with ropivacaine at 7.5 mg/mL-
- sensory block was similar between both drugs at equal concentration-
- onset to motor block was shorter with bupivacaine at equal concentrations-
- mean time to complete recovery was less for ropivacaine at both concentrations-
- clinical signs: shivering in 40%-75% of animals in all groups, front limb paralysis, diaphragmatic breathing, ptosis, emesis, and relaxed nictitating membranes-all signs were of short duration-
- total serum concentration (μg/mL)-

Time (min):	2	4	6	8	10	12.5	15
Ropivacaine 5 mg/mL:	0.66	0.72	0.66	0.60	0.53	0.47	0.43
7.5 mg/mL:	0.95	1.09	1.00	0.93	0.82	0.72	0.63
Bupivacaine 5 mg/mL:	0.77	0.85	0.73	0.61	0.53	0.44	0.40
7.5 mg/mL:	1.13	1.25	1.11	0.99	0.84	0.71	0.61

- serum protein binding for ropivacaine was >98% and >99% for bupivacaine-

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(16) F13 Astra Report 802-550 LF-0229-01 Comparative efficacy of epidurally administered ropivacaine and bupivacaine in the sheep. Evaluation of the local anesthetic effects. Feldman HS. 389/1.17].

This study compared the epidural efficacy of ropivacaine and bupivacaine as local anesthetics in female sheep. The drugs were administered through an indwelling catheter as 5.0 mL solutions of 5.0 mg/mL or 7.5 mg/mL. The study evaluated the time to onset, the duration and frequency of sensory and motor block, and the loss of panniculus reflex. Arterial blood was taken for determining serum concentrations of the drugs - these results are reported in (27) G23 Astra Report 802-550-LF-0204-01 in the ADME section. GLP/QAU statements were present and signed.

RESULTS

- no differences in rectal temperature, Hct, or mean % Hct at day of surgery or after epidural injection-
- no difference in mean onset of sensory block or motor block-
- no difference in duration of sensory motor block-
- mean complete recovery time significantly higher for 5.0 mg/mL bupivacaine vs 5.0 mg/mL ropivacaine-
- sensory block was somewhat higher with 5.0 mg/mL ropivacaine vs bupivacaine-
- time to complete recovery was significantly shorter with 5 mg/mL ropivacaine vs same concentration of bupivacaine-
- blocks were reversible in all groups-
- adverse reactions for ropivacaine were diaphragmatic breathing and ptosis-(1/12); none required treatment-

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(17) F14 Astra Report 802-550 LF-0202-01 Epidural anesthesia in the rhesus monkey with ropivacaine (EA 103). Bridenbaugh PO, Denson DD. [461/1.17]

The epidural (L4-5 or L5-6 interspace) effects of ropivacaine was studied in one male and 5 female Rhesus monkeys. These monkeys were estimated to be 13 to 20 years old. Ropivacaine was administered via an implanted catheter at 5.0, 7.5, and 10.0 mg/Kg (0.5, 0.75, 1.0%) at 2 or 3 mL to each animal. The solutions were injected in 1

mL increments at 5 min intervals, with a washout period of 2-6 weeks allowed between doses. A pilot study was done in 1 monkey with 3 mL of 0.5% ropivacaine administered over 90 seconds. Motor block in the hind legs, mean arterial BP, and foot temperature were recorded. These experiments were done at

RESULTS

- the pilot monkey died after severe respiratory insufficiency- catheter was found to be in subdural space and not in the epidural or subarachnoid space-
- 0.75% and 1.0% with 3 mL dose was more effective than 0.5% in producing onset, blocking score, and duration of motor block-
- ↑ skin (foot) temperature (3.2°C - 4.3°C) with all solutions-
- % ↓ in mean arterial blood pressure (% from baseline)-

2 mL Volume			3 mL Volume		
0.5%	0.75%	1.0%	0.5%	0.75%	1.0%
31.8	54.6	51.3	50.0	44.0	47.2

- % ↑ change (+) in heart rate from baseline-

2 mL Volume			3 mL Volume		
0.5%	0.75%	1.0%	0.5%	0.75%	1.0%
2.8 ± 16.6	24.2 ± 10.7	19.9 ± 16.8	18.5 ± 11.6	22.023.9	0.0 ± 17.5

- moderate/marked hypotension that developed responded to fluids or fluids + ephedrine-
- all monkeys recovered completely without any sequelae-

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(18) Biopharmaceutics and Drug Disposition 1993; 14:773.1-10. Pharmacokinetics of intravenous and epidural ropivacaine in the rhesus monkey. Katz JA, Sehlhorst CS, Thompson GA, Denson DD, Coyle D, Bridenbaugh PO. [495/1.17].

This reprint reports on the absorption and disposition of ropivacaine in six rhesus monkeys in an open two-way crossover study following iv and epidural administration. The monkeys were administered 1 mg/Kg iv over 1 minute or 10 mg epidural (1 mL of 0.5% at 5 minutes apart).

RESULTS

The iv results were as follows: $V_{ss} = 1.11 \pm 0.198$ L/Kg, total CL = 0.711 ± 0.158 L/hr/Kg, and the terminal phase volume of distribution $t_{\frac{1}{2},z} = 2.07 \pm 0.438$ hr. Absorption was biphasic and the mean bioavailability was 0.950 following epidural administration. The pharmacokinetic profile was said to be similar to that of other local anesthetics administered by these routes.

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2. In Vitro

(19) F5 (F15) Astra Report 802-50 AF 13-1, 1986-02-12. Primary evaluation of the local

anesthetic effect of LEA 103. Akerman B, Hellberg I-B and Sperber B. [165/1.17].

See Study N° (6) (F5) above.

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(20) Acta Anaesthesiol Scan 1988;32:571-78. Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). Akerman B, Hellbery IB, and Trosavilz C. [188/1.17].

See Study N° (7) above.

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(21) F16 Astra Report 802-50 AF 74-1, 1986-11-28. Effects of LEA 103 and bupivacaine on action potential propagation in frog sciatic nerve in vitro. Ask A-L, Sperber B, Akerman B. [505/1.17].

LEA 103 and bupivacaine were compared in their ability to block the action potential in a sheathed sciatic nerve of the frog. A Grass stimulator was used to produce the action potential. LEA 103 and bupivacaine were evaluated from 1 μM to 50 μM at pH 7.4. The approximate IC_{50} values were 4 μM for LEA 103 and 5 μM for bupivacaine, when evaluated by the decrease in the amplitude of the action potential. At 50 μM concentration, LEA 103 was significantly greater than bupivacaine in depressing the amplitude of the action potential (100% vs 78%). All blocks were reversible within 2 hours. The study was run by Astra, Sweden in March-April 1986.

B. Effects Related to Possible Adverse Reactions

1. In Vivo

(22) F18 Astra Report 802-50 AF 56-1, 1986-02-20. Effects on electrocardiogram and convulsive properties of LEA 103, bupivacaine and lidocaine in the conscious rat. Forsberg T, Nilsson S, Sperber B, and Oberg E. [124/1.18].

Study N°: AF 8536
Compound: LEA 103, batch F1 (245/16)
Bupivacaine HCl monohydrate
Lidocaine HCl monohydrate
Formulation: Not indicated.
Route: IV, tail vein at 0.50 - 0.54 mL/Kg, over 5 seconds. Catheter flushed with 0.3 mL saline over 10 seconds following drug administration.
Dose Levels: LEA 103 (μmol/Kg): 0 5 7 10 14 20 28
Bupivacaine (μmol/Kg): 5 7 10 14 20
Lidocaine (μmol/Kg): 14 20 28 40 56
Strain: Sprague-Dawley males, 290-360 g body weight, 60-80 days old.
Number: 8/group

Control Treatment: Physiological saline, 9 mg/mL
Study Site: Astra Läkemedel R and D Labs., Sweden
Date: April 22, 1985 - February 20, 1986
GLP/QAU Statements: Both present and signed.

This study was done in conscious restrained rats to evaluate and compare the EKG and convulsive effects of LEA 103 with those of bupivacaine and lidocaine. EKG leads I, II, III were recorded up to 15 minutes after the injection. The PQ, QRS, and QT intervals of the EKG (lead II) at 2-5 seconds after the injection (maximum changes were said to occur at this time) were compared to pretreatment values. Only arrhythmias occurring during the first 60 seconds after the injection were included in the evaluation. This was said to avoid arrhythmias secondary to respiratory arrest and hypoxia. Local anesthesia was with 0.05 mL of prilocaine.

RESULTS

LEA 103

- no effect from control saline solution.
- mortality: 1/8 at 10 μmol/Kg, 4/8 at 14 μmol/Kg, 3/8 at 20 μmol/Kg, and 8/8 at 28 μmol/Kg.
- dose related arrhythmias beginning at 10 through 28 μmol/Kg.
- dose related ↑ in PQ, QRS, and QT intervals from 5 to 14 μmol/Kg.
- significant prolongation of PQ interval and widening of QRS complex.
- return to normal PQ and QRS with 5 and 7 μmol/Kg by 2 minutes.
- heart rate decreased at 5 - 10 μmol/Kg; significant ↓ at 10 μmol/Kg.
- convulsion incidence and duration ↑ with increase in dosage.
- threshold for convulsion, arrhythmia and death was 10 μmol/Kg.

Bupivacaine

- mortality: 2/7 at 7 μmol/Kg, 4/8 at 10 μmol/Kg, 2/8 at 14 μmol/Kg, and 8/8 at 20 μmol/Kg.
- dose related arrhythmias beginning at 5 μmol/Kg through 20 μmol/Kg.
- dose related ↑ in PQ, QRS, and QT intervals from 5 - 10 μmol/Kg; all significant.
- heart rate ↓ (significant) at 5 μmol/Kg (11%) and at 7 μmol/Kg (20%).
- EKGs at 10-20 μmol/Kg not evaluated due to high mortality.
- sinus bradycardia at 7 μmol/Kg.
- convulsion incidence and duration ↑ with increase in dosage.
- threshold for arrhythmias was 5 μmol/Kg.
- threshold for convulsion and death was 7 μmol/Kg.

Lidocaine

- mortality: 2/8 at 28 μmol/Kg, 6/8 at 40 μmol/Kg, and 8/8 at 56 μmol/Kg.
- small but significant ↑ in PQ and QRS intervals.
- high incidence of arrhythmias at 20 μmol/Kg made EKG evaluations impossible.
- arrhythmias beginning at 20 μmol/Kg.
- heart rate ↓ (significant) at 14 μmol/Kg (15%), 20 μmol/Kg (23%), 28 μmol/Kg (35%).
- ↓ heart rate was dependent upon sinus bradycardia.

- convulsion incidence and duration ↑ with increase in dosage.
- threshold for arrhythmia was 20 μmol/Kg
- threshold for convulsion and death was 28 μmol/Kg

With increase in dose, the arrhythmias increased in severity from I to II to III:
I) second degree atrioventricular block (AV-block II) and single ventricular extra beats (VES) to.
II) complex arrhythmias of short duration (< 10 seconds) including early ventricular beats interfering with the preceding T- wave, runs of 2 or more VES, bigeminy and supraventricular tachycardia to.
III) complex sustained arrhythmias (more than 10 seconds), including ventricular or supraventricular tachycardia and slow irregular ventricular rhythm.

Arrhythmias occurred at 10-28 μmol/Kg with LEA 103, at 5-20 μmol/Kg with bupivacaine, and at 20-56 μmol/Kg with lidocaine. The severity of the arrhythmias increased with increasing dose. At equimolar concentrations, fewer animals were affected with LEA 103 than with bupivacaine but more than with lidocaine.

MORTALITY AND CONVULSIONS (from Table 6, p. 145)

Dose	Mortality			Convulsions Incidence/Duration		
(μmol/Kg)	LEA	B	L	LEA	B	L
5	0/8	-	-	0/-	0/-	
7	0/8	2/7	-	0/-	7/29 ± 7*	
10	1/8	4/8	-	2/25,27	8/53 ± 22	
14	4/8	2/8	-	8/50 ± 16	8/94 ± 40	0/-
20	3/8	8/8	-	8/78 ± 30	8/21 ± 8	0/-
28	6/8		2/8	8/		8/19 ± 8
40			6/8			7/23 ± 7
56			8/8			8/15 ± 11

*n = 7

LEA = LEA 103, B = bupivacaine, L = lidocaine

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(23) F39 Astra Report 802-550 LF-0186-01, 1994-01-26. Spinal cord blood flow after intrathecal injection of ropivacaine and other local anaesthetic agents to male rats. Post C, Freedman J. [168/1.18]

Spinal cord blood flow was evaluated in male Sprague-Dawley rats following intrathecal injection of LEA 103 (1.25, 2.5, 5, 7.5, 10 mg/mL), bupivacaine (1.25, 2.5, 5, 7.5 mg/mL), lidocaine (2.5, 5, 10, 20, 50 mg/mL), tetracaine (1, 3, 10 mg/mL), and adrenaline (2.5, 5, 10, 20, 50 μg/mL). The study used a laser Doppler instrument for measuring blood flow. The spinal column was exposed (L_1-L_3) by bilateral laminectomy and fixed in the spinal unit to control minimal respiratory movement of the cord. The study was done in May-July, 1989 at Astra, Sweden. GLP/QAU statements not present.

RESULTS

- all drugs produced a dose dependent ↓ in spinal cord blood flow.
- maximum ↓ was 48% for bupivacaine (7.5 mg/mL), 54% for ropivacaine (7.5-10 mg/mL), 61% for lidocaine (50 mg/mL), 75% for tetracaine (10 mg/mL), and 66% for adrenaline (2.5 µg/mL).

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(24) F40 Astra Report 802-550 LF-0205-01, 1994-05-06. Spinal cord blood flow after intrathecal injection of ropivacaine, bupivacaine with or without epinephrine in rats. Kristensen JD, Karlsten R, Gordh T, Ask, A-L. (182/1.18).

This study measured spinal cord blood flow using the laser-Doppler technique in continuously, spontaneously breathing of enflurane/N_2O in anesthetized male Sprague-Dawley rats. The results indicated ropivacaine and bupivacaine produced a dose-related and transient ↓ in the spinal cord blood flow in the absence of adrenaline. Bupivacaine plus adrenaline (50 ng) produced the same reduction at all doses of bupivacaine. Ropivacaine in the presence of adrenaline was not evaluated.

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(25) F41 Astra Report 802-550 LF 0008-01, 1992-01-16. Effects of subcutaneous injections of LEA 103 (ropivacaine hydrochloride monohydrate), lidocaine hydrochloride, lidocaine hydrochloride with adrenaline and adrenaline on local circulation in the hind paw in the rat. Forsberg T, Carlsson S, Ericson A-C, Akerman B. (204/1.18).

The study was done to determine if LEA 103 can induce ischemia and necrosis when injected subcutaneously in an extremity (hind paw). Male Sprague-Dawley rats (285-345 g body weight) were used in the study. One subcutaneous injection was administered on the dorsal side of the right hindpaw. There were 12 groups of 10/group: (1) saline (1 mL), (2) LEA 103 2.6 mg/mL, (3) LEA 103 5.3 mg/mL, (4) LEA 103 7.9 mg/mL, (5) lidocaine HCl 10 mg/mL with methylparaben, (6) lidocaine HCl 10 mg/mL + 10 µg/mL adrenaline, (7) LEA 103 10.6 mg/mL, (8) lidocaine HCl 5 mg/mL, (9) lidocaine HCl 7.5 mg/mL, (10) lidocaine HCl 10 mg/mL, (11) lidocaine HCl 10 mg/mL + 0.5 mL saline, (12) adrenaline 10 µg/mL.

RESULTS

- no signs of ischemia leading to necrosis were reported for LEA 103 at ≤ 10.6 mg/mL.
- LEA 103 at 10.6 mg/mL caused local irritation and pallor of short duration in 2/10.
- lidocaine with adrenaline produced cyanosis/swelling and skin loss.
- adrenaline caused pallor of short duration.

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(26) F30 Astra Report 802-50 AF 118-1, 1992-09-02. Treatment of acute toxicity resulting from rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Feldman HS. (186/1.25).

Study N°: US 8805
Compounds: LEA 103, batch F3; bupivacaine HCl monohydrate, batch 655-38-01
Formulations: Not indicated.
Route: Rapid bolus (30-60 seconds) in forelimb vein.
Dose Levels: LEA 103: 4.9 mg/Kg - this is a predetermined convulsive dose.
Bupivacaine: 4.3 mg/Kg - this is a predetermined convulsive dose.
Strain: Male Beagles, 12.6 ± 1.7 Kg body weight, 10-27 months of age.
Number: 6/group
Study Site:
Date: April 24, 1989 - September 2, 1992.
GLP/QAU Statement: GLP/QAU statements present with signatures.

The object of this study was to formulate a treatment for acute toxicity resulting from rapid iv administration of ropivacaine and bupivacaine.

A convulsive dose was administered on Day 1 and 2x the convulsive dose (9.8 mg/Kg ropivacaine or 8.6 mg/Kg bupivacaine) at 48 hours after the first injection. Catheters were inserted into the abdominal aorta and inferior vena cava via the femoral vessels 48 hours prior to the first administration, for BP recordings and blood sampling. In addition, a catheter was inserted into the right external jugular vein for the recording of the EKG. The dogs received 600,000 units of Penicillin G-benzathine suspension and allowed to recover 48 hours. The study includes the following determinations: EKG, blood gases, electrolytes, lactic acid, catecholamines, drug concentrations, and observations. Tracheal intubation and mechanical ventilation with O_2 enriched air was started following thiamylal control of any seizures.

RESULTS

Ropivacaine (4.9 mg/Kg):

- no deaths.
- significant ↓ in heart rate (54%), mean arterial BP (27%), inferior vena cava pressure (6.85x), EKG conduction times, blood lactate (3x), K (17%) and catecholamine concentrations (epinephrine 7.2x, norepinephrine 3.7x).
- PR interval ↑ ($p<0.0$, 19%) and PR segment ↑ ($p<0.05$, 23%) after injection.
- QRS and QT intervals ↑ significantly ($p< 0.01$., 0.05, 20%) between 5-15 minutes.
- significant ↓ in arterial blood pH (0.8%) with seizure activity.
- PaO_2 ↓ 3.79x at 3-15 minutes - $PaCO_2$ ↑ 16% at 5 minutes.
- seizures in all dogs 45 ± 14.6 seconds after injection.
- seizures controlled by 10 mg/Kg iv thiamylal.
- at 4.9 mg/Kg, one dog had two premature atrial beats and several premature atrial contractions while on ventilator and at 60-76 min when removed from ventilator.
- blood concentration = μg/mL at minutes to μg/mL at min after end of injection.

Ropivacaine 9.8 mg/Kg

- no deaths.
- hypotension in 1/6 - treated with 0.75 mg iv epinephrine which produced nodal tachycardia that was treated with 20 mg/Kg iv bretylium, converting to normal sinus rhythm.
- convulsions rapidly terminated with 10 mg/Kg iv thiamylal.
- 1/6 developed tachycardia and bigeminy while ventilated.
- 1/6 developed ventricular tachycardia 13 to 15 seconds during and after seizures.
- ↑ heart rate significant (35%-48%).
- ↑ in PR interval significant (28%).
- ↑ significant in QRS (63%) and QT intervals (37%).
- BP increased 32%, not significant.
- ↑ inferior vena cava pressure significant (6.1x control).
- respiration rate decreased but not significant.
- ↑ PaO_2 significant 4.6x control - ↓ K significant (22%).
- ↑ lactate (4.9x).
- ↑ epinephrine and norepinephrine significant.
- blood concentrations decreased from ↓ µg/mL at min to µg/mL at min.

Bupivacaine 4.3 and 8.6 mg/Kg

- significant ↑ in heart rate, mean arterial BP, inferior vena cava pressure, EKG conduction times, blood lactate/K/catecholamine concentrations, and ↓ in blood pH.
- seizures were abolished by 10 mg/Kg iv thiamylal.
- 2/6 high dose dogs developed hypotension, respiratory arrest, ventricular tachycardia, and ventricular fibrillation and could not be saved with intervention.

Both drugs produced significant changes in BP, heart and respiration rate, inferior vena cava pressure, EKG conduction times, arterial blood pH, gas tensions and electrolytes (PaO_2, $PaCO_2$, K), blood lactate concentrations, and catecholamine concentrations (epinephrine and norepinephrine). Convulsions caused by both drugs were abolished with 10 mg/Kg iv thiamylal. Ventricular arrhythmias developed with either drug; however, the severe hypotension, ventricular tachycardia, and ventricular fibrillations that occurred in two 8.6 mg/Kg iv bupivacaine treated dogs resulted in death. Resuscitative efforts with epinephrine (multi doses), bretylium, external cardiac compression, and direct current cardioversion were unsuccessful. One died 7.5 minutes after drug administration; the other died 37 minutes after drug administration.

The results of the study tend to indicate less cardiotoxicity and fewer arrhythmias from convulsive doses of ropivacaine when compared to convulsive doses of bupivacaine.

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(27) Anesth Analg 1991; 73:373-84 Treatment of acute systemic toxicity after the rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Feldman HS, Arthur GR, Pitkanen M, Hurley R, Doucette AM, Covino BG. [396/1.25]

This reprint reports the results from the above study.

(28) F11 (F32) Astra Report 802-50 AF 101-1, 1992-03-04. Hemodynamic effects of epidural anesthesia in the dog with ropivacaine and bupivacaine. Feldman HS. [239/1.18].

Blood concentrations, hemodynamic changes, and local anesthetic effects were examined after epidural injection of 10 mg/mL ropivacaine HCl or 7.5 mg/mL bupivacaine HCl, both without or with 5 μg/mL epinephrine (1:200,000). The volume of injection was 3.0 mL via an indwelling lumber epidural catheter. There were two groups of 6 male beagles. The four solutions were administered at 48 hour intervals.

RESULTS

Noted changes:

- no deaths in the 4 groups:
- heart rate: significantly ↓ (20%-34%) with plain ropivacaine (no epinephrine) over 5-240 minutes.
- EKG conduction time: PR interval significantly ↑ (6%-12%) with ropivacaine plus epinephrine - QRS interval ↑ (4%-10%) in ropivacaine over 10-140 minutes.
- arterial BP: systolic and diastolic ↓ in all 4 groups - mean BP ↓ in all 4 drug groups.
- central venous pressure: ↑ in both bupivacaine groups and plain ropivacaine.
- systolic pulmonary artery pressure: ↑ in 4 drug groups.
- diastolic pulmonary artery pressure: significant ↑ in plain ropivacaine (36%) and bupivacaine (28%).
- mean pulmonary artery pressure: significant ↑ in plain bupivacaine (25%) and ropivacaine (30%).
- pulmonary artery wedge pressure: significant ↑ in plain bupivacaine (52%).
- cardiac output: significant ↓ in the four drug groups.
- stroke volume: reduced at times in 4 groups.
- respiration: significant ↓ in bupivacaine and ropivacaine.
- body temperature: no significant changes.
- sensory block: mean duration of sensory block 70% longer for ropivacaine than with bupivacaine - block duration for ropivacaine decreased with epinephrine and increased with bupivacaine.
- onset of motor block was similar in the four groups.
- onset of sensory block was similar for ropivacaine and bupivacaine and required a longer onset time with added epinephrine.
- toxic signs:

	ropivacaine	bupivacaine
loss of weight support in front limbs	2/6	2/6
ptosis	6/6	3/6
relaxed nictitating membrane	4/6	3/6
salivation	0/6	1/6
seizures during injection	1/6	0/6

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	ropivacaine	bupivacaine	
Cmax (μg/mL)	1.11	0.84	both ↓ with epinephrine
Tmax (min)	8.67	4.00	ropivacaine ↑ with epinephrine

- RBC concentration: ropivacaine (0.13 μg/mL), bupivacaine (0.09 μg/mL) at 4 min.
- plasma concentration: ropivacaine (1.60 μg/mL), bupivacaine (1.51 μg/mL) at 4 min.

The hemodynamic changes were comparable between ropivacaine and bupivacaine. The addition of epinephrine to bupivacaine and ropivacaine did not greatly change the epidural results of either drug. All EKG values were within the clinical limits for the dog.* Hypotension occurred within 5 to 10 minutes after the drugs were administered but did not approach a point where intervention was necessary with vasopressor agents; by 240 minutes recovery had begun. Although the cardiac output was decreased and delayed with epinephrine, the values were said to be within an acceptable clinical range requiring no intervention. Cardiac output and mean arterial blood pressure showed significant reductions in both drugs. The plasma concentration in the dog with seizure was 0.93 μg/mL; this is below the 4 μg/mL shown earlier to produce seizures. The explanation was that it was related to a physical phenomenon, such as a subarachnoid pressure change.

In conclusion, the changes seen with 10 mg/mL ropivacaine were similar to those observed with 7.5 mg/mL bupivacaine.

* Detweiler D, Buchanan J, Fregin G. Cardiovascular system/heart. In: Anderson A, Good L, eds. The Beagle as an Experimental Dog. Ames, Iowa State Univ. Press, 1970: 239-246.

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(29) Reg Anesth 1991;16(6);303-8 The effects of epinephrine on the anesthetic and hemodynamic properties of ropivacaine and bupivacaine after epidural administration in the dog. Hurley RJ, Feldman HS, Latka C, Arthur GR, Covino BG. [321/1.18].

This reprint reports on the results obtained in the above study.

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(30) F33 (G31) Astra Report 802-50 AF 46-1, 1986-02-19. Systemic hemodynamics and myocardial kinetics following intravenous administration of LEA 103, bupivacaine and lidocaine to pentobarbital anesthetized pigs. Reiz S, Haggmark S, Johansson G, Nath S. [327/1.18].

Hemodynamic, electrocardiographic effects, and myocardial kinetics were compared following IV administration of 2 and 4 mg/Kg LEA 103, 1.5 and 3 mg/Kg bupivacaine HCl monohydrate, and 6 and 12 mg/Kg lidocaine HCl monohydrate in pentobarbital anesthetized pigs. The animals (17 females and 4 males) were 6 months old. Body weight was 49-56 Kg for males and 51-56 Kg for females. The pigs were randomly assigned to receive one of the drugs infused over 30 seconds. The low dose was 25 mL, followed four hours later by the high dose in 50 mL.

RESULTS

LEA 103 (2 mg/Kg)

- no deaths.
- significant ↓ in heart rate (18%), LVdP/dT (34%), stroke volume index (17%), mean artery pressure (7%), systolic aortic pressure (6%), arterial CO_2 tension (2%), and arterial to coronary sinus O_2 content difference (4%).
- significant ↑ in diastolic arterial pressure (6%), mean pulmonary artery pressure (35%), left ventricular end-diastolic pressure (59%), arterial to mixed venous oxygen content difference (15%), total body oxygen consumption (16%), and PQ (33%), QRS (33%), and QT (12%) intervals.
- mean peak arterial plasma concentration was 21.9 μg/mL.

LEA 103 (4 mg/Kg)

- no deaths.
- in addition to the above, the following were significant: mean right arterial pressure (↑, 31%), pulmonary vascular resistance (↑, 48%), coronary sinus blood flow (↓, 43%), and myocardial O_2 consumption (↓, 33%).
- no significance was seen in total body O_2 consumption.
- mean peak arterial plasma concentration was 57.5 μg/mL.

In comparing the three drugs, lidocaine decreased the BP at 6 mg/Kg but did not increase pulmonary arterial pressure. All three drugs decreased the BP, heart rate, and left ventricular dP/dt at the high dose. Both lidocaine (12 mg/Kg) and bupivacaine (3 mg/Kg) did not change the pulmonary vascular resistance. Bupivacaine at 1.5 and 3 mg/Kg prolonged the effect on the QRS interval more than did LEA 103. Severe arrhythmias and conduction defects lasting about 10 minutes were observed in one animal each in the high dose bupivacaine and LEA 103 groups. The mean peak plasma concentrations were 17.9 μg/mL and 35.4 μg/mL for the low and high dose bupivacaine, and 86.4 μg/mL and 149.5 μg/mL for the low and high dose lidocaine.

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(31) F42 Astra Report 802-50 AF 102-1, 89-12-20. Effect of ropivacaine on cutaneous capillary blood flow in pigs. Kopacz DJ, Carpenter RL, Mackey DC . [1/1.19].

The local cutaneous blood flow in six Yorkshire piglets was assessed in this study. Ropivacaine (0.25 and 0.75% concentration), without and with 5 μg/mL added epinephrine was injected sq at separate sites on the side of each animal. The skin blood flow was measured by the laser Doppler method. Results were compared with those of 0.25% and 0.75% bupivacaine and saline, with and without added epinephrine. One mL of each of the ten solutions was evaluated.

RESULTS

Blood flow decreased by about 53% for both low and high dose. Blood flow was further decreased with epinephrine. Bupivacaine increased the blood flow by 90% and 82% while saline increased the blood flow by 32%. Epinephrine significantly decreased blood flow when added to saline or bupivacaine, producing vasoconstriction.

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(32) Anesthesiology 1989;71:69-74. Effect of ropivacaine on cutaneous capillary blood flow in pigs. Kopacz DJ, Carpenter RL, Mackey DC. [21/1.19].

This reprint contains the results of the above study.

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(33) F35 Astra Report 802-50 AF 103-1, 1989-12-15. Hemodynamic and central nervous system effects of intravenous bolus doses of ropivacaine (LEA 103) compared to lignocaine and bupivacaine in sheep. Mather LE, Rutten AJ. [124/1.26]

The purpose of this study was to evaluate the cardiac and central nervous system effects of LEA 103 administered iv to sheep. Lidocaine HCl and bupivacaine HCl were also evaluated in this system. Bolus doses of LEA 103 (30, 45, 60, 90, and 120 mg/animal), lidocaine (80 and 320 mg/animal), and bupivacaine (20 and 80 mg/animal) were administered to eleven conscious ewes (47.8 ± 6.3 Kg). These animals had type A hemoglobin.

RESULTS

LEA 103:

- no convulsions with 30 or 45 mg.
- 3/5 animals convulsed at 60 mg.
- 7/7 convulsed at 90 mg with 1/7 deaths (ventricular fibrillations) - 1.76 mg/Kg.
- 5/5 convulsed at 120 mg, with 1/5 deaths (ventricular fibrillations) - 2.93 mg/Kg.
- blood concentration at 60 mg was 20 mg/L.
- mean convulsive dose was approximately 60 mg.

Bupivacaine:

- 0/5 convulsed at 20 mg - no deaths
- 5/5 convulsed at 80 mg - 2/5 deaths (ventricular fibrillations) - 1.67 and 2.05 mg/Kg.
- mean convulsive dose calculated in an earlier study to be 45 mg.
- blood concentration at mean convulsive dose was 14 mg/L.

Lidocaine:

- 0/5 convulsed at 80 mg - no mortality.
- 5/5 convulsed at 320 mg - 2/5 deaths.
- mean convulsive dose calculated in earlier study to be 125 mg
- blood concentration at mean convulsive dose was 40 mg/L.

At convulsive doses increases occurred in heart rate, left ventricular end diastolic pressure, myocardial contractility, mean arterial pressure, mean pulmonary arterial pressure, cardiac output, and systemic vascular resistance.

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(34) Anesth Analg 1989;69:291-9. Hemodynamic and central nervous system effects of intravenous bolus doses of lidocaine, bupivacaine, and ropivacaine in sheep. Rutten AJ, Nancarrow C, Mather LE, Ilsley AH, Runciman WB, Upton RN. [239/1.26].

This reprint reports the data in the above study.

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(35) F36 Astra Report 802-50 AF-120-1, 1992-07-02. Systemic toxicity of ropivacaine in pregnant and nonpregnant ewes. Santos AC. [166/1.22].

See Study Number (10) F36 under II TOXICOLOGICAL EFFECTS, A. Acute

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(36) Anesthesiology 1991; 75:137-41 Systemic toxicity of ropivacaine during ovine pregnancy. Santos AC, Arthur GR, Pedersen H, Morishima HO, Finster M, Covino BG. [208/1.22]

See Study Number (11) under II TOXICOLOGICAL EFFECTS, A. Acute

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(37) F43 Astra Report 802-50 AF 124-1, 1992-07-02. Effects of ropivacaine, bupivacaine and epinephrine on uterine blood flow in pregnant sheep. Santos AC. [27/1.19]

Ten pregnant mixed breed sheep, 1-2 years old, mean body wt of 63.5 Kg, and near term were used in this study. The results of the effects of a low and high dose of LEA 103 on uterine blood flow and fetal well-being were compared with the results of a low and high dose of bupivacaine and a 30 min iv infusion of 0.2 μg/Kg epinephrine. The ropivacaine low dose was infused at a constant rate of 0.1 mg/Kg over 15 minutes, followed by 45 min of infusion at 0.05 mg/Kg. The high dose was 0.2 mg/Kg, followed by 0.075 mg/Kg. The low dose of bupivacaine was 0.077 mg/Kg, followed by 0.039 mg/Kg. The high dose of bupivacaine was 0.1 mg/Kg, followed by 0.058 mg/Kg. Each ewe received two iv infusions. The study was conducted in

A QAU statement was present and signed.

RESULTS

- fetal mean arterial BP and heart rate: not significantly changed by the 3 drugs-
- ropivacaine low dose: heart rate significantly ↓ (9%) at 15 min-
- bupivacaine low dose: heart rate significantly ↓ (15%) at 60 min-
- epinephrine: heart rate significantly ↑ (15%-32%) at 15 and 30 min-
- ropivacaine produced no changes in maternal arterial blood pH and gas tensions-
- high dose bupivacaine: ↓ maternal arterial blood pH and $PaCO_2$-
- epinephrine: ↓ $PaCO_2$ 18%-23%-
- fetal PaO_2: ↓ significant (10%) at 15 min-
- high dose bupivacaine: PaO_2 ↓ (14%)-
- intra-amniotic and central venous pressure not altered-
- uterine blood flow reduced 25% by epinephrine-
- max fetal plasma concentration μg/mL(1 hr): 0.57 ropivacaine HCl, 0.32 bupivacaine HCl-

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(38) Anesth Analg 1992;74(1):62-7. Effect of ropivacaine and bupivacaine on uterine

blood flow in pregnant ewes. Santos AC, Arthur GR, Roberts DJ, Wlody D, Pedersen H, Morishima HO, Finster M, Covino BG. [81/1.19]

Data from the above study were reported in this reprint.

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2. In Vitro

(39) F44 Astra Report 802-550 LF-0184-01, 1994-01-18. Interaction of ropivacaine, bupivacaine and lidocaine with seven selected receptor recognition sites in the rat brain. Fowler CI, Brannstrom G. [87/1.19].

Receptor recognition sites evaluated in this study were α2- and β1- adrenoceptor, histamine H1, muscarine M1, μ-opioid, and serotonin 1A and serotonin 2. The results for ropivacaine were compared to those for bupivacaine and lidocaine. The membranes were derived from male Sprague Dawley rats. Concentrations of 1, 3, 10, 30, and 100 μM were evaluated for each of the three drugs. The results indicated low affinities towards these sites for the three drugs.

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(40) F45 Astra Report 802-50 AF 57-1, 1986-03-17. Monoamine oxidase inhibitory effect of LEA 103. Ross S, Fagerwall I. [111/1.19]

LEA 103, bupivacaine, and lidocaine at the highest dose tested (100 μM) showed weak inhibition of the A (0-26%) or B (16%-23%) forms of MAO.

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(41) F46 Astra Report 802-50 AF 75-1, 1986-12-01. Effects of LEA 103, LEA 104 and bupivacaine on the portal vein in vitro. Forsberg T, Westman I. [116/1.19]

LEA 103 ($1x10^{-5}$, $1x10^{-4}$, $3x10^{-4}$, $4x10^{-4}$, $6x10^{-4}$ M), LEA 104 $1x10^{-4}$, $3x10^{-4}$, $6x10^{-4}$ M), and bupivacaine at $1x10^{-5}$, $3x10^{-5}$, $1x10^{-4}$, $3x10^{-4}$ M) concentrations in saline were studied in vitro on mal Sprague Dawley vascular smooth muscle preparations. Activity was expressed as [illegible] percent of the maximal noradrenaline response, measured as the area under the curve [illegible] periods of one minute.

RESULTS

LEA 103 ($1x10^{-4}$ to $4x10^{-4}$ M) and bupivacaine ($1x10^{-4}$ M) significantly increased the contractile activity of the portal vein 15 minutes after the adding to the organ bath. LEA 104, the R enantiomer of ropivacaine, did not change contractile activity at $1x10^{-4}$ and $3x10^{-4}$ M but inhibited the contractile activity at $6x10^{-4}$M. Bupivacaine significantly increased the contractile activity only at $1x10^{-4}$ M, then inhibited activity at $3x10^{-4}$M.

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(42) Anaesthetist 1988;37:121. Difference in vasoactivity between ropivacaine and

bupivacaine. Forsberg T, Westman I, Akerman B. [128/1.19].

This reprint covers the data from the above study. It was reported at the Annual Meeting of the European Society of Regional Anesthesia 1988.

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(43) F47 Astra Report 802-550 LF-0010-01, 1991-10-08. Effect of ropivacaine, bupivacaine and adrenaline on the rat portal vein in vitro. Forsberg T, Holmstrom -Svensson M , Ericson A- C, Akerman B. [129/1.19].

This study evaluated the in vitro effects of LEA 103, bupivacaine, and epinephrine on the contractile activity in male Sprague-Dawley rat portal vein preparations. Concentrations evaluated were 1.25×10^{-5} to 1.6×10^{-3} M for LEA 103, without and with added epinephrine (5×10^{-7} M) and 1.25×10^{-5} to 8×10^{-4} M for bupivacaine, with and without added epinephrine (5×10^{-7} M). Epinephrine concentrations ranged from 1.25×10^{-8} to 1.6×10^{-6} M when tested alone. The contractile activity was reported as the percent of predrug contractile activity.

RESULTS

A dose related increase in contractile activity was produced with ropivacaine up to 3×10^{-4} M (376% maximum increase), followed by decreasing activity to the high concentration. This same picture was seen for bupivacaine - increase to 1×10^{-4} M (266% maximum increase) then decrease to the high dose. Epinephrine increased activity up to the highest dose tested (1939% maximum increase). In the presence of adrenaline, lower concentrations of either LEA 103 or bupivacaine were not affected by the presence of epinephrine, while higher concentrations of either drug with epinephrine produced a significant decrease in activity.

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(44) F48 Astra Report 802-50 AF 77-2, 1994-05-04. Effects of LEA 103, bupivacaine and lidocaine on the rat heart in vitro. Norrman S. [146/1.19].

Study N°: AF8627
Compound: LEA 103: 4.3×10^{-5}M, 1.3×10^{-4} M, 4.3×10^{-4} M
Bupivacaine: 4.3×10^{-5} M, 1.3×10^{-4} M, 4.3×10^{-4} M
Lidocaine: 4.3×10^{-5} M, 1.3×10^{-4} M, 4.3×10^{-4} M
(concentration used and mentioned in this report:
1×10^{-3}, 3×10^{-3} and 1×10^{-2} M and injection volume was 0.5 ml)
Formulation: Solutions in saline.
Strain: Male Sprague-Dawley, 326-420 g body weight, average of 3 months old.
Number: 6 isolated rat hearts.
Control Treatment: Saline
Study Site: Astra Alab AB, Sweden.
Date: May 1986 - August 1986. The report was dated May 4, 1994.
GLP/QAU Statements: Both present and signed.

Isolated beating hearts were trimmed of surrounding tissues and mounted on an aortic perfusion cannula. Krebs-Henseleit bicarbonate buffer (pH 7.2) equilibrated with O_2:CO_2 (95:5) was the perfusion medium. The drugs were added to the perfusion medium through a cannula in the lower part of the apparatus. Heart rate, contractility, and coronary flow were monitored continuously. EKG was monitored up to 15 minutes.

RESULTS

- dose related ↓ in heart rate and coronary flow with all three drugs-
- at each concentration, heart rate and coronary flow normalized over 15 minutes-
- contractile force ↓ dose related with LEA 103, bupivacaine, and lidocaine-
- dose dependent prolongation of PQ and QT intervals with LEA 103 and bupivacaine-
- QRS broadened with LEA 103, bupivacaine (most pronounced), and lidocaine-

Disturbances in Atrioventricular (A-V) Conduction
(hearts affected/hearts tested)

Drug	Dose	VES*	I°	II°	III°
LEA 103	$3x10^{-3}$ M	1/6			
	$1x10^{-2}$ M	2/6	1/6	2/6	2/6
Bupivacaine	$3x10^{-3}$ M	1/5	1/5	1/5	
	$1x10^{-2}$ M			3/5	3/5

* VES = ventricular extracystolic beats
* I II III = degree of block [see Study (20) F18 for explanation]

- no AV changes with lidocaine-
- bupivacaine caused dose dependent and significant oxygen consumption (PO_2) at 3x10-3 M (↓13%) lasting 10 minutes-
- LEA 103 was more potent than lidocaine and less potent than bupivacaine on heart rate, coronary flow, and atrioventricular conduction-
- arrhythmias as reported by Ericson and Henriksson (F38) were not mentioned in the report.

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(45) F49 Astra Report 802-50 AF 51-1, 1986-02-18. Actions of three local anesthetics: lidocaine, bupivacaine and LEA 103 on guinea-pig papillary muscle sodium channels. Arlock P. [225/1.19]

Heart papillary muscles from guinea-pigs were mounted in a single sucrose gap apparatus for evaluation. Each drug was evaluated for its effect on sodium channel block at equimolar concentrations. LEA 103 was found to have potency between lidocaine and bupivacaine in depressing the sodium channels. The action potential was shortened and the plateau was depressed at high concentrations of each drug. Recovery from bupivacaine block was slow and faster with lidocaine block; LEA 103 recovery was between bupivacaine and lidocaine. LEA 103 moderately diminished the peak force, whereas bupivacaine strongly depressed this action.

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(46) Pharmacol Toxicol 1988;63:96-104. Actions of 3 local anesthetics: lidocaine, bupivacaine and ropivacaine on guinea-pig papillary muscle sodium channels (V max). Arlock P. [255/1.19].

This reprint reports the data from the above study and will not be reviewed.

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(47) F50 Astra Report 802-50 AF 9-1, 1986-01-16. Examinations of the anticholinergic, histaminolytic and spasmolytic activity of LEA 103 and bupivacaine in the guinea-pig ileum. Holm AC. Lennmark M. Ogren SO. [264/1.19].

Acetylcholine, histamine, and $BaCl_2$ induced contractions in the guinea pig ileum were evaluated in this study. The results showed that both LEA 103 and bupivacaine were similar but not potent in blocking acetylcholine, histamine, and $BaCl_2$ induced contractions in the guinea pig ileum. These results were compared with those from atropine, benadryl, and papaverine, which were used as standard antagonists for acetylcholine, histamine, and $BaCl_2$, respectively.

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(48) F51 Astra Report 802-50 AF 54-1, 1986-02-21. Comparative cardiac electrophysiological effects of lidocaine, bupivacaine and LEA 103. Moller RA, Covino B G. [271/1.19]

Hearts from male NZW rabbits were removed for comparative evaluation of LEA 103, bupivacaine, and lidocaine on the transmembrane action potentials of Purkinje fibers and ventricular muscle cells. These tissues were removed and bathed in 36.5° Tyrode's solution. Electrophysiological parameters that were measured included maximum diastolic potential (MDP), action potential amplitude (AP), maximal rate of depolarization (Vmax), action potential duration (APD) at 50% and 75% of repolarization, effective refractory period (ERP), membrane responsiveness, and conduction time between Purkinje fibers and ventricular muscle. Control recordings were taken for 30 and 60 minutes. Preparations were then exposes to three increasing concentrations of lidocaine, bupivacaine, and LEA 103. Recordings were made following 60 minutes of superfusion with each concentration of the three drugs.

RESULTS

- MDP of Purkinje fiber cells significantly changed with 5 μg/mL bupivacaine - no significance with lidocaine or LEA 103-
- Purkinje fiber AP amplitude significantly ↓ with LEA 103 at 3 μg/mL (13%) and 5 μg/mL (17%) - significant ↓ with bupivacaine at 3 (20%) and 5 μg/mL (22%) - lidocaine significantly ↓ at 20 μg/mL (6%)-
- Vmax ↓ significantly and dose related: LEA 103 at 3 μg/mL (42%) and 5 μg/mL (57%); bupivacaine at 1, 3, 5 μg/mL (30% - 76%)- lidocaine at 5 to 20 μg/mL (11% to 37%)-
- APD significant ↓ 5 μg/mL LEA 103, 1-5 μg/mL bupivacaine, and 5-20 μg/mL lidocaine-
- ERP/APD75 ratio ↑ 20% by all concentrations of lidocaine, 40% with bupivacaine at 3

and 5 μg/mL, and 45% with LEA 103 at 5 μg/mL.
- responsiveness of Purkinje fiber membrane ↓ similarly with LEA 103 and bupivacaine but less so with lidocaine.
- dose related ↑ in conduction time between Purkinje fiber and ventricular muscle with all compounds.
- spontaneous Purkinje fiber activity ↓ with all compounds - bupivacaine significant at 3 and 5 μg/mL and lidocaine at 20 μg/mL.
- time for recovery of normal Purkinje fiber excitability and Purkinje fiber-ventricular muscle (PF-VM) conduction was less following exposure to 30 μg/mL LEA 103 than with 30 μg/mL bupivacaine.
- perturbations in AP configuration (notching at the phase 1-2 junction) were seen only with bupivacaine.

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(49) Anesthesiology 1990;72:322-28. Cardiac electrophysiologic properties of bupivacaine and lidocaine compared with those of ropivacaine, a new amide local anesthetic. Moller RA, Covino BG. [307/1.19]

This reprint reports on the data submitted in the above review.

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(50) F52 Astra Report 802-550 LF 0049-01, 1992-05-26. Effect of progesterone on the cardiac electrophysiological alterations produced by ropivacaine and bupivacaine. Moller RA, Covino BG. [315/1.19].

This study was done to determine if elevated progesterone levels can increase myocardial sensitivity to ropivacaine or bupivacaine. Purkinje fibers and ventricular muscles were removed from the hearts of NZW rabbits (two groups of 10) that had been ovariectomized then treated four days with 30 mg/Kg im progesterone. A peanut oil group (10 animals) acted as a control.

RESULTS

The results indicated the cardiac depressant effects of ropivacaine were not enhanced by increasing progesterone levels in vivo, as measured in the isolated tissues. The maximum diastolic potential of Purkinje fibers was not significantly altered by either drug. Action potentials were reduced 24% by 17.4 μM bupivacaine in the progesterone group and by 21% in the placebo group. Ropivacaine at 18.7 μM reduced this potential by 6.4% in the progesterone group and by 11.6% in the control. The maximum rate of depolarization (Vmax) showed a dose related decreased which was significant with both drugs: bupivacaine (82%) at 17.4 μM and ropivacaine (55%) at 17.4 μM vs placebo. Maximum reduction with respect to animals pretreated with progesterone was 43% for ropivacaine and 79% for bupivacaine. The time to recovery to 75% of baseline values was significantly shorter with tissues exposed to ropivacaine and progesterone (27.5 min) vs 47.0 min for bupivacaine and progesterone.

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(51) Anesthesiology 1992;77(4):735-741. Effect of progesterone on the cardiac electrophysiologic alterations produced by ropivacaine and bupivacaine. Moller RA, Covino BG [339/1.19]

This reprint reports on the data from the above study. No further evaluation will be done.

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(52) F53 Astra Report 802-50 AF 119-1 Chronotropic and inotropic effects of lidocaine, bupivacaine and ropivacaine in the spontaneously beating and electrically paced isolated, perfused rabbit heart. Feldman HS. [1/1.20]

Study N°: US 8804 B
Compounds: LEA 103, batch F3, assay 99.1% by HPLC
Bupivacaine hydrochloride monohydrate
Lidocaine hydrochloride monohydrate
Concentrations: LEA 103: 1, 6, 13 µg/mL
Bupivacaine: 1, 6, 13 µg/mL
Lidocaine: 6, 20, 40 µg/mL
Formulation: Solution in Krebs-Henseleit perfusate.
Strain: NZW males, 2.7 Kg body weight.
Number: 6/group - 5 at 13 µg/mL ropivacaine
Control Treatment: NaCl solution, 9 mg/mL
Study Site:
Date: February 1989-January 1994
GLP/QAU Statements: Both present and signed.

This study compared the inotropic and chronotropic effects of LEA 103, lidocaine, and bupivacaine. Their ability to pace the heart electrically in the presence of a local anesthetic was also evaluated. The tissues were exposed for 30 minutes or until a 75% decrease in the left ventricular pressure or cessation of cardiac function occurred. A 30 to 60 minute washout period was done prior to drug treatment. The study includes left ventricular systolic and diastolic pressure, spontaneous heart rate, EKG, dP/dT, pulmonary artery flow, and pacing voltage.

RESULTS

- only 1/6 bupivacaine survived the 30 min washout at 6 µg/mL and none at 13 µg/mL.
- all hearts in lidocaine and ropivacaine groups survived 30 minute of treatment.
- significant ↓ in spontaneous heart rate in all drugs - most significant with bupivacaine.
- O_2 consumption ↓ significantly with all drug groups except 6 µg/mL lidocaine.
- significant ↓ in dP/dT with all drugs - greatest decrease with bupivacaine.
- left ventricular systolic pressure ↓ significantly in all drug groups except 1 µg/mL ropivacaine.
- left ventricular diastolic pressure and pulmonary artery flow not significantly different between drug groups.

- dose related ↑ in PR interval and segment of EKGs in all drug treated groups
- QRS interval ↑ in all drug groups except low dose lidocaine and ropivacaine-
- QT interval ↑ in all drug groups except low dose lidocaine - greater in bupivacaine-
- some preparations of bupivacaine showed A-V block, rhythm disturbances, and inability to electrically pace via the atria-

Occurrence of EKG Normalities
(from P. 42)

Drug	Concentration (µg/mL)	Abnormalities AV	VE	VR	Pacing success Atrial	Ventricular
Lidocaine	6	-	-	-	6 of 6	-
	20	-	-	-	6 of 6	-
	40	-	-	-	6 of 6	-
Ropivacaine	1	-	-	-	6 of 6	-
	6	1 of 6	1 of 6	-	6 of 6	-
	13	3 of 5	1 of 5	-	2 of 5	3 of 3
Bupivacaine	1	-	-	-	6 of 6	-
	6	5 of 6*	-	1 of 6	3 of 6	2 of 3
	13	2 of 6	-	4 of 6*	0 of 6**	1 of 6*
Saline		-	-	-	6 of 6	-

AV: atrioventricular block; VE: ventricular ectopy; VR: ventricular rhythm
* $p<0.05$ compared to lidocaine and ropivacaine at the equivalent dose
** $p<0.05$ compared to lidocaine at the equivalent dose
* $p<0.05$ compared to ropivacaine at the equivalent dose

Lidocaine was the least cardiotoxic and bupivacaine the most cardiotoxic. Ropivacaine fell between the lidocaine and bupivacaine.

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(53) Anesthesiology 1990;73 (Suppl 3A):A844. Effects of ropivacaine bupivacaine and lidocaine upon the isolated spontaneously beating rabbit heart (abstract). Feldman HS, Pitkanen M, Arthur GR, Manning T, Covino BG. [250/1.20]

This abstract covers the data submitted in the above study.

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(54) F54 Astra Report 802-550 LF-0166-01, 1993-11-11. Local anesthetics do not affect protein kinase C function in intact neuroblastoma cells. Martinsson T, Fowler CJ. [251/1.20]

Ropivacaine, bupivacaine, lidocaine, and staurosporin were studied in cultured mouse Neuro-2a blastoma cells to determine their effect on protein kinase C (PKC). Staurosporin, a known PKC inhibitor, was used as a positive control. The results did not show bupivacaine at 1000 or 3000 µM, lidocaine at 1000 or 3000 µM, or ropivacaine at

10, 100, or 1000 μM to be inhibitors of PKC. Staurosporin produced marked neuritogenesis at 10, 30, and 100 nM concentrations. Ropivacaine (0.1 and 1mM), lidocaine (1 and 3 mM), and bupivacaine (1 mM) showed no effect, nor did they have an effect on the inhibition produced by 80 nM phorbol 12-myristate 13-acetate (PMA).

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(55) Life Sciences 1993;53:1557-1565. Local anaesthetics do not affect protein kinase C function in intact neuroblastoma cells. Martinsson T, Fowler CJ. [270/1.20]

This reprint reports on the data from the above study.

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(56) F55 Astra Report 802-550 LF-0196-01 1994-03-17. Comparison of vascular effects of ropivacaine and lidocaine on isolated rings of human arteries. Gherardini G Samuelson U, Jernbeck J, Aberg B, Sjostrand N. [279/1.20].

Lidocaine and ropivacaine were evaluated on isolated human internal mammary arteries and radial artery ring preparations with intact or mechanically removed endothelium. Both drugs produced equipotent biphasic action on the arteries. At low concentrations vasoconstriction was shown. At high concentrations a relaxation occurred.

C. Drug Interactions

(57) F22 Astra Report 802-50 AP 82-1, 1986-12-12. Cardiac effects of intravenous injection of LEA 103 in conscious rats premedicated with atropine. Nilsson S, Ogenstad S, Sperber B, Westman I . [1/1.21]

When iv saline was injected 5 minutes prior to LEA 103 (10 μmol/Kg iv) there was an 18% decrease in the heart rate. No change occurred with saline. The administration of atropine (0.05 mg/Kg iv) increased the heart rate by 21%, but when followed 5 minutes later with LEA 103 (10 μmol/Kg iv), the heart rate decreased to near control rates.

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(58) F23 Astra Report 802-50 LF 0143-01, 1994-03-30. The effect of atropine on bradycardia produced by intravenous injection of ropivacaine, bupivacaine and lidocaine in conscious rats. Nilsson S, Sperber B, Westman I. [19/1.21].

Ropivacaine (10 μmol/Kg), bupivacaine (7 μmol/Kg), or lidocaine (28 μmol/Kg) decreased the heart rate by 29%, 27%, and 13%, respectively, when injected iv over 5 seconds in a volume of 1.25 mL/Kg. When 0.05 mg/Kg atropine was injected 70 seconds later (0.1 mL/Kg), the bradycardia was normalized within 30 seconds in all groups, was transient, and the heart rate slowly decreased. The addition of saline did not reverse the bradycardia. When atropine was administered after saline, the heart rate

increase lasted more than 10 minutes. Three of the 11 treated rats died after the injection of atropine. The heart rate was <200 in two rats at the time atropine was injected; one had aggravating bradycardia. Three of the ten rats treated with bupivacaine-atropine died, showing second degree AV block, followed by ventricular arrhythmia. No deaths occurred with ropivacaine-saline or bupivacaine-saline. There were 5/13 deaths in the lidocaine treated animals after the atropine injection and 2/7 deaths after saline injection.

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(59) F24 Astra Report 802-50 AF 79-1, 1986-12-12. Effects of intravenous injection of LEA 103 in conscious rats premedicated with diazepam, morphine or atropine. Nilsson S, Westman I, Oberg E. [41/1.21].

This study evaluated the administration of saline (sc), diazepam (2.5 mg/Kg ip), morphine (5.0 mg/Kg ip), and atropine (0.05 mg/Kg sc) 30 minutes prior to intravenous treatment with LEA 103 (8 or 16 μmol/Kg). With saline-LEA 103 (low dose), transient convulsions occurred; the high dose produced convulsions and death in 6/6 animals. No deaths, convulsions, or other signs occurred in the diazepam treated animals with either the low or high dose LEA 103. The low dose LEA 103-morphine group developed convulsions, rigidity, muscle twitches, foamy discharge from the nostrils, and 1/6 died within 90 seconds; at the high dose, all animals died within 60-90 seconds. Convulsions occurred in the low dose LEA 103-atropine group; the high dose group had 5/6 deaths.

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(60) F25 Astra Report 802-550 LF-0144 02, 1994-06-28. Protective effects of midazolam and diazepam on convulsions induced by intravenous infusion of ropivacaine, bupivacaine and lidocaine in the rat. Nilsson S, Sperber B. [62/1.21].

The protective effects of midazolam (2.5 mg/Kg ip) and diazepam (2.5 mg/Kg ip) on convulsions induced with ropivacaine (12 μmol/Kg/min infusion), bupivacaine (10 μmol/Kg/min infusion), or lidocaine (50 μmol/Kg/min infusion) were evaluated in male rats. Saline was administered as a placebo. Infusions were stopped at the onset of convulsions or after 120 seconds.

RESULTS

Pretreatment with midazolam prevented convulsions in ropivacaine (0/10 deaths), lidocaine (2/10 deaths), and bupivacaine (3/10 deaths) treated rats. Diazepam prevented convulsions in the ropivacaine (1/10 deaths) and bupivacaine (3/10 deaths) groups; however, with lidocaine, 2/10 developed convulsions (4/10 deaths). The saline pretreatment did not prevent convulsions in any group; there were, however, 5/10 deaths in the ropivacaine group, 2/10 in the bupivacaine group, and 0/10 in the lidocaine group. The study clearly showed that midazolam and diazepam were effective in preventing convulsions when administered 30 minutes prior to the intravenous infusion of convulsant doses of ropivacaine, bupivacaine, or lidocaine. Deaths were reduced in the ropivacaine group with midazolam and diazepam. With bupivacaine, the mortality was

slightly increased; with lidocaine the mortality was increased 20% to 40%. Loss of righting reflex was frequent in the animals pretreated with midazolam or diazepam. The saline group did not show this effect.

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(61) F26 Astra Report 802-50 AF 83-1, 1986-12-12. Inhibitory effects of diazepam and thiopentone sodium on convulsions induced by an intravenous injection of LEA 103 in the rat. Nilsson S, Sperber B, Westman I, Oberg E. [76/1.21].

The duration of LEA 103 (8 μmol/Kg iv) induced convulsions was reduced with 2.5 mg/Kg iv diazepam or 25 mg/Kg iv thiopentone sodium when administered after the onset of convulsions. The study was done in male SD rats, 7-9 weeks old.

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(62) F27 Astra Report 802-550 LF-0145-02, 1994-06-28. Inhibitory effects of midazolam and diazepam on convulsions induced by intravenous infusion in ropivacaine, bupivacaine and lidocaine in the rat. Nilsson S, Sperver B. [93/1.21].

The object of the study was to determine the ability of midazolam and diazepam to arrest convulsions caused by iv infusions of ropivacaine, bupivacaine, or lidocaine.

This study is similar to the above study (60) F25. Ropivacaine 6 μmol/Kg/min, bupivacaine 6 μmol/Kg/min, or lidocaine 28 μmol/Kg/min were infused in male Sprague-Dawley rats weighing 232-336 g and 7-9 weeks old. At the onset of convulsions, the infusion was stopped and midazolam (0.7 mg/Kg) or diazepam (0.7 mg/Kg) were administered intravenously. Saline (0.15 mL/Kg) was used as the placebo. There were 10 rats per group. GLP and QAU statements were not present. The study was done in February - March 1988.

RESULTS

Convulsant doses were: LEA 103 3.8 ± 0.6 mg/Kg, (12 ± 2 μmol/Kg, n = 28), bupivacaine HCl 3.2 ± 1.0 mg/Kg (10 ± 3 μmol/Kg, n = 30), and lidocaine HCl 16 ± 2.4 mg/Kg (58.9 μmol/Kg, n = 26). Administration of midazolam rapidly reduced convulsions in all groups. No significance was seen between midazolam and diazepam or between the three anesthetics. As reported in the above study, most of the rats lost the righting reflex after dosing with midazolam and diazepam. This was not seen in the saline group administered ropivacaine or bupivacaine but occurred with the saline-lidocaine group.

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(63) F19 Astra Report 802-50 AF 80-1, 1986-12-12. Effects of fentanyl and morphine in conscious rats pretreated with subcutaneous injection of LEA 103, bupivacaine or lidocaine. Nilsson S, Sperber B. [107/1.21]

Administration of saline (1.0 mL/Kg sq) or LEA 103 (85 μmol/Kg sq or ip) followed one hour later by 0.1 mg/Kg ip fentanyl produced rigidity, sedation, and

decreased motor activity in 6/9 rats. When morphine (5.0 mg/Kg sq) was used, a high incidence and significantly longer duration of sedation and decreased motor activity occurred, compared to the saline control. GLP/QAU statements were present and signed. The study was done by Astra, Sweden in 1986.

RESULTS

In a blinded repeat study, no significant differences were seen in sedation or decreased motor activity between groups pretreated with saline (1 mL/Kg sq), LEA 103 (85 μmol/Kg sq), bupivacaine (60 μmol/Kg sq), or lidocaine (240 μmol/Kg sq), followed by fentanyl (0.1 mg/Kg ip). Rigidity occurred in 2/10 LEA 103 (2 deaths), 3/10 bupivacaine, 8/10 lidocaine (2 deaths), and 5/10 saline pretreated rats. Fentanyl caused convulsions and death in 1/10 LEA 103 rats and 2/10 lidocaine rats. The results indicated the effect of fentanyl (sedation, decreased motor activity, and rigidity) was not influenced by pretreatment with LEA 103, bupivacaine, or lidocaine.

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(64) F56 Astra Report 802-50 AF 81-1, 1986-12-12. Effect of thiopentone sodium, enflurane, pancuronium and suxamethonium in conscious rats pretreated with subcutaneous injection of LEA 103, bupivacaine or lidocaine. Nilsson S Sperber B, Westman I, Oberg E. [136/1.21].

Rats were pretreated with LEA 103 (85 μmol/Kg sq), followed 60 minutes later by saline (1 mL/Kg sq), thiopentone sodium (25 mg/Kg iv), enflurane (inhalation of 5% mixture 2 min), pancuronium (0.15 mg/Kg iv), or suxamethonium (0.4 mg/Kg iv). Bupivacaine and lidocaine were used as reference compounds.

With thiopentone sodium, the righting reflex time was significantly prolonged with the three anesthetics when compared to saline. The change was in the order: saline < LEA 103 < bupivacaine < lidocaine. Convulsions lasting about 15 seconds occurred in 1/8 rats in the saline group.

The time for recovery of the righting reflex after enflurane inhalation was prolonged with saline and LEA 103, with little differences seen between the two groups.

Pancuronium produced dyspnea/apnea and loss of righting reflex in the saline group. These signs were increased in the three anesthetic groups. In addition, 8/10 deaths occurred with LEA 103 and 2/10 deaths occurred with bupivacaine. There were no deaths in the lidocaine animals. The time for recovery of the righting reflex was increased in the three anesthetic groups in the order: saline < LEA 103 < bupivacaine < lidocaine.

Suxamethonium produced muscle twitching and dyspnea in all rats of the saline and LEA 103 groups. The duration of muscle twitches was reduced in the LEA 103 group when compared to saline. The time for recovery from dyspnea was about the same in the saline and LEA 103 groups. One of the LEA 103 rats died. Loss of righting

reflex did not occur in the saline but was present in 9/10 LEA 103 rats.

Using thiopentone sodium, pancuronium, or suxamethonium with LEA 103, an additive effect occurred. From the results of this study, the sponsor stated this combination of drugs should not be use together; however, the following study refutes these results. No drug interactions were reported for LEA 103 and enflurane.

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(65) F57 Astra Report 802-550 LF 0146-02, 1994-06-28 Influence of the local anesthetics, ropivacaine, bupivacaine and lidocaine on the effects of the muscle relaxants pancuronium and suxamethonium in anaesthetized rats. Nilsson S, Sperber B. [170/1.21]

This study was done to further evaluate the adverse effects seen with the concomitant use of pancuronium or suxamethonium with LEA 103 and to evaluate the effect of ventilation in prevent deaths. Rats were administered LEA 103 (80 μmol/Kg sq), bupivacaine HCl monohydrate (60 μmol/Kg sq), lidocaine (240 μmol/Kg sq), or saline (2.5 mL/Kg). One hour later they were anesthetized with thiopentone (25 mg/Kg iv) and administered pancuronium (0.15 mg/Kg iv) or suxamethonium (0.3 mg/Kg iv). Artificial ventilation was used on all rats that developed apnea. The study was done by Astra, Sweden in August - October 1988. No GLP/QAU statements present.

RESULTS

Apnea, dyspnea, and loss of righting reflex was present in the three anesthetic drug groups. Apnea was present in only one saline treated rat, and one lidocaine rat died after pancuronium treatment. No significant differences were reported between the four groups.

With suxamethonium, apnea and dyspnea occurred in all groups except LEA 103. The incidence was not over 105-130%. Loss of righting reflex was present in all four groups; the duration was in the order saline < ropivacaine < bupivacaine < lidocaine. One lidocaine treated rat died after 4 minutes and could not be saved by ventilation. Death was due to excessive pulmonary edema.

These results were in opposition to those reported in the previous study in which the concomitant use of LEA 103 with pancuronium and suxamethonium produced an additive adverse effects. Analysis of the pancuronium and suxamethonium formulations indicated variations in the concentrations, but no dose-response could be observed. The conclusion from this study was that the three anesthetics did not potentiate the effects of pancuronium or suxamethonium.

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(66) F28 Astra Report 802-550 LF 0009-01, 1991-04- 25. Interactions of LEA-103 (ropivacaine hydrochloride monohydrate) with cardiovascular effects of acetylcholine, adrenaline, noradrenaline and carotid occlusion after intravenous injection in

anaesthetized cats. Forsberg T, Carlsson S, Lindeberg A, Ericson A-C. [186/1.21].

The results of this study indicated that LEA 103 (1.1 or 2.1 mg/Kg iv) did not significantly reduce the mean arterial BP or heart rate in the α-chloralose (40 mg/Kg) anesthetized cat in response to epinephrine, norepinephrine, or carotid occlusion; however, at 4.2 mg/Kg significance was seen in the blood pressure and heart rate. Plasma concentrations of LEA 103 were 2.48, 5.4, and 10.79 μmol/L after 1.1, 2.1, and 4.2 mg/Kg LEA 103, respectively. The mean arterial BP was decreased (27%) in response to acetylcholine with 4.2 mg/Kg LEA 103. Based on plasma levels, it is concluded that LEA 103 had only minor effects on the response to epinephrine, norepinephrine, or acetylcholine, and did not change the occlusion response.

The study was conducted by Astra, Sweden in May - June 1990. GLP/QAU statements were present.

II. TOXICOLOGICAL EFFECTS

A. Acute

(1) A2 Astra Report 802-50 T1731, 1994-04-18. Acute toxicity of LEA 103 in mice after single intravenous administration. Astra Toxicology Laboratories, Sodertalje, Sweden. [63/1.22]

Study Nº: 85057
Compound: LEA 103, batch F 2, assay 99.5%
Formulation: Solution in physiological saline.
Route: IV via the tail vein.
Dose Levels: 20, 28, 42, 60 μmol/Kg. Infusion was at 0.35 mL/minute.
Strain: NMRI, ♂ 16-20 g, ♀15-19 g, age range 25-30 days.
Number: 5/sex/group
Study Site: Astra, Sweden
Date: January 1985 - 1994
GLP/QAU Statements: Both present and signed.

RESULTS

Dose: μmol/Kg	20	28	42	60
Conc: μmol/mL	1.0	1.4	2.1	3.0
Mortality:	0/10	0/5♂ 1/5♀	1/5♂ 0/5♀	5/5♂ 2/5♀

Decreased motor activity occurred at all dose levels. Irregular breathing occurred at ≥ 28 μmol/Kg and convulsions appeared in half the animals at ≥ 42 μmol/Kg. At 60 μmol/Kg, all animals developed clonic convulsions immediately after dosing, with death

occurring immediately after the infusion. Surviving animals recovered within 2 hours. Body weight increased in all surviving mice. The 50% mortality was between 42 and 60 μmol/Kg (14-20 mg/Kg) for males and 85 μmol/Kg (28 mg/Kg) for females.

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(2) F17 Astra Report 802-550 LF 0224-01, 1994-04-27. Evaluation of the behavioral toxicity of ropivacaine and bupivacaine in male NMRI mice. Holm AC, Amkeus E, Lennmark M, Ogren SO. [80/1.22]

Compound: LEA 103, batch F2; bupivacaine HCl monohydrate, batch 38557-01
Formulation: Solutions in isotonic sodium chloride
Route: IV and SC
Dose Levels: ropivacaine 25 50 60 75 90 100 125 mg/Kg sq
5 7.5 10 15 mg/Kg iv
bupivacaine 15 25 40 50 60 75 mg/Kg sq
5 8 10 12 mg/Kg iv
Strain: NMRI males, 18-23 g body weight
Number: 6/group
Study Site: Astra, Sweden
Date: September 1985 to April 1994
GLP/QAU Statements: Not present.

The object of this study was to determine the behavioral toxicity caused by ropivacaine and bupivacaine in male mice. Behavior was observed at intervals for up to 15 minute after iv and up to 45 minutes after sq administration. Fifty percent mortality and CD_{50} (convulsive dose) were determined. The following data are from Tables 2 and 3, pp. 89 and 91.

RESULTS

IV Administration:

	Ropivacaine (mg/Kg)				Bupivacaine (mg/Kg)			
	5	7.5	10	15	5	8	10	12
Convulsions:[1]	0/6	6/6	6/6	6/6	0/6	6/6	6/6	6/6
Mortality:[2]	0	0	0	5/6	0	0	4/6	6/6
50% mortality:	13				9.7			

SQ Administration

	Ropivacaine (mg/Kg)							Bupivacaine (mg/Kg)					
	25	50	60	75	90	100	125	15	25	40	50	60	75
Convulsions:[3]	0/6	1/6	1/6	0/6	1/6	1/6	6/6	0/6	1/6	6/6	6/6	6/6	6/6
Mortality:[2]	0/6	0/6	0/6	0/6	1/6	1/6	6/6	0/6	1/6	0/6	0/6	3/6	4/6
50% mortality:	104							65.8					

[1]N° convulsing within first 2 minutes-
[2]N° dying within 24 hours-
[3]N° convulsing within first 15 minutes-

Behavioral signs reported for ropivacaine were: touch response (i iv), staggering gait (sq), decreased righting reflex (iv and sq), inability to perform on the rotating rod (iv and sq), reduced pinna reflex (iv and sq), reduced corneal reflex (iv, not tested in sq), pupillary dilation (iv and sq), and ptosis (iv and sq). All deaths were due to convulsions and no additional deaths occurred up to 5 days after drug administration. Ropivacaine appears less toxic than bupivacaine under these conditions. The CD_{50} dose was 110 mg/Kg for ropivacaine and 30 mg/Kg for bupivacaine sq.

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(3) A1 Astra Report 802-50 T1729, 1986-01-30. Acute toxicity of LEA 103 in mice after a single subcutaneous administration. Astra Toxicology Laboratories, Sodertalje, Sweden. [93/1.22]

Study Nº: 85014
Compound: LEA 103, batch F2, assay 99.5%
Formulation: Solution in sterile water.
Route: SC
Dose Levels: 70 - 360 μmol/Kg, at 20 mL/Kg
Strain: NMRI, 36-44 days old, ♂ 17-25 g and ♀ 15-21 g body weight,
Number: 30♂ and 20♀
Study Site: Astra, Sweden
Date: October 1985 - January 1986
GLP/QAU Statements: Both present and signed.

RESULTS

Clinical signs were clonic convulsions and/or spasms at 100-360 μmol/Kg during 1/2 hour after dose, decreased motor activity, and irregular breathing. Body weight increased in animals that survived. Death was due to convulsions which occurred within 5 minutes after dosing.

	Dose (μmol/Kg):						
Dose: μmol/Kg	70	100	150	210	250	300	360
Mortality (♀):	0/5(-)	2/4(-)	1/3(0/5)	1/3(1/3)	2/5(1/5)	1/5(1/5)	1/5(2/3)

50% mortality: 320 μmol/Kg (105 mg/Kg) ♀; males could not be calculated from the data.

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(4) F1 Astra Report 802-50 AF 15-1, 1986-02-12. On the local anesthetic effect and the acute toxicity of enantiomers and the racemate of 1-propyl-2',6'-pipecoloxylidide. Akerman B, Hellberg I-B, Trossvik C. [51/1.17]

See Study Nº (1) F1 under PHARMACOLOGICAL ACTIONS, Therapeutic Indications

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(5) A4 Astra Report 802-50 T1730, 1986-01-30. Acute toxicity of LEA 103 in rats after single intravenous administration. Astra Toxicology Laboratories, Sodertalje,

Sweden. [109/1.22].

Study Nº: 85056
Compound: LEA 103, batch F2, assay 99.5%
Formulation: Solution in physiological saline; dosing volume was 10 mL/Kg.
Route: IV via the tail vein - infusion rate was 0.5 mL/minute.
Dose Levels: 15, 24, 30, 38 μmol/Kg (4.9, 7.9, 9.9, 12 mg/Kg)
Strain: Sprague-Dawley - age 45-50 days - body weight ♂ 180-210 g, ♀ 150-180 g
Number: 2/sex in the low dose and 5/sex in all other groups.
Study Site: Astra, Sweden
Date: July 1985-January 1986
GLP/QAU Statement: Both present and signed:

RESULTS

- clonic convulsions or spasms at ≥ 7.9 mg/Kg (24 μmol/Kg).
- irregular breathing and reduced consciousness in animals convulsing.
- reduced motor activity and slight piloerection.
- mortality:

4.9		7.9		9.9		12 mg/Kg	
0/2♂	0/2♀	1/5♂	0/5♀	1/5♂	2/5♀	5/5♂	2/5♀

- deaths occurred immediately after dosing and were preceded by convulsions.
- increased body weight in surviving animals.
- 50% mortality: ♂ = 9.9 mg/Kg (30 μmol/kg), ♀ = 12 mg/Kg (37 μmol/kg).

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(6) F21 Astra Report 802-50 AF 89-2, 1987-06-05. Acute toxicity of adrenaline containing solutions of LEA 103, bupivacaine and lidocaine after intravenous administration in conscious rats. Forsberg T, Westman I, Oberg E. [126/1.22].

Study Nº: AF 8636
Compound: LEA 103, batch F3; bupivacaine HCl, lidocaine HCl
Formulation: Not indicated.
Route: IV, at 0.2 to 0.6 mL/Kg over 20 seconds followed by 0.15-0.2 mL saline
Dose Levels: (mg/Kg)

	without adrenaline				with adrenaline			
LEA 103	1.5	2	2.5	3	1.5	2	2.5	3
Bupivacaine HCl	1	1.5	2	2.5	1	1.5	2	2.5
Lidocaine HCl	6	8	10	12	4	6	8	10

Adrenaline was administered at 1.0 to 2.5 μg/Kg.
Strain: Sprague-Dawley males, 250-350 g body weight, 70-85 days old.
Number: 10/group
Study Site: Astra, Sweden
Date: October 1986-June 1987
GLP/QAU Statements: Both present and signed.

The acute toxicity was determined for LEA 103, bupivacaine, and lidocaine. Dosage for LEA 103 is expressed as mg of anhydrous/Kg. The toxicity of each was also

evaluated in the presence of 5 μg/mL of adrenaline. There were 23 groups in this study. All animals were observed during the first 5 minutes and at 1 and 2 hours.

RESULTS

		Convulsions		Mortality	
	Dose	Without	With	Without	With
LEA 103	1.5	1	0	0	0
	2	5	7	0	2
	2.5	4	7	0	4

		Convulsions		Mortality	
	Dose	Without	With	Without	With
LEA 103	3	8		3	
Bupivacaine	1	1	0	0	0
	1.5	2	4	0	0
	2	6	10	0	8
	2.5	10	9	5	9
Lidocaine	6	0	1	0	0
	8	7	4	0	0
	10	8	9	1	2
	12	10	10	5	7

- duration of the convulsions was not changed with the addition of adrenaline-
- pulmonary edema caused bloody froth in nostrils-
- statistical ↓ in convulsion dose (CD) 50 occurred with lidocaine and adrenaline-
- duration of convulsions not changed with the three drugs-

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(7) A3 Astra Report 802-50 T1728, 1986-01-30. Acute toxicity of LEA 103 in rats after single subcutaneous administration. Astra Toxicology Laboratories, Sodertalje, Sweden. [150/1.22]

Study Nº: 85013
Compound: LEA 103, batch 245/16, 99.9% assay
Formulation: Sterile water
Route: SQ
Dose Levels: 100, 175, 210, 300 μmol/Kg - 33, 58, 69, 99 mg/Kg
Strain: Sprague-Dawley, 65-70 days old, body weight ♂ 270-340 g, ♀ 180-220 g
Number: 5/sex/group
Study Site: Astra, Sweden
Date: March 1985 - January 1986
GLP/QAU: Both present and signed.

RESULTS

- no mortality at 33 mg/Kg.
- convulsions preceded death.
- 50% mortality: ♀ 75 mg/Kg (230 μmol/Kg), ♂ 58-69 mg/Kg (175-210 μmol/Kg).
- slight ↓ in motor activity and slow/deep respiration at 33 mg/Kg.
- signs ↑ at higher dose levels - piloerection, tremors, ataxia, clonic convulsions.
- duration of convulsions was 0.5 to 5 min and began within 5 min after dosing.
- all surviving animals recovered within 24 hours.

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(8) F30 Astra Report 802-50 AF 118-1, 1992-09-02. Treatment of acute toxicity resulting from rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Feldman HS. [186/1.25]

See Study Nº (26) F30 under PHARMACOLOGICAL ACTIONS.

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(9) Anesth Analg 1991;73:373-84. Treatment of acute systemic toxicity after the rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Feldman HS, Arthur GR, Pitkanen M, Hurley R, Doucette AM, Covino BG. [396/1.25]

See Study Nº (27) under PHARMACOLOGICAL ACTIONS.

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(10) F36 Astra Report 802-50 AF 120-1, 1992-07-02. Systemic toxicity of ropivacaine in pregnant and non pregnant ewes. Santos AC, Arthur GR, Pedersen H, Morishima HO, Finster M, Covino BG. [166/1.22]

Study Nº: US 8703
Compound: LEA 103, batch F3
Formulation: Not indicated
Route: IV infusion at 0.5 mg/Kg/min
Dose Levels: 5 mg/mL
Strain: Mixed breed sheep.
Number: 7 nonpregnant, 41.5 to 70.5 Kg body weight, 2 years of age
5 pregnant, 56.1 to 71.7 Kg body weight, 2 years of age
Study Site:

Date: October 1987 - July 1992
GLP/QAU: Both present and signed.

This study was done to determine if the systemic toxicity of ropivacaine would be affected by pregnancy. The ewes used in this study were used in a ropivacaine PK study 2-10 days prior to this study. Infusions of the drug were given until circulation collapsed. Heart rate, mean arterial blood pressure, pH, and gas tensions were recorded.

Drug concentrations in plasma, brain, and heart were also determined in ewes. Plasma concentrations, pHs, gas tensions, and brain and heart concentrations were determined in some of the fetuses.

RESULTS

MEAN DOSAGE TO PRODUCE TOXIC SIGNS (from Table 2, p. 187)

	Dose (mg/Kg)		Plasma Concentration (µg/mL)		
	n = 7	n = 5	n = 7	n = 5	n = 3
Signs	Nonpregnant	Pregnant	Nonpregnant	Pregnant	Fetus
Convulsions	6.1 ± 1.6	5.9 ± 1.2	4.3 ± 1.4	5.0 ± 1.5	0.9 ± 0.1
Hypotension	10.5 ± 2.9	11.7 ± 2.1	5.8 ± 1.5	6.9 ± 0.8	1.8 ± 0.6
Respiratory Arrest	10.8 ± 2.9	12.0 ± 1.9	6.4 ± 1.3	7.0 ± 1.2	2.1 ± 0.5
Circulatory Collapse	11.3 ± 2.8	12.4 ± 2.0	7.3 ± 0.9	9.6 ± 4.6	2.3 ± 0.2

- toxic signs began with shivering, twitching, clonic convulsions with episodes of hypertension, tachycardia, frank hypotension, respiratory arrest, and circulatory collapse.
- doses producing toxicity were similar in nonpregnant and pregnant ewes.
- plasma concentration was similar in nonpregnant and pregnant ewes.
- plasma concentration producing toxic manifestations in fetuses was 18% to 30% lower than in pregnant ewes.

MEAN HEAR RATE AND ARTERIAL PRESSURE AT ONSET OF SIGNS (from Table 3, p. 188)

	Heart Rate (beats/min)		Arterial Pressure (mmHg)	
Signs	Nonpregnant	Pregnant	Nonpregnant	Pregnant
Control	97 ± 10(7)	106 ± 37(4)	106 ± 17(7)	95 ± 17(5)
Convulsions	193 ± 35(7)*	166 ± 48(4)*	221 ± 18(6)*	189 ± 50(5)*
Hypotension	181 ± 38(7)*	143 ± 339(4)*	100 ± 30(7)	91 ± 36(5)
Respiratory Arrest	147 ± 42(5)*	150 ± 25(4)*	66 ± 33(7)*	29 ± 15(5)*

Nº of animals in parenthesis.
* Significantly different from control

- heart rate and arterial pressure were similar between nonpregnant and pregnant ewes.
- ↑ in heart rate was 1.99x in nonpregnant and 1.57x in pregnant animals vs control.

MEAN VALUES IN NONPREGNANT/PREGNANT EWES AND FETUSES (from Table 4, p. 189)

	Control	Convulsions	Hypotension	Respiratory Arrest	Circulatory Collapse
Nonpregnant					
pHa	7.52 ± 0.02(6)	7.53 ± 0.04(6)	7.24 ± 0.07(5)	7.22 ± 0.07(5)	7.20 ± 0.08(5)
$PaCO_2$	32.9 ± 1.4(6)	29.2 ± 2.4(6)	53.8 ± (5)	55.2 ± 6.6(5)	59.5 ± 6.2(5)
PaO_2	83.0 ± 9.4(6)	80.8 ± 11.0(6)	31.6 ± (5)	25.4 ± 5.9(5)	21.4 ± 5.4(5)
Pregnant					
pHa	7.53 ± 0.04(5)	7.55 ± 0.05(5)	7.31 ± 0.05(5)	7.29 ± 0.06(5)	7.25 ± 0.03(4)
$PaCO_2$	29.6 ± 2.7(5)	27.6 ± 2.0(5)	46.9 ± 8.8(5)	45.6 ± 8.2(5)	50.5 ± 7.1(4)
PaO_2	82.8 ± 6.3(5)	80.8 ± 12.6(5)	38.8 ± 18.1(5)	32.0 ± 20.5(5)	20.5 ± 2.1(4)
Fetuses					
pHa	7.39 ± 0.02(3)	7.39 ± 0.02(3)	7.16 ± 0.20(3)	7.06 ± 0.19(3)	6.89 ± 0.11(2)
$PaCO_2$	44.5 ± 4.7(3)	40.4 ± 3.6(3)	60.9 ± 17.2(3)	77.1 ± 17.2(3)	99.4 ± 7.0(2)
PaO_2	21.7 ± 1.5(3)	20.0 ± 3.5(3)	15.3 ± 3.1(3)	13.3 ± 1.5(3)	11.5 ± 2.1(2)

N° of animals in parenthesis.

MEAN CONCENTRATION OF ROPIVACAINE HCl IN BRAIN AND HEART (from Table 5) AT THE TIME OF CIRCULATORY COLLAPSE
(from Table 5, p. 190)

	Brain (µg/g)	Heart (µg/g)
Nonpregnant	30.1 ± 6.6 (6)	25.6 ± 5.5 (7)
Pregnant	35.0 ± 1.6 (5)	30.5 ± 2.7 (5)
Fetus	11.6 ± 4.1 (3)	7.7 ± 3.4 (3)
(N° of animals)		

DOSAGES AND PLASMA CONCENTRATION OF ROPIVACAINE HCl AT ONSET OF CONVULSIONS (CNS) AND CIRCULATORY COLLAPSE (CC)
(from Table 6, p. 191)

	Ropivacaine	Bupivacaine
Nonpregnant		
CNS	6.1 ± 1.6*	2.7 ± 1.2
CC	11.1 ± 2.8	8.9 ± 2.7
Plasma concentrations		
CNS		
CC		
Pregnant		
CNS	5.9 ± 1.2*	1.9 ± 1.7
CC	12.4 ± 2.0*	5.1 ± 0.3
Plasma concentrations		
CNS		
CC		

* these results show that toxicity was not altered in pregnant ewes.

- results from an earlier study indicated the dose to produce equivalent signs of toxicity was greater with ropivacaine-
  Morishima HO, et al., Bupivacaine toxicity in pregnant and nonpregnant ewes. Anesthesiology 1985;63:134-9
- few ventricular arrhythmias reported in this study:
  nonpregnant: a brief episode of ventricular tachycardia in two animals, beginning at 8.19 mg/Kg and 10.83 mg/Kg after starting infusion-
  pregnant: ventricular fibrillation at 9.85 mg/Kg after starting infusion, which continued until cardiovascular collapse at 10.9 mg/Kg-

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(11) Anesthesiology 1991;75;137-41. Systemic toxicity of ropivacaine during ovine pregnancy. Santos AC, Arthur GR, Pedersen H, Morishima HO, Finster M, Covino BG. [208/1.22]

This reprint contains essentially the same data as in the above study.

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(12) F35 Astra Report 802-50 AF 103-1, 1989-12-15. Haemodynamic and central nervous system effects of intravenous bolus doses of ropivacaine (LEA 103) compared to lignocaine and bupivacaine in sheep. Mather LE, Rutten AJ. [124.1.26]

See Study Nº (33) F35 under PHARMACOLOGICAL ACTIONS.

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(13) Anesth Analg 1989;69:291-9. Hemodynamic and central nervous system effects of intravenous bolus doses of lidocaine, bupivacaine, and ropivacaine in sheep. Rutten AJ, Nancarrow C, Mather LE, Ilsley AH, Runciman WB, Upton RN. [239/1.26].

This reprint reports on the data in the above study.

B. Multidose

(14) B1 Astra Report 802-50 T1745, 1986-02-27. Dose range finding study of LEA 103 given subcutaneously to rats for two weeks. Astra Toxicology Laboratories, Sodertalje, Sweden. Appendix contains report G3 802-50 AF11-2, 1994-06-28. [1/1.23]
Study Nº: 85031
Compound: LEA 103, batch F2, assay 99.5%
Formulation: Solution in sterile water.
Route: SQ in the neck region at 2.5 mL/Kg.
Dose Levels:

Group	1	2	3	4	5
µmol/mL:	0	4	12	36	36
µmol/Kg:	0	10	30	90	90
mg/Kg:	0	3.3	9.9	30	30

Strain: Sprague-Dawley, body weight ♂ 210-250 g, ♀ 160-190 g, 44 to 48 days old.
Number: 6/sex/dose
Control Treatment: Physiological saline
Study Site: Astra, Sweden. Date: April 1989 - August 1994.
GLP/QAU: Both present and signed.

This study was done to determine the dose level for the one month toxicity study. Day 0 was designated the first day of dosing. Included in the study were clinical signs, body weight (2x/week), food consumption (2x/week), and water consumption (daily estimation). Drug plasma concentrations were determined Day 0 in Group 5 and in Group 1-4 on Days 14-17. Blood samples were taken predose and at 0.5, 1, 3, and 5 hours after drug administration on the last day of dosing. Analysis was by GC. Statistical analysis was done using the Wilcoxon rank sum test.

RESULTS

- signs: tissue irritation (small ulceration/incrustations in all dose groups)- spasms or convulsions 5 minutes after dosing at 30 mg/Kg-
- mortality: Group 4: 2♂ Days 2 and 10 and 1♀ Day 3-
- body weight/food/water consumption: no significant differences-
- 30 mg/Kg was the lethal dose and occurred Day 2-
- plasma concentrations:

Single Dose
Mean Concentration (ng/mL)[1]
(from Table 5, p. 33)

Time (hr)	♂	♀
0	-	-
0.5	2200 ± 884	1560 ± 828
1.0	1840 ± 488	1270 ± 671
3.0	701 ± 212	696 ± 93
5.0	278 ± 91	335 ± 157

Repeat Dose (from Table 2, p. 30)

	3.3 mg/Kg		9.9 mg/Kg		29.7 mg/Kg	
Time (hr)	♂ (n = 6)	♀ (n = 6)	♂ (n = 6)	♀ (n = 6)	♂ (n = 4)	♀ (n = 5)
0	-	-	-	-	-	-
0.5	226 ± 65	199 ± 37	600 ± 52	409 ± 103	1670 ± 338	1320 ± 423
1.0	184 ± 45	142 ± 39	586 ± 58	344 ± 23	1470 ± 298	1290 ± 352
3.0	85 ± 9	65 ± 26	272 ± 56	236 ± 14	838 ± 105	765 ± 71
5.0	35 ± 22	< 10	57 ± 28	95 ± 55	117 ± 51	378 ± 196

[1] Detection limit: 10 ng/mL

AUC Values Following Single And Repeat SQ Administration
(from Table 6, p. 34)

Dose	Male		Female	
(mg/Kg)	Day 0	2 Weeks	Day 0	2 Weeks
3.3	-	545 ± 75(n = 6)		448 ± 85 (n = 4)
9.9	-	1640 ± 168(n = 6)		1190 ± 60 (n = 4)*
29.7	5170 ± 1180(n = 5)	4460 ± 486(n = 4)	4400 ± 1570(n = 4)	4180 ± 368(n = 5)

* Significantly different from males

- a linear relation with AUC values after repeat dosing-
- the 90 μmol/Kg (30 mg/Kg) dose was too high for sq toxicity studies-

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(15) B2 Astra Report 802-50 T1749, 1986-03-05. General toxicity of LEA 103 given subcutaneously to rats for one month. Astra Toxicology Laboratories, Sodertalje, Sweden. Appendix contains report G4 802-50 AF12-2, 1994-06-28. [38/1.23]

Study Nº: 85053
Compound: LEA 103, batch F2, assay 99.5%
Formulation: Solution in saline.
Route: SQ in dorsal area at 2.5 mL/Kg, once a day for 1 month.
Dose Levels:

Group	1	2	3	4
mg/Kg:	0	3.3	9.9	26
μmol/Kg:	0	10	30	80

Strain: Sprague-Dawley, 2 months old, body weight ♂ 230-280 g, ♀ 160-210 g
Number: 10/sex/group
Control Treatment: Physiological saline
Study Site: Astra, Sweden.
Date: August 1985 - August 1994
GLP/QAU: Both present and signed.

The actual drug concentrations were between 94%-95% of the intended dose. Included in the study were clinical signs, body weight (weekly), food consumption (weekly), water consumption (daily estimation), hematology/blood chemistry/urinalysis (Week 3), gross and histopathology (all control, Group 4, and all preterminal dead), and organ weights (brain, lungs, liver, heart, spleen, thymus, kidneys, testes, ovaries). The concentration of the drug in the plasma was determined using satellite animals. Statistical analysis was by the Wilcoxon rank sum test. Significant differences were indicated by * (T values = 0.01).

RESULTS

- signs: short clonic convulsions and cyanosis in 1♂ Group 4 on one occasion-
- mortality: 1 ♀ Group 3, Day 24 shortly after dosing-
- body weight: no significant changes-
- food/water consumption: no significant changes-
- hematology: ↓ WBC ♂ Group 2*(15%)-
- blood chemistry:

cholesterol ↑ ♂ Group 3*(21%)-
potassium ↓ ♂, dose related, Group 3*(8.6%), Group 4*(12.1%)-
↓ ♀ dose related, Group 4*(11.5%)-
calcium ↑ ♀ Group 4*(8.3%)
magnesium ↓ ♂ Group 4*(11%)-

- organ weights: kidney absolute wt ↑ dose related (Group 4 ↑ 5% from control)-
testes absolute wt Group 4 significant ↓ (6%)-
- gross pathology: no treatment related changes-
- histopathology: ♀ Group 3 that died Day 24 had evidence of murine pneumonia and signs of circulatory failure with blood congestion and slight hypoxic fatty changes in the liver and kidneys-
liver: 1♂ Group 4 developed micro focal necrosis with leukocyte infiltration-
heart: there were no lesions reported in any of the drug treated animals-

From this and the previous study, the 26 mg/Kg (80 μmol/Kg) dose is close to the threshold dose for inducing convulsions. Only one convulsion was observed at this dose.

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(16) B3 Astra Report 802-50 T1746, 1986-02-28. A dose range finding and MTD study of LEA 103 given subcutaneously to dogs for 3 days. Astra Toxicology Laboratories, Sodertalje, Sweden. Appendix contains report G14 802-50AFI0-I, 1986-01-22. [182/1.23]

Study Nº: 85018
Compounds: LEA 103, batch 245/16, 99.9% assay
Bupivacaine HCl monohydrate, batch 35191-01, 100.2% assay
Formulation: Solution in physiological saline
Dosage: LEA 103: 0 5 10 20 50 μmol/Kg (1.6, 3.3, 6.6, 16.4 mg/Kg)
Bupivacaine: 0 5 10 20 50 μmol/Kg (1.6, 3.2, 6.5, 16.2 mg/Kg)
Volume: 2.5 1.0 1.0 1.0 2.5 mL/Kg
Route: Subcutaneous in the neck region.
Strain: Beagle, 10-20 months old, body weight ♂ 13.5-14.5 Kg, ♀ 8.5-14 Kg
Number: 3/sex
Control Treatment: Physiological saline
Study Site: Astra Sweden Date: March 1985 - February 1986
GLP/QAU Statements: Both present and signed.

This study evaluated a three day toxicity study of LEA 103 administered to dogs subcutaneously. Physiological saline was administered to three males and three females. After 6 days of recovery, LEA 103 was administered once a day for 3 consecutive days. Between each dose level there was a recovery period of at least 5 days. After a dose free period of 5 weeks, bupivacaine was administered according to the above design. Clinical signs, body weight, food consumption, rectal temperature, and EKGs were monitored. Drug concentrations in the blood plasma were also determined.

RESULTS

LEA 103

- neurological signs - nausea, vomiting, mild body tremor, involuntary extension of hind legs, urination, ataxia, general muscular tonus, periodic clonic convulsions - mostly in high dose-
- body weight, food consumption, and rectal temperature normal-
- irregular/occasional increases in heart rate, prolongation of PR and QRS intervals, and slight QRS axis deviations - all values were said to be within the normal range-
- no arrhythmias reported-
- periodic clonic convulsions for 10 min at 36 minutes after dose on Day 2 at 50 μmol/kg-

Bupivacaine

- itching at the injection site ≥ 3.2 mg/Kg - vomiting and body tremors at 6.5 mg/Kg - vomiting and severe body tremors at 16.2 mg/Kg-
- body weight, food consumption, and rectal temperature normal-
- irregular/occasional changes in PR and QRS, and slight QRS-axis deviations - all values were said to be within normal range-
- no arrhythmias reported-
- severe tonic/clonic convulsions 44 minutes after dosing at 50 μmol/kg on the first day of dosing in one dog-
- short clonic convulsions/severe tonic convulsion 26-39 minutes after dosing at 50 μmol/kg on the first day-

LEA 103 PK Results

- similar mean plasma Conc in ♂ and ♀ - higher at 6.6 mg/Kg than at 16.4 mg/Kg-
- AUC_{0-t} hr were lower in ♂ and ♀ LEA 103 animals vs bupivacaine at 1.6 and 3.3 mg/Kg-

Dose/Dose LEA 103/Bupivacaine	♂ Mean + SD (n = 3)	♀ Mean + SD (n = 3)
1.6/1.6	969 + 175/1190 + 255	1210 + 718/2160 + 2220
3.3/3.2	2290 + 143/3070 + 749	1890 + 718/2480 + 418
6.6/6.5	14900 + 1380/4510 + 701	10900 + 7617/4740 + 1160
16.4/16.2	8310 + 1330/8240*	7370 + 415/7910*

* n = 1

No significant differences were reported between LEA 103 and bupivacaine for AUC values. Plasma elimination was shorter for LEA 103 than for bupivacaine. At 24 hours no detectable levels (limit = 10 ng/mL) of LEA 103 were found in any of the dose groups; however, bupivacaine was found in some of the 3.2 and 6.5 mg/Kg samples at 24 hours. In summary, bupivacaine was again seen as more toxic than LEA 103.

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(17) B4 Astra Report 802-50 T1748, 1992-10-20. General toxicity of LEA 103 given subcutaneously to dogs for 1 month. Astra Toxicology Laboratories, Sodertalje, Sweden. Appendix contains report G15 802-50 AF 19-1, 1986-01-23 [278/1.23]

Study Nº: 85058
Compound: LEA 103, batch F2, 99.5% assay
Formulation: Solution in physiologic saline
Route: Subcutaneously in the neck region.
Dosage Levels: 0, 10, 20, 40 μmol/Kg (0, 3.3, 6.6, 13.2 mg/Kg) daily for 1 month.
Strain: Beagle, 6.5 to 14.5 months old; body weight ♂ 11 to 15.5 Kg, ♀ 9.5 to 12 Kg
Number: 3/sex/group
Control Treatment: Physiologic saline
Study Site: Astra, Sweden
Date: August 1985 - October 1992
GLP/QAU: Both present and signed

This study evaluated the toxicity of LEA 103 in dogs treated daily for one month by subcutaneous injection. The study followed clinical signs, body weight, food consumption, rectal temperature, EKGs, ophthalmoscopy, clinical chemistry, urinalysis, blood plasma concentrations, gross and histopathology, and organ weights. Blood samples were taken before dosing and at ¼, ½, 1, 2, 4, 7, and 24 hours after drug administration on Day 1 and Day 21 of dosing.

RESULTS

- tremors/emesis/local irritation at the injection site - all more noticeable in ♀ high dose-
- body weight: no large changes-
- food consumption: some minor changes in all groups-
- rectal temperature: normal during the study-
- ophthalmoscopy: no abnormalities were seen during the last week of dosing that were not reported prior to start of dosing-
- EKGs: " all EKGs showed a normal sinus rhythm, hence no arrhythmias were detected" - deviations in QRS axis (↑ 16%) occurred in 1♂ and 1 ♀ 30 minutes after 6.6 mg/Kg dosing, and in 1 ♀ 13.2 mg/Kg (40 μmol/Kg)-
- clinical chemistry/urinalysis: minor changes in some parameters-
- gross pathology: atrophy of epididymides (1 high dose), focal hemorrhage in urinary bladder (1 high dose ♀)-
- organ weights: due to uneven distribution of body weights in the groups, organ weights tended to vary also-
- histopathology: liver: portal leukocyte infiltration 1/3 ♂ 6.6 mg/Kg, 1/3 ♀ 13.2 mg/Kg-
  lymph nodes: resorbed blood 1/3 ♀ 13.2 mg/Kg-
  urinary bladder- submucosal hemorrhage 1/3 ♀ 13.2 mg/Kg-
  testes: occasional slightly atrophic tubules 1/3 13.2 mg/Kg-
  epididymides: unilateral suppurative epididymitis 1/3 13.2 mg/Kg-
  prostate: focal chronic prostatitis 1/3 13.2 mg/Kg-
  lymphocyte infiltration 1/3 13.2 mg/Kg-

Dose (mg/Kg)	Male AUC_{0-7} Day 1	Male AUC_{0-7} Day 21	Female AUC_{0-7} Day 1	Female AUC_{0-7} Day 21
3.3	2900 ± 1060	5700 ± 3400	3400 ± 1420	5140 ± 4400
6.6	6490 ± 2130	6900 ± 1940	9290 ± 5010	11580 ± 6510
13.2	6900 ± 1450	10690 ± 5750	13840 ± 8200	18890 ± 10970

note: n = 3

- AUC_{0-7} hr values were higher and appeared to be linear in ♀s.
- maximum plasma concentrations were seen at 15-30 minutes after administration.
- plasma levels could be seen 24 hours after the high dose on Day 1 but were near the limit of detection by Day 21 at 24 hours--

There was no frank toxicity seen in this study that could be related to LEA 103. The no effect dose was 6.6 mg/Kg (20 μmol/Kg) when administered subcutaneously to dogs.

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(18) B5 Astra Report 802-24 T2465, 1991-12-13. General toxicity study of ropivacaine (LEA 103) given subcutaneously and rectally to dogs for 6 months. Astra Safety Assessment, Sodertalje, Sweden. Appendix contains report G16 802-524 LF-0005-01 1991-11-12 [1/1.24]

Study Nº: 90139, Project Nº: 802-24
Compound: LEA 103, batch Nº F8, 100.2% assay
Formulation: Solution in physiological saline for SQ administration and vehicle gel for the rectal administration. The gel formulation consisted of hydroxypropyl methylcellulose 4000 cps and water adjusted with HCl to pH4.5-5.2.
Route: Subcutaneous (neck and back region) and rectally.
Dose Levels: Groups 1 2 3 4
SQ - 0 10 20 40 μmol/Kg (0, 3.3, 6,6, 3.2 mg/Kg)
Rectal - 0 320 640 1300 μmol/dog (0, 110, 210, 420 mg/dog)
Dose Volume: 2 mL/Kg for subcutaneous and 10 mL/dog for rectal administration.
Strain: Beagle, 7 to 8.5 months old, body weight ♂ 13.5 to 18.5 Kg, ♀ 10.0 to 16.0 Kg
Number: 5/sex/group
Control Treatment: Physiological saline
Study Site: Astra, Sweden.
Date: November 1990 - December 1991
GLP/QAU Statements: Both present and signed.

The object of this study was to evaluate the subcutaneous and rectal administration of ropivacaine in dogs for 6 months, as these are proposed therapeutic routes in humans.

Each dog in each group received both a subcutaneous dose followed immediately by a rectal dose. One dog (3654/90) in Group 2 was mistakenly dosed with 178 μmol/Kg sq instead of 148 μmol sq on Days 98 to 104. The first day of administration was called Day 0. This study included clinical signs, body weight (before dosing and

weekly), food consumption (daily), rectal temperature (before dosing and weekly prior to dosing), EKGs (before dosing and ½, 1, 2, 4, 6, and 24 hours after dosing on Day 0 and after 1, 3, and 6 months of dosing), ophthalmoscopy (before dosing and after 6 months of dosing), clinical chemistry and urinalysis (before dosing and at 2, 4, and 6 months), plasma concentrations (Day 0 and after 1, 3, and 6 months - samples were collected at ½, 1, 2, 4, 6, and 24 hours after dosing), gross and histopathology, and organ weights.

RESULTS

- clinical signs: defecation after rectal administration (dose related) - itching at injection site (dose related) - body tremors increased in ♀ Group 4 - vomiting increased in ♀ Group 2.
- body weight: Group 1 (1 ♂, 1 ♀), Group 2 (2 ♂), Group 3 (1 ♂,), Group 4 (1 ♂) showed a loss of 2.3 Kg (12.5%) in weight from the predose value.
- food consumption: small differences observed.
- rectal temperature: increased in a few dogs on occasion.
- EKG: individual variables were recorded - none were said to be related to treatment.
- ophthalmoscopy: (seen last week of dosing but not before start of study)
  1 ♂ Group 1 (focal superficial chronic keratitis, right eye).
  1 ♀ Group 1 (minimal opacities posterior lens capsule, right eye).
  1 ♂ Group 4 (persistent hyaloid vessel posterior lens capsule, left eye).
- PCV, Hb, and RBC values were reduced in Group 3 and 4.
- gross pathology: heart- 1 ♀ Group 3 (subendocardial hemorrhagic streaks).
  urinary bladder: 1 ♀ Group 4 (mucosal ecchymoses).
- histopathology:
  ♂: lung: inflammatory changes in drug groups.
  cervical lymph node: all drug groups (hemosiderosis, venous congestion).
  liver: inflammatory changes, Group 2 and 4.
  ♀: rectum: mucosal/submucosal hemorrhage in 1 each drug groups.
  anal canal: inflammatory changes Group 4.
  liver: foci of mononuclear cells all drug groups.
  kidneys: pyelitis all drug groups.
  urinary bladder: focal inflammatory changes Groups 2, 3. focal hemorrhage Group 4.
  vagina: inflammatory changes Groups 2 and 3.
  parathyroid: cysts Groups 3 and 4.
  myocardium: in two sections; an area of moderate subendocardial fresh hemorrhage
- PK data:

Six Month PK data: (from Table 4, pp.307 and 308)

Male: mean total dose:	C_{max} (μmol/L)	T_{max} (h)	AUC (μmol·/L)	t ½ (h)
483.0 ± 12.8 μmol:	3.79 ± 2.18	0.25-0.5	22.30 ± 8.15	12.98 ± 11.98
976.2 ± 17.3 μmol:	6.12 ± 1.85	0.5	33.45 ± 8.43	7.92 ± 5.19
1968.2 ± 40.5 μmol:	11.85 ± 3.14	0.25-0.5	69.03 ± 25.88	5.08 ± 1.88

Female: mean total dose:	C_{max} (μmol/L)	T_{max} (h)	AUC (μmol·/L)	t½ (h)
457.4 ± 21.0 μmol:	1.94 ± 0.70	0.5-4	19.01 ± 6.46	7.75 ± 3.60
934.4 ± 25.6 μmol:	7.16 ± 8.21	0.25-1	59.59 ± 31.47	8.89 ± 4.51
1872.1 ± 92.3 μmol:	10.80 ± 7.73	0.5-1	106.15 ± 50.87	16.80 ± 14.11

- C_{max} increased linearly with dose - AUCs ↑ after 6 months in females-
- protein binding was 90% to 96% and was concentration dependent-
- mean C_{max} (at 0.5 hours) did not vary over the six months with all doses-
- maximum plasma concentrations at T_{max} (0.25 hr) for ♂ high dose was 37.3 μmol/L on Day 0 and 24.0 μmol/L at 6 months in ♀-
- from the increase in the AUC

Rectal administration of the formulation used in this study produced a dose related increase in feces and itching at the subcutaneous injection site was increased with increasing dose. Other drug related changes were seen as decreased hemoglobin, RBCs, and packed cell volume in both male and female animals. The focal inflammatory and hemorrhage seen in the urinary bladder were not considered as being treatment related by the sponsor; nevertheless, it should be considered drug related. No EKG changes were reported in this study. This may be due to the low plasma concentrations observed.

C. Special

1. In Vivo

a. Cardiovascular/CNS Toxicity

(19) F20 Astra Report 802-50 AF 76-1, 1986-12-02. Cardiovascular effects and convulsive properties of adrenaline containing solutions of LEA 103 after intravenous administration in conscious rats. Forsberg T, Westman I, Sperber B, Oberg E. [30/1.25]
Study Nº: AF 8628
Compound: LEA 103, batch F3
Adrenaline bitartrate, batch 54143
Formulation: Not stated.
Dosage: LEA 103: 0 2.5 5 mg/Kg without adrenaline; 2.5 mg/Kg with adrenaline
Adrenaline: 2.8 μg/mL without LEA 103: 1.4 1.8 2.8 μg/Kg with LEA 103.
Route: IV via the caval vein. Administration at 1.0 mL/Kg over 20 seconds, followed by 0.3 mL saline wash over 20 seconds.
Strain: Sprague-Dawley males, 300 to 400 g body weight, 70 to 85 days old.
Number: 6/group
Control Treatment: Physiological saline
Study Site: Astra Alab AB, Sweden.
Date: May 1986 - December 1986
GLP/QAU Statements: Both present and signed.

Convulsive and cardiovascular effects of LEA 103, with and without added

adrenaline, were studied in conscious male restrained rats following rapid iv administration. The dose of LEA 103 and adrenaline were chosen to mimic the inadvertent iv bolus injection of a high clinical dose intended for an epidural procedure. EKGs were recorded predose, at 0.3-0.5, 1, 2, 3, 5, 10, 15, and 30 minutes after the start of the injection. BP was also recorded.

RESULTS

No adrenaline:
Saline: no adverse effects noted-

2.5 mg/Kg: moderate/short lasting ↓ (30%) in mean arterial BP - 17% ↓ in heart rate - ↑ in PQ (25%), QRS (37%), QT (17%) - 2° AV block and singular ectopic beats in 2/6 - complex sustained arrhythmias (2/6) - no deaths-

5.0 mg/Kg: marked ↓ in MAP (52%) and near convulsive dose - rapid ↓ in BP - 3/6 deaths within 1 to 3 min - ↓ heart rate (29%) over 30 min - marked ↑ in PQ (62%), QT (40%), QRS (86%) - 2° AV block and single ventricular ectopic beats (2/6) - complex sustained arrhythmias (4/6) - convulsions (6/6) - pulmonary edema (2/6) - deaths (3/6) occurring within 3 min-

2.8 µg/Kg adrenaline: moderate short lasting ↓ in MAP (34%) - ↓ in heart rate (12%) - slight↑ in PQ and QT (10% to 13%) - 2° AV block and single ventricular ectopic beats (1/6) - complex sustained arrhythmias (5/6)-

2.5 mg/Kg LEA 103 + 1.4 µg/Kg adrenaline: ↓ MAP (50%) - ↓ heart rate (38%) - ↑ PQ (36%), QRS (38%), QT (32%) - 2° AV block and single ventricular ectopic beats (2/6) - complex arrhythmias (1/6) - convulsions (3/6) - pulmonary edema (2/6) - deaths (2/6)-

2.5 mg/Kg LEA 103 + 1.8 µg/Kg adrenaline: ↓ MAP (48%) - ↓ heart rate (33%) - ↑ PQ (32%), QRS (37%), QT (28%) - 2° AV block and single ventricular ectopic beats (3/6) - convulsions (2/6) - no pulmonary edema or deaths-

2.5 mg/Kg LEA 103 + 2.5 µg/Kg adrenaline: ↓ MAB (52%) - ↓ heart rate (38%) - ↑ PQ (41%), QRS (45%), QT (31%) - 2° AV block and singular ventricular ectopic beats (3/6) - complex arrhythmias (2/6) - convulsions (4/6) - pulmonary edema (4/6) - deaths (3/6) occurring within 4 min-

- adding adrenaline to LEA 103 increases the cardiovascular toxicity-
- deaths were attributed to pulmonary edema and/or ventricular arrhythmias-

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(20) F29 Astra Report AF 8534, 1986-02-11. Comparative overt central nervous system and cardiovascular system toxicities of lidocaine, bupivacaine and LEA 103 administered intravenously to unanesthetized, unsedated dog Feldman H S, Arthur G R, Covino B C. [69/1.25]

Study N°: AF 8534
Compound: LEA 103, Batch N° LA-455-1-6
Bupivacaine HCl monohydrate (commercial product Sensorcaine)
Lidocaine HCl H_2O
Formulation: Stock solutions of the drugs were diluted with sterile water for injection.
Route: IV, via the cephalic vein.

Dose Levels: (mean)	LEA 103	Bupivacaine	Lidocaine
Convulsant Dose: (mg/Kg)	4.88	4.31	20.84
(mg/Kg/min)	1.96	1.98	7.87
Convulsant Dose x2 (mg/Kg)	9.75	8.60	41.69
Convulsant Dose x3 (mg/Kg)	14.74	-	43.86

Strain: Beagle males, 10.0-12.7 Kg body weight, 10.4-10.7 months old.
Number: 6/group
Study Site:
Date:
GLP/QAU Statements: Both present and signed.

This study evaluated the iv dose of LEA 103, bupivacaine, and lidocaine required to cause convulsions in the conscious unsedated dog and determined the effects on the cardiovascular system of convulsant and super convulsant doses of the three drugs. In the infusion study (convulsant dose), LEA 103 and bupivacaine were infused at 2.0 mg/Kg/minute; lidocaine was infused at 8.0 mg/Kg/minute. The infusion studies were used to determine the convulsant dose. On Day 2 the dogs received an iv bolus equivalent to 2x the convulsant dose. On Day 3 the survivors were given a dose equivalent to 3x the convulsant dose. Blood drug concentrations were also determined.

RESULTS

IV Infusion Study (convulsive dose):

- LEA 103 signs: head tremors (3/6), generalized body tremors (5/6), salvation (1/6), lip licking (2/6), emesis (1/6), pedaling (3/6), ventral arrhythmia (1/6), convulsions (6/6).
- no deaths in any group.
- seizure duration (sec): LEA 103 = 190 ± 53, bupivacaine = 307 ± 39, lidocaine = 200 ± 58
- convulsive activity of LEA 103 associated with marked acidosis.
- heart rate: significant ↑ in LEA 103 (66%), bupivacaine (59%), lidocaine (57%).
- respiratory rate: significant ↑ in bupivacaine (19%) and significant ↓ in lidocaine (7%).
- QT: significant ↓ in lidocaine (12%).
- QRS: nonsignificant ↑ in LEA 103 (15%), bupivacaine (23%), and lidocaine (8%).
- PR: significant prolongation with bupivacaine at start of seizure.
- MABP: significant ↑ LEA 103 (53%) and bupivacaine (57%).
- pH: significant ↓ with bupivacaine (0.9%) and LEA 103 (2%).
- PaO_2: significant ↓ LEA 103 (44%), bupivacaine (19%), lidocaine (11%).
- $PaCO_2$: significant ↑ in LEA 103 (30%), bupivacaine (23%), and lidocaine (11%).
- Na : significant ↓ bupivacaine after 3 minutes of seizure activity.
- K: ↑ within 1 minute of seizure onset in all groups - significant with LEA 103 (29%).
- Hct: significant ↑ in LEA 103 (28%), bupivacaine (30%), and lidocaine (19%).

The above data is for the start of the seizures or at maximum value. Values were near or at control values five minutes after seizures stopped. Few arrhythmias were observed -ventricular tachycardia was sen in one LEA 103 dog. Plasma concentrations (µg drug base/mL) at the start and end of seizure were: LEA 103 (11.4, 3.97), bupivacaine (18.0, 3.22), and lidocaine (47.2, 9.81).

Two Times Convulsant Dose:

- mortality: LEA 103 (1/6), bupivacaine (5/6), lidocaine (2/6)-
- greater occurrence of ventricular arrhythmias in the bupivacaine group (5/6), with one progressing to ventricular fibrillation-
- no arrhythmias observed in lidocaine or LEA 103 group (one LEA 103 dog showed signs of atrioventricular dissociation)-

Three Times Convulsant Dose:

- 1 bupivacaine dog survived the 2x convulsant dose to receive 3x the convulsant dose-
- bupivacaine venous concentration at death was 10 µg/mL-
- 3/4 deaths in LEA 103 and lidocaine group-

This study indicated that bupivacaine produces a greater frequency of ventricular arrhythmias than LEA 103 or lidocaine. The duration of seizure activity is somewhat longer with bupivacaine than with LEA 103 or lidocaine at mean seizure doses, but lower plasma concentrations are observed with lidocaine. Both LEA 103 and bupivacaine were more CNS potent than lidocaine; however, bupivacaine appears to show more cardiotoxicity than LEA 103 or lidocaine. At dosages used in this study, no ventricular arrhythmias occurred with lidocaine.

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(21) Anesth Analg 1989;69:794.-801. Comparative systemic toxicity of convulsant and supra convulsant doses of intravenous ropivacaine, bupivacaine, and lidocaine in the conscious dog. Feldman HS. Arthur GR. Covino BG. [178/1.25].

This is a reprint of the above study.

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(22) F11 (F32) Astra Report 802-50 AF 101-1, 1992-03-04. Hemodynamic effects of epidural anesthesia in the dog with ropivacaine and bupivacaine. Feldman HS. [239/1.18].

See Study N° (28) F11 (32) under PHARMACOLOGICAL ACTIONS, B. Effects Related to Possible Adverse Reactions.

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(23) Reg Anesth 1991;16(6);303-8. The effects of epinephrine on the anesthetic and hemodynamic properties of ropivacaine and bupivacaine after epidural administration in the dog. Hurley RJ. Feldman HS. Latka C. Arthur GR. Covino BG. [321/1.18]

See Study N° (28 and 29) under PHARMACOLOGICAL ACTIONS, B. Effects Related to Possible Adverse reactions.

(24) F30 Astra Report 802-50 AF 118-1, 1992-09-02. Treatment of acute toxicity resulting from rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Feldman HS. [186/1.25]

This study evaluated a regimen to treat acute toxicity in male dogs resulting from rapid iv administration of LEA 103 or bupivacaine HCl monohydrate. Convulsive and 2x convulsive doses of ropivacaine (4.9 and 9.8 mg/Kg) and bupivacaine (4.3 and 8.6 mg/Kg) were administered as iv bolus injections via a forelimb catheter over 30-60 seconds. The volume was 10 mL for the convulsive dose and 20 mL for 2x the convulsive dose. Heart rate, BP, EKG, blood lactate concentrations, potassium, catecholamine concentrations, and blood pH were followed. There were 3 dogs per group. The study was done be Astra, Sweden in April-August 1989. GLP/QAU statements were present and signed.

RESULTS

Both LEA 103 and bupivacaine produced significant increases in heart rate, MABP, inferior vena cava pressure, EKG conduction times, blood lactate concentration, potassium, and catecholamine concentrations at the convulsive dose. A decrease in arterial blood pH was seen. Statistically significant differences between LEA 103 and bupivacaine were seen at various times and include the following: heart rate, PR segment, QT interval systolic BP, mean arterial BP, respiration, PaO_2, Na, and epinephrine. No ventricular arrhythmias were observed in either drug groups after administration of the convulsive dose.

All dogs treated with 2x the convulsive dose of ropivacaine survived the treatment, but two animals treated with bupivacaine developed hypotension, respiratory arrest, ventricular tachycardia, and ventricular fibrillation and could not be survived with closed chest cardiac massage, treatment with epinephrine, bretylium, atropine, and direct current cardioversion. The administration of 10 mg/Kg iv thiamylal abolished seizures caused by both drugs. Tracheal intubation and mechanical ventilation with room air enriched with oxygen was started following the control of seizures

With rapid treatment it was possible to reduce the mortality in both the LEA 103 and bupivacaine treated groups. Mortality was reduced from 83% to 33% in the bupivacaine group and from 17% to 0% in the LEA 103 group.

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(25) Anesth Analg 1991;73:373-84. Treatment of acute systemic toxicity after the rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Feldman HS, Arthur GR, et al. [396/1.25]

This reprint covers the data reported and reviewed in the above study.

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(26) F31 Astra Report 802-50 AF 104-1, 1994-06-22 Cardiovascular toxicity and

resuscitation studies with ropivacaine (LEA 103), bupivacaine and lidocaine in the anesthetized dog - a blinded comparison study. [1/1.26]

In this study 12 pentobarbital anesthetized dogs (4 ♂, 8♀) 2 to 6 years old were administered cumulative bolus doses of LEA 103, starting at 2.66 mg/Kg iv. This was followed by 5.33 mg/Kg iv 2 hours later and 10.66 mg/Kg 4 hours after the initial dose. The two LEA 103 animals that did not require resuscitative intervention received an additional high dose of 10.66 mg/Kg two hours later, i.e., 6 hours after the first dose.

Twelve dogs (6♂, 6♀) also received bolus doses of bupivacaine at 2, 4, and 8 mg/Kg iv. The one dog not requiring resuscitative intervention received an additional high dose of 8 mg/Kg administered as above.

The lidocaine group (2♂, 4♀) was administered a bolus of 8, 16, and 32 mg/Kg. The one dog not requiring resuscitative intervention received an additional 32 mg/Kg iv dose 6 hours after the first dose.

BP, heart rate, and EGGS were monitored at regular intervals during the study. Animals that required resuscitation (systolic BP <45 mm Hg) first received open chest heart massage followed by epinephrine (5 μg/Kg up to 20 μg/Kg maximum). If ventricle tachycardia developed, direct current cardioversion was applied (10 joules). If no pulse or bradycardia was present, atropine (20-60 μg/Kg iv) or epinephrine (2-10 μg/Kg iv) was administered. Dogs with blood gas values outside the normal range were administered a sodium bicarbonate injection to correct for acidosis. The study was conducted by Astra, Sweden in August - December 1987. GLP/QAU statements were not present.

RESULTS

- initial doses of all drugs produced small hemodynamic changes-
- ↓ in MAP, heart rate, and cardiac output after the higher doses (dose-dependent)-
- central venous, pulmonary artery, and pulmonary capillary wedge pressures were unaltered by the drugs-
- cardiac output showed a dose related ↓ with all doses of each drug-
- effective refractory period (ERP) dispersions were ↑ dose related with all drugs, occurring at 1 to 10 minutes after the end of each dose-
- all but 1 dog in each group showed signs of cardiovascular toxicity requiring resuscitative intervention-
- resuscitation was needed after the third dose (11/12 for LEA 103 and bupivacaine and 5/6 for the lidocaine group-
- mortality: 1/12 ropivacaine, 2/12 bupivacaine-
- ventricular tachycardia and/or fibrillation (19/27) resulted in resuscitation efforts-
- duration time for resuscitation was: lidocaine (20.9 min) < LEA 103 (36.7 min) < bupivacaine (54.8 min)-
- serum concentrations were higher with LEA 103 than with bupivacaine after the second dose at all times - lidocaine levels were higher than LEA 103 and bupivacaine at all measurement times-

The results of the study indicated no great differences in cardiovascular toxicity, mortality, or resuscitation results between the three drugs at comparable doses. Resuscitation required rapid controlling of the hemodynamic changes and preventing metabolic acidosis.

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(27) F34 Astra Report 802-50 AF 67-1, 1987-01-08. Cardiotoxicity of LEA 101 - a new amide local anaesthetic agent. Reiz S, Haggmark S, Johansson G, Nath S. [92/1.26].

Compounds: LEA 101 (AL 381) ropivacaine HCl, Batch 8308
Bupivacaine HCl monohydrate
Lidocaine HCl monohydrate
Formulation: Not stated.
Route: Left descending coronary artery.

Dose Levels: LEA 101:	0	0.33	0.66	1.33	2.66	5.33 mg/animal
Bupivacaine:	0	0.25	0.5	1	2	4 mg/animal
Lidocaine:	0	1	2	4	8	16 mg/animal

Volume of Injection: 2 mL over 10 seconds.
Control Treatment: Normal saline - 2 mL preceded and followed each series of drug.
Strain: Swedish domestic pig; 6 months old, 46-47 Kg body weight.
Number: 1 ♂ and 7♀
Study Site:
Date:
GLP/QAU Statements: Not present.

This study was a random, crossover, dose response design which evaluated the cardiotoxicity of the three drugs in pigs lightly anesthetized throughout the study with continuous 7.5 mg/Kg/h of pentobarbital. The animals were connected to a volume cycled servo ventilator. EKGs, aortic, pulmonary arterial, right atrial pressures, and left ventricular dP/dT were recorded continuously. Cardiac output was also determined. An interval of 5 minutes or longer was allowed between doses in order to allow hemodynamics to return to the pre-injection pattern. A one hour interval between dosing with the next anesthetic was allowed. The doses were said to be equivalent analgesic doses. Animals that survived the randomized drug administration of all three drugs were dosed with 10.66 mg of LEA 101. Wilcoxon and Mann-Whitney was used for statistical analyses.

RESULTS

- mortality: 2/8 from intractable ventricular fibrillation 2 to 30 seconds after receiving 4 mg of bupivacaine as the last (third) drug.
- hemodynamic changes: significant ↓ MAP (9%-13%), ↑ LVEDP (23%-32%), and ↓ LvdP/dT (29%-35%) from base values after highest doses of each drug - changes were similar at equivalent analgesic doses - significant ↓ (29%) in great cardiac venous blood flow (29%) from baseline only with 5.33 mg LEA 101.

- EKG changes: significant ↑ QRS and QT intervals with 5.33 mg LEA 101 and 2 and 4 mg bupivacaine - both functions were dose related - LEA 101 (10.66 mg) ↑ 18% above the 5.33 mg dose - bupivacaine changes 30% higher than LEA 101 at 2 and 4 mg - no significant change in QRS or QT interval with lidocaine, but was significant from bupivacaine-
- heart rate and cardiac output was not changed by these three drugs-
- body temperature, urine volume, Hct, and plasma pentobarbital concentration were similar after administration of each drug-

The hemodynamic effects maximized about 5 seconds after drug administration and returned to control values after one minute. In this study the prolongation of the QRS interval in the EKG was regarded as a measure of electrophysiologic toxicity and the ratio was calculated as a 15:6.7:1 (bupivacaine : ropivacaine : lidocaine). Recovery times between equal analgesic doses of the drugs was no different. Ropivacaine appeared to be less toxic than bupivacaine when evaluated under the conditions in which this study was conducted.

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(28) Acta Anesthesiol Scand 1989;33:93-98. Cardiotoxicity of ropivacaine - a new amide local anaesthetic agent. Reiz S, Haggmark S, Johansson G, Nath S. [118/1.26]

This paper reported the results of the above study.

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(29) F35 Astra Report 802-50 AF 103-1, 1989-12-15. Haemodynamic and central nervous system effects of intravenous bolus doses of ropivacaine (LEA 103) compared to lignocaine and bupivacaine in sheep. Mather LE, Rutten AJ. [124/1.26].

Ropivacaine HCl (30, 45, 60, 90, 120 mg/animal iv bolus), lidocaine HCl (80, 320 mg/animal iv bolus), and bupivacaine HCl (20, 80 mg/animal iv bolus) were evaluated in conscious Merino ewes for cardiac and central nervous system effects. Only one dose was administered to any animal on any day. The sheep were between one and two years old with a mean body weight of 47.8 ± 6.3 Kg. The ewes had type A hemoglobin. The animals were allowed to recover from catheter surgery for at least five days before drug therapy. Eleven ewes were in this study. The study was done in

The animal work was done
'. GLP/QAU statements were not present.

RESULTS

- convulsions (mortality):
  ropivacaine: 3/5 at 60 mg (0/5), 7/7 at 90 mg (1/7), 5/5 at 120 mg (1/5)-
  bupivacaine: 0/5 at 20 mg (0/5), 5/5 at 80 mg (2/5)-
  lidocaine: 0/5 at 80 mg (0/5), 5/5 at 320 mg (0/5)-
- estimated convulsive dose 50% (CD_{50}) = 60 mg for ropivacaine
  = 45 mg for bupivacaine (from previous study)

= 125 mg for lidocaine (from previous study)

- deaths in ropivacaine (1/7 at 90 mg, 1/5 at 120 mg) and bupivacaine (2/5 at 80 mg) animals were due to sudden onset of ventricular tachycardia/ventricular fibrillation-
- arterial blood concentrations at CD_{50} = 20 μg/mL for ropivacaine þ
  = 12 μg/mL for bupivacaine þ
  = 52 μg/mL for lidocaine þ
  þ these values are only approximate
- sub-lethal doses produced increases in heart rate, left ventricular end diastolic pressure (LVEDP), dP/dt_{max}, mean arterial pressure (MAP), cardiac output (CO), mean pulmonary artery pressure (MPAP), and systemic vascular resistance (SVR)-

Convulsion times were shorter with ropivacaine than with lidocaine and bupivacaine, although it is not clear that these were equivalent anesthetic doses; in addition, cardiovascular changes were somewhat less with ropivacaine than with bupivacaine, but again these changes may not be comparable if the doses were not equivalent anesthetic doses.

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(30) Anesth Analg 1989;69:291-299 Hemodynamic and central nervous system effects of intravenous bolus doses of lidocaine, bupivacaine and ropivacaine in sheep. Rutten AJ, Nancarrow C, Mather LE, Ilsley AH, Runciman WB, Upton RN. [239/1.26]

This reprint reports the results of the above study.

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b. Potential for methemoglobinemia

(31) G41 Astra Report 802-50 AF 65-1, 1986 10-15. An investigation on the formation of methemoglobinemia after an intravenous infusion of 10 μmol/kg ropivacaine (LEA-103) in dog. Hallidin M. Elofsson S. [1/1.27]

LEA 103, Batch Nº F2 (3.3 mg/Kg, 10 μmol/Kg iv) in saline was administered to one male beagle dog. No formation of methemoglobin was observed in blood samples taken up to 240 minutes after drug administration. The detection limit for the method used was 2 mg/mL. The study was performed by Astra, Sweden in May 1986.

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c. Local Irritation

(32) H10 Astra Report T2748, 1993-12-23. Effect on peripheral nerve tissue of ropivacaine (LEA 103) and bupivacaine (LEA 131) after single perineural and intraneural administration to rats. Astra Safety Assessment, Sodertalje, Sweden. [11/1.27]

The objective of the study was to evaluate the effect of LEA 103 and bupivacaine HCl monohydrate (LEA 131) on the peripheral nerve tissue in male Sprague-Dawley rats. The animals were about 10 weeks old and weighed 330 to 386 g. There

were 4 groups of 5 rats each. LEA 103 (7.9 mg/mL - 24 μmol/mL) or bupivacaine (7.9 mg/mL - 23 μmol/mL) was applied to the exposed left sciatic nerve, either topically (0.2 mL) or intraneurally (0.02 mL) by intrafascicular injection. The study was carried out by Astra, Sweden in June 1993. The study was signed on 23 December 1993; however, the pathology reports were dated 10 January 1994. GLP/QAU statements were present and signed.

RESULTS

There were no signs of neurotoxic effects in five male rats after exposing the sciatic nerve to perineural or intrafascicular (intra neurally) injections of ropivacaine or bupivacaine. The right sciatic nerve acted as the control and received physiological saline. Inflammatory changes (perineural granulation-nonspecific mononuclear cell infiltration-suppuration) occurred in most of the rats exposed perineurally, including controls, and in some of the rats receiving intrafascicular nerve injections of the drugs. Slight myelin vacuolization and disintegration were seen in about half the rats. The changes reported for bupivacaine were more pronounced. The changes were considered to be from inflammation.

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(33) H11 Astra Report 802-50 T2621, 1993-03-17. Histopathology Report: Effects of LEA 103 (ropivacaine) on the spinal cord of the rat, following repeated intrathecal administration via an indwelling catheter for 14 days. Astra Safety Assessment, Sodertalje, Sweden. [74/1.27]

The objective of this investigation was to study the effects on the spinal cord of rats treated with LEA 103 for 14 days via an indwelling intrathecal catheter.

Ropivacaine was administered into the subarachnoid space at 0, 0.026, 0.053, and 0.11 mg/rat (0.08, 0.16, 0.32 μmol/rat) twice a day for 14 days. Each group contained 6 males. At histopathology, slight or minimal inflammatory focal granulomatous changes were obvious at the injection site (L1) in most of the animals. This was considered to be due to irritation from the catheter tip. In half the animals a micro focal degeneration of myelin sheaths was seen in a single nerve root. The study was done by Astra, Sweden and dated 17 March 1993 and revised 13 April 1994. GLP/QAU statements were present and signed.

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(34) H8 Astra Report 802-50 T1788, 1994-05-03. Effect of LEA 103 on peripheral nerve tissue following sciatic nerve block in guinea pigs. Astra Safety Assessment, Sodertalje, Sweden. [94/1.27]

The objective of this study was to evaluate the local morphological effects of LEA 103 on peripheral nerve tissue in guinea pigs following sciatic nerve block after a single perineural injection.

LEA 103 was evaluated on peripheral nerve tissue following sciatic nerve block. The results were compared with those of bupivacaine and lidocaine. There were seven groups of six Dunkin Hartley White guinea pigs per group. Single injections of 0.2 mL ropivacaine (10.6 mg/mL) without and with 5 μg/mL epinephrine, bupivacaine (7.92 mg/mL, 23 μmol/mL) without and with 5 μg/mL epinephrine, and lidocaine (21.3 mg/mL, 74 μmol/mL) without and with 5 μg/mL epinephrine were administered in the perineural tissues of the left sciatic nerve. The control group received physiological saline. GLP/QAU statements were present and signed. The study was done by Astra, Sweden in January 1986.

RESULTS

There were no adverse clinical signs in any of the animals, and no gross lesions were reported at the injection site or in the sciatic nerves. Minimal foci of epineural inflammation with mononuclear cell infiltration or slight epineural inflammation with mononuclear cell infiltration and minimal fibroplasia were reported in all groups. In the LEA 103 and bupivacaine groups, the latency to onset of motor block was about 1 minute and to sensory block about 2-4 minutes. The duration of the block was about 150 minutes for LEA 103 with or without epinephrine. Bupivacaine block duration was 130 minutes without and 167 minutes with epinephrine. With lidocaine, motor block duration was 30 minutes without and 73 minutes with epinephrine. Sensory block duration was about 28 minutes without and 60 minutes with epinephrine. With bupivacaine, the anesthetic effect was improved with epinephrine but not with ropivacaine.

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(35) H9 Astra Report 802-50 T1789, 1994-05-03. Effect of LEA 103 on peripheral nerve tissue following sciatic nerve block in guinea pigs. Complementary study. Astra Safety Assessment, Sodertalje, Sweden. [116/1.27]

This study was similar to the above study. Only LEA 103 was evaluated. There were 3 groups of 12 animals per group. The amount of LEA 103 administered was 6.4 μmol/animal (2.1 mg/animal) at 0.2 mL/animal. The study was done by Astra, Sweden in April 1986. GLP/QAU statements were present and signed.

RESULTS

The latency to onset of motor block was about 1 minute, with a duration of 150-160 minutes. Sensory block latency was about 2 minutes, with a duration of 130-140 minutes. Of the 23 sciatic nerves treated with LEA 103, one (a) showed slight epineural inflammation with mononuclear cell infiltration and minimal fibroplasia, three (b) showed degeneration and disintegration of a few axons in a single nerve fascicle with vacuolization of Schwann cells and demyelination associated with minimal mononuclear cell infiltration and slight epi- and perineurial fibroplasia, and one (c) revealed degeneration and disintegration of some axons as in b). Saline treatment produced 1/46 as in (a) and 2/46 as in c). No definite conclusions regarding the neurotoxicity of ropivacaine could be shown from the results, although it appeared there were more

lesions in the LEA 103 than the saline treated animals.

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(36) H5 Scantox T2451, 1991-10-07. Primary skin irritation study in rabbits. [136/1.27]

Skin irritation was evaluated on intact rabbit skin with a solution of ropivacaine (43 mg/mL, 130 μmol/mL). The solution was applied to 2.5 cm^2 areas of clipped dorsal skin and covered with surgical gauze. After an exposure period of 4 or 24 hours the gauze patches were removed and the skin examined. The results were compared with lidocaine (550 μmol/mL), oxymetazoline (3.4 μmol/mL), and physiological saline. This study was performed by

RESULTS

No skin edema or erythema was observed, but the vasoconstrictive properties of ropivacaine produced a distinct paleness 1/2 hour after the patch was removed from the 4 hour exposure. At 24 hours no effects were reported. Oxymetazoline, a vasoconstricting agent, also produced paleness in the 4 hour exposure but not in the longer exposure.

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(37) H6 Scantox T2452, 1991-10-21. Primary skin irritation study in rabbits with iontophoresis. [148/1.27]

LEA 103 (130 μmol/mL) and lidocaine (550 μmol/mL) were evaluated after a 15 minute exposure with iontophoresis current densities of 0.5 or 0.9 mA/cm^2. The results indicated no erythema, edema, or paleness with either drug. The study was evaluated by GLP/QAU statements were present and signed.

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(38) H7 Scantox T2501, 1992-02-10. Primary skin irritation study in rabbits with iontophoresis. [161/1.27]

This study was similar to the above study. Epinephrine, however, was also added to ropivacaine (37 mg/mL, 113 μmol/mL + 20 μg/mL epinephrine) and lidocaine (150 mg/mL, 550 μmol/mL + 20 μmol/mL epinephrine) solutions. Skin was exposed for 15 minutes in combination with 0.5 or 0.9 mA/cm^2 iontophoresis. There were 4 groups of 6/group. No skin erythema, edema, or paleness were observed in any of the groups.

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(39) H2 Astra Report 802-50 T1733, 1994-04-22. Vaso- and tissue irritation study in dogs of LEA 103 given intravenously and subcutaneously for 5 days. Astra Toxicology Laboratories, Sodertalje, Sweden. [175/1.27]

The purpose of this study was to evaluate the vaso- and tissue irritation

properties of LEA 103 administered intravenously and subcutaneously (paravenously) to dogs for five days.

LEA 103 was infused at 0.05 mL/Kg/min at 2.1, 4.3, and 6.2 mg/Kg/day x 5. The low dose also received a daily subcutaneous injection of 1.0 mL/dog in the left foreleg. The infusions were for 8, 16, or 24 minutes. A control group received both the sq and iv injection of physiological saline. Autopsy was done on all animals 3 days after the last dose. Each group contained 1 male and 1 female. GLP/QAU statements were present and signed. The study was done by Astra, Sweden in December 1985.

No clinical signs were reported, other than one episode of vomiting immediately after dosing on Day 4 in the high dose female. Slight to moderate body tremors and increased salivation was said to appear on occasion in all animals. A slight reduction in body weight occurred in most of the groups, including the controls, while food consumption was reduced at times in the treated groups. There was no change in rectal temperature. Microscopic examination did not show vasoirritation or tissue irritation to be greater in the treated animals.

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(40) H12 Astra Report 802-50 T1786, 1994-04-22. Local effects of LEA 103 given to dogs as a single subarachnoid or epidural injection. Astra Safety Assessment, Sodertalje, Sweden. [199/1.27]

The objective of the investigation was to study the clinical and local morphological effects of a single lumbar epidural or subarachnoidal injection of ropivacaine. The effects were compared to those of bupivacaine, the reference compound.

This study contained 13 treatment groups, each containing 2 males and 2 female dogs. The dosages of ropivacaine were 23.7 mg/dog (epidural), 31.5 mg/dog (epidural), 10.5 mg (subarachnoid), 31.8 mg/dog + 15 μg epinephrine (epidural), and 10.6 mg + 5 μg epinephrine (subarachnoid). Bupivacaine dosage was 23.7 mg/dog (epidural), 7.9 mg (subarachnoid), 23.7 mg/dog + 15 μg epinephrine), and 7.9 mg + 5 μg epinephrine (subarachnoid). In addition, there were four saline groups with and without epinephrine. Clinical signs, body weight, food consumption, rectal temperature, and pathology of the spinal cord and meninges were determined. Necropsy was done on one male and female after 5 days and on the remaining animals 14 days after treatment. GLP/QAU statements were present and signed. Astra, Sweden conducted the study in February 1986.

RESULTS

Most of the treated animals developed paralysis of the hindlegs, tail and anal sphincter, with urinary and fecal incontinence being observed. Epidural treatment produced the longest paralysis time. All animals recovered from the injections within 24 hours. Body weights and food consumption were comparable. Rectal temperature was normal during the study. At necropsy, no gross lesions were noted in the spinal cord.

Microscopic changes that were noted in about 30% of the animals were micro focal calcification in the subarachnoidal space and were seen in all groups. This was said to be a normal finding in mature dogs. Inflammatory reactions were not observed in the meninges, nor were spinal cord lesions reported. Slight focal degenerative changes occurred in the dorsal lumbar nerve root of one dog given a subarachnoid dose of 10.5 mg LEA 103, and was considered to be iatrogenic in nature. It was said no signs of diffuse neuronal damage or damage of certain cell types from these drugs could be observed.

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(41) H13 Astra Report 802-50 T2724, 1993-10-25. Pilot/dose-range finding epidural (continuous infusion) tolerance study in the Beagle dog of ropivacaine (LEA 103) and bupivacaine (LEA 131). Astra Safety Assessment, Sodertalje, Sweden. [1/1.28]

Study Nº: 265/510
Compound: LEA 103, batch Nº: 201/91 (F13), purity 100.2%
LEA 131 (bupivacaine HCl monohydrate), batch Nº: 45345-01, purity 99.7%
Formulation: Solution in 9 NaCl in water for injection.
Route: Epidural at 0.083 mL/Kg/hr for both drugs.
Dose Levels: ropivacaine 0.76 1.5 3.0 μmol/Kg/hr (0.25 0.50 1.0 mg/Kg/hr)
bupivacaine 0.73 1.5 2.9 μmol/Kg/hr (0.25 0.50 1.0 mg/Kg/hr)
Strain: Beagle, 5 to 7 month old, body wt: ♂ 8.5-9.3 Kg, ♀ 6.5-8.7 Kg
Number: 3♂ and 3♀
Study Site:
Date:
GLP/QAU Statements: Both present and signed.

Objectives of this study were to determine the local tolerance of the two drugs. to determine a suitable dose in a subsequent toxicity study, and to develop a method for continuous infusion in the dog.

A catheter was implanted into the epidural space between lumbar vertebra 5 and 6 or 6 and 7 three days prior to drug administration. The injection sites were between lumbar vertebra 1 and 5. Ropivacaine was administered by continuous infusion at 18 μmol/mL to 2 each ♂ and ♀ for 12 hrs. The next day 36 μmol/mL was infused only 4 hours and 20 minutes due to severe clinical signs. On Day 3, 9.1 μmol/mL was infused for 12 hours. After 4 days without treatment, 18 μmol/mL was infused for 5 consecutive days to the same animals. One female was necropsied on Day 36. After a recovery period of 9 days, a similar procedure was done with bupivacaine. One female was necropsied Day 29 - the remaining animals on Day 36. Blood samples were taken at various times to determine plasma concentrations after continuous epidural infusion for 5 consecutive days.

The study looked at clinical signs, body weight, and food consumption. Blood sampling was done during the 5 days of dosing to determine plasma concentrations. Gross examination was done on the spinal cord to determine the location of the catheter

tip.

RESULTS

- mortality: no treatment related-
- clinical signs: ataxia, paresis and paralysis when the dose increased, anxiety, absence of muscle tone and patellar/pedal/panniculus reflexes, absence of superficial pain sensation and profound pain sensation when the dose level increased, negative extensor postural thrust and negative proprioception-
- body weight: ↓ of 12% to 28% from pre-dose with both drugs-
- food consumption: ↓ during the 3 and 5 day treatment periods-
- thickening and/or induration of the meninges (1 ♂ and 3 ♀s) - dark red coloration of meninges (2 ♀s) - no abnormality seen in 2 ♂s-

- PK data:

	Dose (mg/Kg/h)	T_{max} (h)	C_{max} (μmol/L)	C_{ss} (μmol/L)	CL (mL/min·Kg)	$AUC_{0\text{-}120\ h}$ (μmol·h/L)
ropivacaine:	0.5	48	1.64-3.78	1.14-3.15	8.2-23.2	132.87-348.81
bupivacaine:	0.25	48-72	0.74-1.03	0.59-0.88	14.0-20.4	70.29-103.63

Neurological signs were more marked with bupivacaine. At necropsy the catheter tips were generally in the epidural space. The report indicated there was no clear sign of local intolerance. Body weight and food consumption did not return to pre-dose levels. Large variations in some of the PK parameters were noted, and with so few animals the mean values showed rather large standard deviations. The plasma levels seen in this study were below those producing toxic symptoms.

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(42) B5 Astra Report 802-24 T2465, 1991-12-13. General Toxicity Study of Ropivacaine (LEA 123) given subcutaneously and rectally to dogs for 6 months. Astra Safety Assessment, Sodertalje, Sweden. Appendix contains report G16 802-524 LF 0005-01, 1991-11-12. [1/1.24].

See Study (18) B under TOXICOLOGICAL EFFECTS, A. Acute

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(43) H3 Astra Report 802-24 T2318, 1991-01-07. Dose finding and pilot irritation study in dogs of ropivacaine (LEA 103) given rectally for up to 5 days. Astra Safety Assessment, Sodertalje, Sweden. Appendix contains G18 report 802-24AF 1-1, 1990-06-18. [151/1.28].

Study Nº: 89120
Compound: LEA 103, batch F5, assay 99.4%
Formulation: Gel containing LEA 103 and hydroxymethyl cellulose 4000 cps adjusted to pH 6.2 to 6.6.
Route: Rectal, 10 mL/dog

Dose Levels: Gels contained 1, 5, 10, 20, and 40 mg LEA 103/mL-
Strain: Beagle, 10.5 to 12.5 months old, body wt: ♂ 12.0-14.5 Kg, ♀ 12.5-14.5 Kg-
Number: 1/sex/group
Groups: Two
Study Site: Astra AB, Sweden
Date: January 7, 1991
GLP/QAU Statements: Both present and signed.

The objective of this dose range finding study was to determine the local tolerance of ropivacaine administered rectally to dogs for five days.

Group 1 animals were treated with 5 different dose levels (32 to 1300 μmol/dog equivalent to 10 to 400 mg/dog) on 5 separate occasions, with 6 dose free days between dosing. Those animals in Group 2 were treated with a single dose of 1300 μmol/dog/day (400 mg/dog/day) of 5 consecutive days. The study looked at clinical signs, body weight, food consumption, rectal temperature, EKGs (measured in Group 2 only) plasma concentration, and gross- and histopathology.

RESULTS

- clinical signs: small amounts of watery or mucoid feces seen at times-
- body weight: no large variation - one dog showed a 4% decrease from predose value-
- food consumption: no large changes-
- rectal temperature: normal range (37.8 -39.0°C)-
- EKG: values were said to be within the normal range-
  - St-segment (mV): ♂ -0.018 to -0.02, ♀ -0.06 to 0.00
  - PR (seconds): ♂ 0.076 to 0.091, ♀ 0.098 to 0.118
  - QRS (seconds): ♂ 0.045 to 0.062, ♀ 0.044 to 0.058
  - QT (seconds): ♂ 0.199 to 0.230, ♀ 0.159 to 0.199
- gross pathology: no gross changes in colon, rectum, or anal region-
- microscopic pathology: no inflammation, irritation, or other changes in the mucosa of the colon, rectum or anal canal-
- PK data: five day values for 400 mg rectal administration (from Table 5, p. 196).

t_{max} (h):	♂ 1.0	♀ 1.0
C_{max} (μmol/L):	♂ 2.11	♀ 3.36
$t_{½}$ (h):	♂ 5.9	♀ not calculated
Tn (h):*	♂ 24	♀ 24
AUC_{0-Tn}	♂ 14.3	♀ 21.0
$AUC_{0-\infty}$	♂ 15.0	♀ not calculated
F (%):	♂ 21.8	♀ 30.5*

* AUC_{0-Tn} (Tn = last data point) used in the calculation, otherwise $AUC_{0-\infty}$

The watery/mucoid feces that were seen at times during the study could be treatment related. Because of the limited solubility of LEA 103 in the formulation, higher dosages could not be studied. Ropivacaine was rapidly absorbed from the rectum, with similar plasma concentrations occurring after single or five day repeat doses; however,

due to the small number of animals in this study, most of the parameters shows wide variability.

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(44) H4 Astra Report 802-24 T2324, 1991-01-21. Local tolerance study in dogs of ropivacaine given rectully for 1 month. Astra Safety Assessment, Sodertalje, Sweden. Appendix contains report GI9 802-24AF 3-1, 1990-08-31. [202/1.28]

Study N°: 90036
Compound: LEA 103, batch F6, 99.2% assay
Formulation: Gel containing LEA 103 and hydroxypropyl methyl cellulose 4000 cps adjusted to pH 4.8-5.2
Route: Rectal, 10x2 mL/dog

Formulation N°:	I	II	III	IV
Daily Dose:	0	100x2	200x2	400x2 mg/dog
	0x2	320x2	640x2	1300x2 μmol/dog
Dose Volume:	0	10x2	10x2	10.2 mL/dog

Strain: Beagle, 7 to 11 months old, body wt- ♂ 11.0-16.0 Kg, ♀ 8.0-15.5 Kg
Number: 3/sex/group
Control Treatment: Gel without LEA 103
Study Site: ASTRA, Sweden.
GLP/QAU Statements: Both present and signed.

The object of the study was to evaluate the local tolerance of ropivacaine administered to dogs for one month.

Ten mL of the gel was inserted about 4 cm into the rectal lumen twice a day with about 6 hours between treatments. The parameter studied were clinical signs, rectal temperature and examination, body weight, food consumption, gross pathology, microscopic pathology, and PK evaluation on Days 1, 21, and 22.

RESULTS

- clinical signs: dose related loose or mucoid feces frequently seen after 1-2 hours - gel discharge was also noted from control animals-
- body weight: 1 Group II ♀ ↓ 15%, 1 Group IV ♀ ↓ 12.3% by Day 28-
- food consumption: no large variations-
- rectal temperature: normal range 37.5 - 38.9 °C-
- gross pathology: no gross changes observed in colon, rectum, or anal region-
- histopathology: 1 Group II ♂ with slight hyperplasia of the perianal glands and dilated ducts filled with cellular debris and neutrophils-
  1 Group III ♀ with slight hyperplasia of perianal glands and duct dilatation-
  1 Group IV ♀ with slight focal crypt dilatation with atrophic or

proliferating epithelium with loss of goblet cells. Occasional debris contents but no inflammatory reaction-

- PK data: mean values for high dose after last dosing (n = 3)-

t_{max} (h):	♂ 1	♀ 1-3
C_{max} (μmol/L):	♂ 3.08	♀ 3.08
$t_{½}$ (h):	♂ 5.1*	♀ 4.6*
$AUC_{0-24\,h}$ (μmol/h·L):	♂ 57.4	♀ 36.5 (nonlinear increase with dose)
F (%):	♂ 35.4	♀ 22.2

* n = 2

The absorption, which was dose-dependent but not linear, was fairly rapid in this study as in the previous study. There were variations in the individual parameter values, some of which were large. The only dose or drug related toxicity observed was the discharge of soft mucoid feces. Microscopic examination did not reveal any inflammation or irritation in the lower intestinal tract. In summary, no clear signs of toxicity were reported in this study.

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2. In Vitro

(45) H1 Astra Report 802-50 T1740, 1986-02-06. Hemolysis and protein flocculation in human blood of LEA 103 studied in vitro. Astra Toxicology Laboratories, Sodertalje, Sweden. [298/1.28]

When LEA 103 (5.3 mg/mL = 16 μg/mL in physiological saline) was evaluated in blood or plasma from a 42 year old female donor at 10:100, 3:100; and 1:100, no hemolysis or plasma flocculation occurred. The study was done by Astra, Sweden in January 1986. GLP/QAU statements were present and signed.

III. REPRODUCTION EFFECTS

A. Segment I

(1) C1 Astra Report 802-50 T2328, 1991-01-23. Multigeneration study in rats of LEA 103 given subcutaneously. Astra Safety Assessment, Sodertalje, Sweden. [1/1.29]

Compound: Ropivacaine hydrochloride monohydrate (LEA103), batches F3 (99.1% purity) & F6 (99.2% purity).

Dosage:

Group	Animals		Dosage	
	Males	Females	mg/kg	µmol/kg
1	22	34	control	-
2	22	34	6.3	19
3	22	34	12	35
4	22	34	28→23*	84→71*

* Dose level was lowered after 4 days
Route: Subcutaneously in the neck region
Strain: Sprague-Dawley, males ≈60 days old (271-323 g body weight)
females ≈100 days old (235-293 g body weight)
The males were dosed once a day for 9 weeks before mating and during mating. The females were dosed daily for 2 weeks before mating and then during the mating, pregnancy and lactation, up to day 42 post coitus. Half of the females were killed on day 21 of pregnancy and the remaining at weaning (on days 21-25 post parturition).
GLP/QAU Statements: Both present and signed.

Measurements and Observations:

1 - F0 Maternal

Clinical signs: Daily
Body weight: Day of mating (0), then on days 3, 6, 9, 12, 18, 21 of partus then days 29, 36 and 43 post coitus
Food consumption: Days 1, 6, 12, 18, 21, 29, 36, and 43
Water consumption: Not measured
Parturition, nursing and Lactation: Observed carefully
Postnatal observations: Litters from half of the females were examined for litter size, stillborn, viable pups and gross abnormalities.
Functional development of the pups before weaning: Pinna unfolding (from day 23 post coitus), tooth eruption (from day 31 post coitus), eye opening (from day 36 post coitus), surface righting (from day 24 post coitus), negative geotaxis (from day 27 to 29 post coitus), auditory startle reflex (after day 36 post coitus), and pupillary reflex (after day 43 post coitus).
Functional development of the pups after weaning: Rota-rod (at 25-30 days old), water-M-maze (at 30-42 days old), radial arm maze (at 36-45 days of age).
Preterminal sacrifice: Half of the dams were sacrificed on day 21 of pregnancy and examined for number of corpora lutea, placental weights, number of implantation sites, sex and number of viable fetuses, number of dead fetuses, number of resorption sites, fetal weights and litter weights, and external abnormalities.

Mating of F1-generation: At three months of age - F2-generation
Final sacrifice of the males: After completed mating.
Final sacrifice of the females: On day 21 post parturition.

Results: F0 Maternal

Mortality: control - 2
28 mg/kg - 2 ♀ on 4th day of dosing
23 mg/kg - 1 ♀ on 9th day of dosing
Clinical signs: Local irritation at the injection sites and deaths in convulsions in upper dose group animals
Body weight: No effect in both males and females.
Food consumption: No difference
Mating: No intergroup difference

Dams Sacrificed on Day 21 of Pregnancy

Litter size, preimplantation and fetal loss, F1: No difference in all groups.
Litter and mean fetal weight, F1: No difference
Total and placental weights, F1: Nearly the same in all groups
Abnormalities, F1: Control - Subcutaneous hemorrhage on the head in one pup.
High dose group - Umbilical hernia in one pup.

Dams Allowed to Litter

Gestation period, F0: 21-22 days in all groups except for one dam in high dose group (23 days).
Parturition, nursing and lactation, F0: High dose group - Nursing misbehavior by few dams.

Clinical Observations of The Litters

Litter size, F1: No differences at birth
Pup loss, F1: High dose group - Increased (≈ 2 fold) in the first three days after delivery. No pup loss in any group after 3 days post parturition
Litter and mean pup weights, F1: No differences
Body weights, F1: No intergroup differences
Food consumption, F1: No differences
Clinical signs, F1: None
Functional/behavioral tests, F1: No intergroup differences in surface righting reflex development, pinna unfolding, tooth eruption, eye opening, negative geotaxis, rota-rod performance, water M-maze performance, and radial arm maze.
Mating performance, F1: No differences in mating rate and pregnancy rate in all groups. The mean precoital interval in the high dose group was prolonged (4.9 days) as compared to control (3.8 days).
Gestation period, F1: No differences

Litter Data - F2-Generation

Litter size, F2: No differences
Pup loss, F2: High dose group - One dam lost all her pups within the first 3 days after partus.
Litter and mean body weights of offspring, F2: No differences

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B. Segment II

(2) C2 Astra Report 802-50 T2047, 1988-10-25. Pharmacokinetic and dose range finding teratology study of LEA103 given subcutaneously to pregnant rats. Astra Safety Assessment, Sodertalje, Sweden. Appendix contains report GS 802-S0-AF 90-2, 1988-09-26. [137/1.29].

Species: Rat
Strain: Sprague-Dawley
Age: Approximately 11 weeks, 225-325 g body weight
Mating procedure: Five females and two males were housed together overnight, mated females were kept individually in each cage.
Compound: Ropivacaine hydrochloride monohydrate (LEA103), batch F 3
Dosing: 5.3, 11.0, 26.0 mg/kg, subcutaneously in the neck region on days 6-15 of pregnancy
GLP/QAU Statements: Both present and signed.

Clinical Observations

Clinical signs: Daily
Body weight: Days 0, 3, 6, 9, 12, 15, 18, and 21 of pregnancy
Food consumption: Days 6, 9, 15, and 21 of pregnancy
Water consumption: Daily
Blood samples: Unlabelled compound on days 5, 6 and 15 of pregnancy
Labelled compound (blood, amniotic fluid and fetuses) on day 16 of pregnancy
Terminal investigations: Sacrificed on day 21 of pregnancy and examined number of corpora lutea, placental weight, number of implantation sites, sex and number of viable fetuses, number of dead fetuses, number of resorption sites, fetal weights and litter weights, and external abnormalities. Visceral and skeletal anomalies were also determined.

Results:

Clinical Observations (Dams)

Clinical signs: Irritation at the injection sites in all animals.
Mortalities: One in medium dose and one in high dose-groups due to blood sampling.

Body weight: No difference
Food consumption: Same in all groups
Water consumption: No difference
Terminal autopsy: No abnormalities in gross examination of thoracic and abdominal cavities.

Litter Data

Litter size, preimplantation and fetal loss: No intergroup differences
Litter and mean fetal weights: No differences
Total and mean placental weights: Same in all groups
Abnormalities: No gross malformations

Concentration of LEA103 in blood plasma, amniotic fluid and fetuses: Rapid absorption, C_{max} between 0.5 - 1 h, $t_{1/2}$ range 0.9 - 3.6 h. The mean fetal uptake after one hour exposure was about 45%, 50% and 46% as the ratio fetal tissue/maternal blood for the three doses tested (16, 32 and 81 μmol/kg). This indicates that the uptake of LEA103 was not dose dependent in the concentration range tested.

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(3) C3 Astra Report 802-50 T2049, 1988-10-28. Effect upon pregnancy in rats of LEA -103 given subcutaneously. Astra Safety Assessment, Sodertalje, Sweden. [203/1.28].
Test compound: LEA103, batch F3 and F4
Strain: Sprague-Dawley rats
Age: Approximately 75 days
Number and sex; 80 females
Body weight range: 230-300 g.
Dose groups:

Group	Number of animals	Daily dose μmol/kg	Daily dose mg/kg	Dose volume (ml/kg)
1	20	-	-	2.5
2	20	16	5.3	2.0
3	20	32	11	2.0
4	20	81	26	2.5

Dosing: On days 6-15 of pregnancy, subcutaneously in the neck region.
GLP/QAU statements: Both present and signed

Clinical Observations

Clinical signs: Daily
Body weight: Days 0, 3, 6, 9, 12, 15, 18, and 21 of pregnancy
Food consumption: Days 6, 9, 15, and 21 of pregnancy

Water consumption: Daily
Terminal investigations: Sacrificed on day 21 of pregnancy and examined for number of corpora lutea, placental weight, number of implantation sites, sex and number of viable fetuses, number of dead fetuses, number of resorption sites, fetal weights and litter weights, and external abnormalities. Visceral and skeletal anomalies were also determined.

Results:

Clinical Observations (Dams)

Clinical signs: Irritation of the skin at the injection sites in all animals
Mortalities: None
Body weight: No differences
Food consumption: Same in all groups.
Terminal autopsy: No gross abnormalities in thoracic and abdominal cavities

Litter data

Litter size, preimplantation and fetal loss: No intergroup differences
Litter and mean fetal weights: No differences
Mean placental weights: Same in control and high dose group. Low dose (6%↑), medium dose (4% ↑)
Abnormalities: Control - Umbilical hernia (1 pup), spina bifida and anophthalmia (1 pup).
Medium dose - Universal edema (2 pups).
No intergroup differences in visceral and skeletal anomalies.

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(4) C4 Astra Report 802-50 T2048, 1988-10-25. Pharmacokinetic and dose range finding teratology study of LEA 103 given subcutaneously to pregnant rabbits. Astra Safety Assessment, Sodertalje, Sweden. Appendix contains report G9 802-50 AF 91-2 1988-09-26 and report G38 802-50 AF 92-2 1988-09-26, [265/1.29].

Test compound: LEA103, batch F3
Test species: Rabbit
Strain: New Zealand White
Number and sex: 24 females
Age and body weight: >5 months, 3410- 4910 g
Dose groups:

Group	Number of animals	Daily dose µmol/kg	Daily dose mg/kg	Administration vol. (ml/kg)
1	8 F	-	-	2.0 (saline)
2	8 F*	32	10.5	2.0
3	8 F*	64→48**	21→15.75	2.0

The first four animals in each group were assigned to PK. The remaining 4 animals were assigned to the teratology part of this study.
*Radioactive dose on days 6 and 16 for PK.
**Dose 64 μmol/kg was changed to 48 μmol/kg on day 10 of pregnancy

Dosing: Subcutaneously in the neck region in saline
Dosing period: Days 6-18 of pregnancy
GLP/QAU Statements: Both present and signed.

Clinical Observations

Clinical signs: Daily
Body weight: Days 1, 6, 10, 14, 19, 24, and 28 of pregnancy in teratology study
Days 1, 6, 10, 14, and 16 of pregnancy in PK study
Food consumption: Days 6, 10, 14, 19, 24, and 28 of pregnancy in teratology study.
Days 6, 10, 14, and 16 of pregnancy in PK study.
Water consumption: Daily
Blood samples: On days 6 and 15 of pregnancy at 0.25, 0.5, 1, 3, 6, and 24 hours after the administration.
Urine and feces: On day 6 at 24 hours intervals after radioactive administration for 96 hours. Dams were killed one hour after administration on day 16 of pregnancy and amniotic fluid and fetuses were collected.

Terminal investigations: Sacrificed on day 29 of pregnancy and examined number of corpora lutea, placental weight, number of implantation sites, sex and number of viable fetuses, number of dead fetuses, number of resorption sites, fetal weights and litter weights, and external abnormalities. Visceral and skeletal anomalies were also detected.
Statistical Analysis: Nonparametric Wilcoxon rank test

Results:

Clinical Observations (Dams)

Clinical signs: Control & LD group - No adverse effects
HD group - Decreased motor activity, convulsions.
Mortalities: HD group - Two (in 64 μmol/kg) on day 10 of pregnancy, one (in 48 μmol/kg) on day 14 of pregnancy.
Body weight: No significant difference
Food consumption: Pharmacokinetic animals - LD (10%↓), HD (20%↓)
Teratology animals - LD (49%↓), HD (56%↓)
Water consumption: No difference
Terminal autopsy: No abnormalities in gross examination of thoracic and abdominal cavities.

Litter Data

Litter size, preimplantation and fetal loss: No intergroup differences
Litter weights : HD group (23%↓)
Mean fetal weights: Dose-dependent decrease in LD (5%↓) and HD (12%↓) group
Total and mean placental weights: HD group (17%↓)
Abnormalities: No gross malformations
Concentration of LEA103 in blood plasma, amniotic fluid and fetuses:

The absorption was rapid, C_{max} was reached between 0.25 - 0.5 h. The plasma half-life was 7.1 h and 3.6 h on day 6 and 15, respectively, in t low dose group, and 5.3 h and 4.1 h, respectively in the high dose group. The mean plasma protein binding of LEA 103 was higher on day 15 of pregnancy compared to day 6 in both dose groups. The placental transfer showed a fetal tissue/maternal blood ratio of 25% and 54% after administration of 32 and 64 μmol/kg, respectively.

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(5) C5 Astra Report 802-50 T2052, 1988-11-09. Effects upon pregnancy in rabbits of LEA 103 given subcutaneously. Astra Safety Assessment, Sodertalje, Sweden, [361/1.29].

Test compound: LEA103, batch F3 & F4, 99.1% and 99.6% pure
Strain: New Zealand White rabbits, 6-7 months old, 3-4.5 kg body weight
Dose groups: Mated does were assigned to the following groups:

Group	Number of animals	Daily dose μmol/kg	Daily dose mg/kg	Dose vol. (ml/kg)
1	15 F	-	-	1.2
2	15 F	4	1.3	0.5
3	15 F	13	4.2	0.8
4	15 F	39	13	1.2

Dosing: Subcutaneously in the neck region, daily on days 6-18 of pregnancy.
GLP/QAU Statements: Both present and signed.

Clinical Observations

Clinical signs: Daily or twice daily
Body weight: On days 1, 6, 10, 14, 19, 24, and 28 of pregnancy
Food consumption: On days 6, 10, 14, 19, 24, and 28 of pregnancy
Water consumption: Daily

Terminal Investigations: The does were killed on day 29 of pregnancy and carefully

examined for
- number of corpora lutea
- placental weights
- total number of implantation sites
- sex and number of viable fetuses
- number of dead fetuses
- number of resorption sites
- fetal weights and litter weights
- external abnormalities

Statistical analysis: Fisher's exact test

Results

Clinical Observations (Does)

Clinical signs and mortalities: None
Body weight: No effect
Food consumption: Same in all groups
Water consumption: No difference
Terminal autopsy: No abnormalities in thoracic and abdominal cavities.

Litter Data

Litter size and fetal loss: No differences
Preimplantation loss: LD & MD - 46%↑
HD group - 68%↑
Postimplantation loss: No intergroup differences
Litter and mean fetal weights: No differences
Mean placental weights: No differences
External/visceral defects: HD group - 2 (1.8%) major defects (both lacked one kidney)
Skeletal defects and variants:
- Minor skeletal defects and variants - No intergroup differences
- Major skeletal defects: LD (1, 1%), MD (2, 1.7%) and HD (2, 1.8%) mainly unossified thoracic vertebrae and skull.
- Skeletal variants: No intergroup differences.

C. Segment III

(6) C6 Astra Report 802-50 T2249, 1990-06. Peri- and Postnatal study in rats of LEA 103 after subcutaneous administration during late pregnancy and lactation. Astra Safety Assessment, Sodertalje, Sweden, [1/1.30].

Materials and Methods

Test compound: Ropivacaine hydrochloride monohydrate (LEA103), batch # F3 & F4, 99% pure.
Strain: Sprague-Dawley rats, ~10 weeks old, 205-267 g body weight

Dose groups:

Group	Number of animals and sex	Daily dose µmol/kg	mg/kg
1	23 F	0	0
2	23 F	16	5.3
3	23 F	32	11
4	23 F	81	26

Dosing: Subcutaneously, from day 15 of pregnancy to day 20 of post parturition.

Clinical Observations of the Dams

Clinical signs: Twice daily
Body weight: Every third day during gestation, and on days 1, 7, 14 and 21 post parturition.
Food consumption: Days 6, 9, 15, 18, 21 of pregnancy, and days 3, 7, 14 and 21 post parturition.

Clinical Observations of the Litters

Clinical signs: Daily
Litter size, mortality and abnormalities: At delivery and on days 1, 3, 7, 14 and 21 post parturition.
Physical development: Pinna unfolding, tooth eruption and eye opening were recorded.

Terminal Investigations: Day 21 post parturition.
Statistical Analysis: Wilcoxon rank test.

Results:

Clinical Observations of the Dams

Clinical signs: Dose-dependant necrosis at the injection sites.
Mortalities: High dose group: One on day 2 post parturition and one on day 3 post parturition.
Body weight: Same in all groups.
Food consumption: No difference
Gestation period: No differences except one rat in high dose group (1/19) delivered on day 23 of pregnancy

Parturition, nursing and lactation: Same in all groups.

Clinical Observations of the Litters

Litter size and pup loss: No intergroup differences.
Litter and mean pup weights: No differences at birth and on days 7, 14 and 21 post parturition.
Physical development: No difference
Abnormalities: One litter in each group contained pups with skinless paws, ear and genitalia. All these pups died within three days.

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(7) Anesthesiology 1990;73 (Suppl 3A) A927. Effects of ropivacaine on uterine blood flow in pregnant sheep [abstract]. Santos AC, Wlody DJ, Pedersen H, Morishima HO, Finster M. [45/1.30]. The preliminary results from four pregnant ewes indicated that maternal and fetal plasma concentrations of 2.64 and 0.81 μg/ml of ropivacaine, respectively, have no adverse effects on the uterine blood flow.

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(8) G6 Astra Report 802-550 LF 0058-01, 1992-04-20. Effects of LEA 103 and LEA 131 given subcutaneously to pregnant rats from day 15 of pregnancy until day 3 post parturition - a dose finding study. Astra Pain Control AB, [46/1.30]. Sprague-Dawley rats (7-10 animals/group) were dosed subcutaneously (dorsally) at 79 μmol/kg/day LEA103 or 43, 48, 53, 58, 60, 65, and 70 μmol/kg/day LEA131 from day 15 of pregnancy until day 3 post parturition. In this dose finding study, the results showed that LEA103 (ropivacaine) was less toxic such as maternal deaths, convulsions and postnatal pup deaths than LEA131 (bupivacaine). The highest recommended dose of LEA131 was 53 μmol/kg.

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(9) C7 Astra Report 802-50 T2639, 1993-04-06. Comparative study of effects during the peri- and postnatal period in rats of ropivacaine (LEA 103) and bupivacaine (LEA 131) given subcutaneously. Astra Safety Assessment, Sodertalje, Sweden. Appendix contains report G7 802-550 LF 0068-01, 1993-04-01, [141/1.30]. Sprague-Dawley rats (206-281 g body weight, ≈2 months old) were dosed subcutaneously from day 15 of pregnancy to day 20 post parturition daily as shown below.

Group	Number of animals	Compound	Daily dose μmol/kg	mg/kg	Batch
1	15	Control	0	0	
2	15	LEA103	16	5.3	F7
3	15	LEA103	43	14	F7
4	15	LEA103	75	25	F7

Group	Number of animals	Compound	Daily dose µmol/kg	mg/kg	Batch
5	15	LEA131	16	5.5	98428-01
6	15	LEA131	43	15	98428-01
7	15	LEA131	53	18	98428-01

GLP/QAU Statements: Both present and signed.

Clinical Observations of the Dams

Clinical signs - 2-3 times a day
Body weights - Days 0, 6, 15, 18, 20, and 21 during gestation
Days 1, 3, 7, 14, and 21 post parturition
Food consumption - Days 6, 15, 18, 20, and 21 of pregnancy
Days 3, 7, 14, and 21 post parturition
Gestation, parturition, nursing and lactation - Special attention

Clinical Observations of Litters

Litter size, mortality and abnormalities - Daily
Litter weights - Days 1, 3, 7, 14, and 21 post parturition
Physical development (pinna unfolding, tooth eruption, eye opening - Special attention
Clinical signs - Daily
Terminal investigations - Day 21 post parturition
Statistical analysis - Wilcoxon rank test

Results

Clinical Observations of the Dams

Clinical signs: Group 6 (43 µmol/kg LEA131) - Piloerection, increased salivation, chewing and irregular breathing
Group 7 (53 µmol/kg LEA131) - Same symptoms but more severe than in group 6.

Mortalities: 43 µmol/kg LEA131 - One on day 12 post parturition
53 µmol/kg LEA131 - One on day 21 of pregnancy
- One on day 20 post parturition
- One on day 9 post parturition

Body weight: No effect
Food consumption: Same in all groups
Gestation period: No shortening or prolongation of the gestation period
Parturition, nursing and lactation: No difference

Clinical Observations of Litters

Litter size and pup loss: No intergroup differences in litter size and pup loss.

Litter and mean pup weights:: No intergroup differences at birth and on days 7 and 21 post parturition.

Physical development: No intergroup differences in pinna unfolding (day 4), teeth eruption (days 11 & 12), eye opening (day 17) and locomotion on days 4, 11 and 17.

Abnormalities: Group 2 (16 μmol/kg LEA103) - One pup with hydronephrosis of the left kidney and extreme dilation of the ureter..

Group 5 (16 μmol/kg LEA131) - One pup showed hyperplasia of the left oral angle.

- One pup showed marked enlarged left kidney, extreme dilation of the ureter, and the right kidney, adrenal and ureter were absent.

Concentration of the Test Compound in Blood Plasma: The peak plasma concentration (C_{max}) reached within the first sampling interval (30 min) for both drugs indicating the rapid absorption from the injection sites. Both drugs were rapidly eliminated from the plasma as shown in the table below. The protein binding was significantly higher for LEA131 compared with LEA103 in the pregnant rats.

Dose μmol/kg	Compound	C_{max} μmol/L	t_{max} h	AUC $_{total}$ μmol/L.h	$t_{1/2}$ h	F %
16	LEA103	1.09 ± 0.38	0.8 ± 0.3	3.69 ± 0.48	2.31 ± 0.96	93.02 ± 12.22
43	LEA103	1.79 ± 0.46	1.0 ± 0.9	15.01 ± 3.77	6.54 ± 2.58	140.93 ± 35.42
75	LEA103	4.83 ± 1.70	0.6 ± 0.2	18.01 ± 2.27	2.67 ± 0.63	96.94 ± 12.24
16	LEA131	0.66 ± 0.16	0.6 ± 0.2	8.74 ± 5.12	14.99 ± 12.25	-
43	LEA131	2.17 ± 0.43	0.8 ± 0.3	10.92 ± 0.87	5.16 ± 0.75	-
53	LEA131	3.97 ± 1.43	0.5	11.25 ± 1.63	2.73 ± 2.17	-

D. MUTAGENICITY

1. In Vitro

(10) D1 Astra Report 802-50 T1671, 1985-06-11. Mutagenicity evaluation of LEA 103

in the Ames Salmonella/mammalian microsome mutagenicity test. Astra Toxicology Laboratories, Sodertalje, Sweden. [1/1.31]

LEA 103 (Batch N° F2, 99.5% assay) was dissolved in methanol and evaluated in Salmonella strains TA1535, TA100, TA1538, TA98, and TA 1537 at concentrations of 0.0164 to 49.1 μmol/plate (5.38 to 16100 μg/plate) in the study. Rat liver S9 was prepared from liver of male Wistar rats treated with Aroclor 1254 and purchased from NoTox, The Netherlands. Positive controls were: sodium azide (H2O), 2-nitrofluorene (DMSO), 9-aminoacridine MeOH), and 2-aminoanthracene (DMSO). The study was done at Astra, Sweden in June 1985. GLP/QAU statements were present and signed.

RESULTS

At the highest doses tested in the toxicity test (43.5, 45.4, and 49.1 μmol/plate), LEA 103 was toxic, both with and without S9 activation. In the mutagenicity test, no increase occurred in the number of revertant colonies in the presence or absence of S9. No two fold increase was seen in the number of revertant colonies without or with S9 metabolic activation. All positive controls were active in their respective tester strain. In conclusion, LEA 103 was not mutagenic in the above Ames mutagenicity test.

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(11) D2 Astra Report 802-50 T1894, 1994-02-28. Mutagenicity evaluation of LEA 103 in the L5178Y mouse lymphoma cell thymidine kinase locus mutagenicity test. Astra Safety Assessment, Sodertalje, Sweden. [21/1.31]

LEA 103 (batch F3) was tested at 0.293-293 mmol/L in the toxicity study. LEA 103 was tested at 1.51 to 2.71 mmol/L without S9 activation and 0.0246 to 0.491 mmol/L with metabolic activation in the mutagenicity part of the study. The solvent was DMSO. The L5178Y mouse lymphoma TK+/- cells were obtained from Dr. D. Clive at Burroughs Wellcome, USA. Positive control compounds were 2-nitrofluorene used in the absence of S9 and 9,10-dimethyl-1,2-benzanthracene in the presence of S9. The solvent in the study was DMSO. The study was done in June 1987. GLP and QAU documents were present and signed.

RESULTS

In the absence of metabolic activation, LEA 103 increased the mutation frequency 1.75 to 1.97 above the solvent control at concentrations of 2.46 and 2.71 mmol/L. The positive control (2-nitrofluorene) increased the mutation frequency 5.46 times above the solvent control in the absence of S9. In the presence of S9 metabolic activation, the mutation frequency was increased 1.6 to 5.9 times above the solvent control by LEA 103 at concentrations of 0.0733 to 0.491 mmol/L.. Increases were dose related. The conclusion is that LEA 105 was mutagenic at the thymidine kinase locus in L5178Y mouse lymphoma cells.

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(12) D3 Astra Report 802-50 T1977, 1994-02-28. Mutagenicity evaluation of LEA 103 in the L5178Y mouse Lymphoma cell thymidine kinase locus mutagenicity test - repeat. Astra Safety Assessment, Sodertalje, Sweden. [46/1.31]

This study was done to confirm the results of the above mouse lymphoma TK+/- cell mutagenicity test with LEA 103 (batch F3). The study was done by Astra, Sweden in February 1988. GLP/QAU statements were present and signed. The solvent was changed from DMSO to Fischer's medium Fop "to achieve a higher toxicity under non-activation conditions." Concentrations evaluated were 0.0533 to 0.640 mmol/L with metabolic activation and 1.07 to 5.33 mmol/L without metabolic activation. The cells were obtained from the same source, and rat liver S9 was prepared from male SD rats treated with Aroclor 1254 rather than purchased from a commercial source, as in the above study. GLP/QAU statements were present and signed. The study was conducted by Astra, Sweden in February 1988.

RESULTS

the absence of S9, the mutation frequency was 1.21 above the control at 5.33 mmol/L LEA 103, the highest concentration tested. The positive control (2-nitrofluorene) increased the mutation frequency 8.4 times above the solvent control. In the presence of S9, the mutation frequency from LEA 103 was dose related, increasing from 1.9 to 3.3 times above the solvent control. The positive control (9,10-dimethyl-1,2-benz-anthracene) increased the mutation frequency 5.5 times above the solvent control. The results again indicated LEA 103 to be mutagenic in the presence of metabolic activation, albeit not of the same magnitude as occurred in the above study.

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(13) D4 Astra Report 802-50 T2278, 1994-04-11. Genotoxicity evaluation of LEA 103 in the E.coli differential repair test in vitro. Astra Safety Assessment, Sodertalje, Sweden. [70/1.31].

This study compared the DNA repair of two strains of E. coli in the presence of LEA 103 (batch F6). The deficient DNA repair strain was E. coli K-12 343/591, and the proficient DNA repair strain was E. coli 343/636. LEA 103 concentrations used in the study ranged from · mmol/L. A study was considered negative if:

(a) "the test compound produces no significant reduction of the number of colonies of the DNA repair deficient strain, or

(b) if a significant reduction of the number of colonies appears at the same concentration for the DNA repair proficient strain compared to the DNA repair deficient strain."

The result is classified as positive when:

(a) "the viability of the DNA repair deficient strain is significantly reduced at a lower concentration than that of the DNA repair proficient strain."

It is classified as weakly positive when, in addition to the significant reduction of the DNA repair deficient strain, a slight dose dependent, but not significant reduction of the wild type strain is also seen. If both strains give similar reductions with the same

concentration, the implication is that a genotoxic mechanism is probably not responsible for the decrease in viability. "If the number of colonies are lower than the confidence limit for each strain, the number of colonies are classified as significantly reduced." The study was evaluated in the presence and absence of S9 mixture. The solvent in the study was distilled water, and the positive control was 4-nitroquinoline-N-oxide (4NQO). The incubation period was 90 minutes. Astra conducted the study in Sweden in May 1990. GLP/QAU statements present and signed.

RESULTS

The number of colonies in the deficient strain divided by the number of colonies in the proficient strain was reduced to 1.8 or 78% of the control values at the two high concentrations (3.21 and 9.64 mmol/L; 1.06 and 3.17 mg/mL) in the absence of S9. In the presence of S9, the number of colonies of deficient strain was reduced to 108, the proficient strain was reduced to 0.74, and the reduction was 41% of the control at this concentration. No statistical significance was reported in the reduction of the number of colonies of DNA repair deficient or proficient strains. From the data, LEA 103 is not considered genotoxic in the E. coli differential DNA repair test in vitro.

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(14) D5 Astra Report 802-50 T2020, 1988-06-23. Analysis of structural chromosome aberrations in human lymphocytes treated with LEA 103 in vitro. Astra Safety Assessment, Sodertalje, Sweden. [85/1.31]

LEA 103 (batch F3, 99.1% assay) was tested at 0.7 to 2.7 mmol/L concentrations. The high dose (2.7 mm/L) was at maximum solubility in 1% DMSO. The positive control was a 0.1 mmol/L cyclophosphamide concentration. S9 fraction was from Aroclor treated male SD rats. LEA 103 was added to the culture medium after 22 hours of culturing. Since the S9 gemisch was toxic to the cells, only 2 hours of exposure was possible. Slides were read blinded. Two hundred metaphase per concentration were scored. Scoring included chromatic aberrations, gaps breaks, acentric fragments, and chromatic exchanges. The study was done by Astra, Sweden in December 1987. GLP/QAU statements were present and signed.

RESULTS

The results showed no increase in the aberration frequency in the absence of S9 at 1.9 mmol/L LEA 103. Likewise, in the presence of S9 at 2.7 mol/L LEA 103, no significant increase was reported in the aberration frequency. The study was deemed inconclusive in the presence of metabolic activation by the sponsor, as no mitotic inhibition was obtained at the maximum attainable concentration. Cyclophosphamide with S9 metabolic activation significantly increased the number of chromosome aberrations and gaps. From the results of the study, it can be concluded LEA 103 was negative in the human lymphocyte chromosome aberration test in the absence of metabolic activation but inconclusive in the presence of S9.

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2. In Vivo

(15) D6 Astra Report 802-50 T1893, 1987-06-09. Mouse micronucleus test of LEA 103. Astra Safety Assessment, Sodertalje, Sweden. [103/1.31].

LEA 103 (batch F3, 99.1% assay) was evaluated in 9-10 week old male and female NMRI mice, 19.5 -32.2 g body weight. The dose levels used were 90 and 180 μmol/Kg in sterile water. Methyl methanesulfonate (MMS) was used as the positive control at 455 μmol/Kg in sterile water; physiological saline was the negative control. All test solutions were administered subcutaneously. Smears of femoral bone marrow were prepared at 24, 48, and 72 hours after treatment with LEA 103 and at 24 hours after administration of MMS. The incidence of micronucleated polychromatic erythrocytes with and without micronuclei were determined for the first 1000 examined. Kruskal-Wallis statistical analysis was used to determine significance. This study was done by Astra, Sweden in March 1987. GLP/QAU statements were present and signed.

RESULTS

No significant increase in the incidence of micronucleated polychromatic erythrocytes (MPCEs) was reported for LEA 103 at any of the time periods or at any dose level. On the other hand, MMS produced a significant increase ($p<0.001$, 26.4x over control) in the frequency of MPCEs. Bone marrow depression was not reported in the study. It can be concluded that LEA 103 did not show any indication of a clastogenic potential in the mouse micronucleus test.

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(16) D7 Astra Report 802-50 T2285, 1990-06-15. Genotoxicity evaluation of LEA 103 in the E.coli host mediated DNA repair test. Astra Safety Assessment, Sodertalje, Sweden. [125/1.31]

This test was done according to Mohn et al. Mutation Res 1983;113:403-405. This is a differential DNA repair test using mixtures of E. coli K-12 strains in liquid suspension and animal mediated assays.

The study consisted of injecting MNRI mice (7♂/group, 5 weeks old) intravenously with a 1:1 ratio of DNA repair deficient strain and DNA repair proficient strain of E. coli, followed by a single iv dose of 3 mg/Kg (9 μmol/Kg) or 9 mg/Kg (27 μmol/Kg) LEA 103. A saline control was also included in the study. After 2 hours the mice were killed and samples of blood, liver, lung, kidney, and testis were homogenized. Aliquots of the diluted homogenates were applied to petri dishes with agar containing neutral red as a pH indicator. The tissue samples were incubated for 1 day. Colonies were counted and the survival determined for each strain, as these strains differ in ability to ferment lactose. Red colonies were observed for the DNA deficient strains and white colonies for the DNA proficient strains.

A compound is classified positive if the viability of the DNA repair deficient strain is significantly reduced in any orgen and the viability of the DNA repair proficient strain is not, when compared to the mean of the fraction in the control group. The fraction is expressed as follows:

$$\frac{\text{Nº of colonies of the DNA repair deficient strain}}{\text{Nº of colonies of the DNA repair proficient strain}}$$

The study was conducted by Astra, Sweden in April 1990. GLP/QAU statements were present and signed.

RESULTS

The results did not show a significant decrease in the number of colonies of DNA repair deficient strain divided by the number of colonies of the DNA repair proficient strain. With the positive control, 4-nitroquinolinoxide (4-NQO), the number of colonies of the DNA repair deficient strain was significantly reduced and the number of colonies of the DNA repair proficient strain was not, compared to the solvent DMSO.

Astra indicated this test has been evaluated using 35 compounds, some of which were carcinogenic. The sensitivity and specificity of this test was said to be similar to that of the micronucleus test. They also indicate that the data from various organs may detect genotoxic compounds that are not detected in bone marrow.

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(17) D8 Astra Report 802-50 T2283, 1990-06-15. Somatic mutation and recombination test in Drosophila melanogaster of LEA 103. Astra Safety Assessment, Sodertalje, Sweden. [157/1.31].

In this assay, somatic mutations/recombinations produced by genotoxic compounds will show up on Drosophila melanogaster wings as spots. Females from drosophila larvae stock mwh and males from stock flr3/TM3, Ser were mated. The larvae were placed in vials containing medium and 5 mmol/L LEA 103 test solution and allowed to remain until pupation and emergence of flies. These larvae are trans-heterozygous for mutations of multiple wing hair and flare (mwh +/+ flr3). A toxicity study evaluated distilled water solutions of 5, 10, 20, or 30 mmol/L of LEA 103 (batch F6, assay 99.2%). A solution of ethyl methanesulfonate (EMS) was used as the positive control. Two hundred wings were analyzed from both the negative control and the 5 mmol/L LEA 103 groups and 100 wings from the EMS treated group. Spots were grouped as single spots with one or two affected cells, large single spots with three or more affected cells, and twin spots containing both mwh and flr cells. The study was initiated March 1990 by Astra, Sweden. Both QAU and GLP statements were present and signed.

RESULTS

Relative survival in the toxicity test was 100%, 93%, 85.6%, 47.4%, and 16.2% for the solvent control, 5, 10, 20, and 30 mmol/L LEA 103, respectively. The number of spots per wing were 0.24, 0.22, and 14.14 for the control, LEA 103, and EMS, respectively. EMS increases were significant in all three of the above groupings of spots. To conclude, LEA 103 did not show somatic genotoxic potential in this Drosophila melanogaster assay at 5 mmol/L.

IV. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION STUDIES

A. Absorption and Pharmacokinetics

(1) G1 Astra Report 802-550 LF 0002-01 Pharmacokinetics of ropivacaine after oral administration in male rats, Eloffson S. [58/1.32]. Ropivacaine was administered orally at 10, 40 and 90 μmol/kg and intravenously at 10 μmol/kg to male S-D rats (≈180 g body weight, 5 animals/group). Blood samples were drawn at 0.08, 0.25, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 8.0 (only po groups), and 24 hours after administration from the orbital venous plexus. Plasma samples were analyzed by gas chromatography.

After intravenous administration, the drug was rapidly eliminated with an elimination half-life of about 0.5 hours. Plasma clearance and volume of distribution at steady state were 91.8 ± 14.1 ml/min and 3.64 ± 0.75 l/kg, respectively. The plasma elimination half-life after oral administration was 0.4 to 0.6 hours.

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(2) G2 Astra Report 802-550 LF 0057-01, 1992-04-20. Pharmacokinetics of LEA 103 (ropivacaine) in male rats, Halldin M., [72/1.32]. The drug was dissolved in saline and administered intravenously (tail vein, 10 μmol/kg, 3.3 mg/kg) and subcutaneously (neck region, 10 μmol/kg & 80 μmol/kg, 3.3 & 26.3 mg/kg) in male S-D rats weighing 275-330 g (5 animals/group). Blood samples (0.5 ml) were collected at 0.1, 0.3, 0.5, 0.75, 1.0, 1.5, 2.0, 3, 4, 5, 8, and 24 h after administration. Total radioactivity and amount of LEA103 in samples were analyzed by standard techniques.

Pharmacokinetic parameters are presented on the next page.

Route and dose	AUC_0– μmol h/l	C_{max} μmol/l	$t_{1/2}$ h	CL ml/min kg	Vd l/kg	V_{ss} l/kg	F %
IV (10 μmol/kg)	2.67 ± 0.15	4.21 ± 0.52	0.60 ± 0.06	67.39 ± 2.62	3.52 ± 0.29	2.83 ± 0.34	-
SC (10 μmol/kg)	2.28 ± 0.34	0.89 ± 0.14	1.13 ± 0.32	67.3	6.6 ± 1.9	8.4 ± 1.1	100.5 ± 16.7

Route and dose	$AUC_{0-\infty}$ µmol h/l	C_{max} µmol/l	$t_{1/2}$ h	CL ml/min kg	Vd l/kg	V_{ss} l/kg	F %
SC (80 µmol/kg)	17.09 ± 0.94	3.71 ± 0.67	1.52 ± 0.25	67.3	8.8 ± 1.5	13.6 ± 1.7	90.5 ± 5.5*
IV (10 µmol/kg) radioactive	25.56 ± 4.27	3.38 ± 0.34	14.45 ± 4.19	6.73 ± 0.88	8.18 ± 1.39	7.10 ± 1.21	
SC (10 µmol/kg) radioactive	21.92 ± 1.89	1.52 ± 0.21	9.57 ± 1.81	6.6	5.5 ± 1.0	5.4 ± 0.9	86.3 ± 8.1
SC (80 µmol/kg) radioactive	191.98 ± 22.69	12.76 ± 2.41	9.32 ± 1.95	6.6	5.3 ± 1.1	5.3 ± 1.0	93.8 ± 9.4

The peak plasma concentration after an IV administration (3.29-4.55 µmol/l) was higher than SC administration (0.77-1.03 µmol/l) at equal doses of drug administration. The systemic availability of 101% and 91% was found after low and high dose subcutaneous administration, respectively. The elimination half-life for the total radioactivity after IV or oral administration was longer than for the unchanged drug. True elimination half-life might not have been reached due to low sensitivity of the bioassay.

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(3) G8 Astra Report 802-550 LF 0056-01, 1993-03-18. Pharmacokinetic evaluation of LEA 103 (ropivacaine) after repeated intrathecal administration to male rats for 14 days. Lindstrom BE, Halldin M, Engman M., [112/1.32]. LEA103 (Batch no: F3) was administered to male S-D rats (60-75 day old, 300-350 g body weight) intrathecally via an indwelling catheter at a dose of ≈0.9 µmol/kg twice daily for 14 days. Blood samples were collected at 0.08, 0.25, 0.5, 1.0, 2.0, and 4.0 hours after dosing on days 1 and 14. GLP/QAU statements: both present and signed

Dosing	C_{max} (nmol/l)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (nmol.h/l)	CL ml/min/kg	V_{ss} (l/kg)	F (%)
Single	271.2 ± 61.9	0.09 ± 0.01	0.41 ± 0.06	167.8 ± 18.34	61.96	2.27 ± 0.33	71.5 ± 8.4
Repeated	447.8 ± 199.4	0.11 ± 0.07	0.42 ± 0.09	233.99 ± 58.98	61.96	2.21 ± 0.50	101.5 ± 26.8

As shown above the drug was rapidly absorbed from the injection sites. The Cmax ranged from 271 to 357 nmol/l and from 226 to 711 nmol/l after single and repeated dosing, respectively. An increase in AUC values is most likely the accumulation of LEA103 after repeated dosings.

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(4) G3 Astra Report 802-50 AF 11-2, 1994-06-28. Pharmacokinetic considerations of

the study: Dose range finding study of LEA103 given subcutaneously to rats for 2 weeks. Halldin M. Osterlof G., [133/1.32]. Sprague-Dawley rats (6/sex/group) received 0.0, 3.3, 9.9, and 29.7 mg/kg/day LEA103 for 2 weeks subcutaneously. Blood samples were collected before and 0.5,1.0 and 5 hours after drug administration. A linear relationship between dose and AUC was obtained after repeated administration of LEA103.

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(5) G4 Astra Report 802-50 AF 12-2, 1994-06-28. Pharmacokinetic evaluation of the study: General toxicity of LEA 103 given subcutaneously to rats for 1 month. Halldin M, Osterlof G., [151/1.32]. Sprague-Dawley rats (160-280 g body weight, 4/sex/group) received LEA103 by subcutaneous injection in the neck region daily at doses of 0.0, 3.3, 9.9, and 26.3 mg/kg (0, 10, 30 and 80 μmol/kg, respectively) for 1 month. Blood samples were taken before dosing and at 0.5, 1.0, 3.0, and 6.0 hours after the first (Day 0) and last day (1 Month) of dosing. Quality Assurance Statement: Yes

Results:

AUC values (0-6 hr; ngxhxml^{-1}) following single and repeated subcutaneous administration in rats are given below.

Group	3.3 mg/kg/day	9.9 mg/kg/day	26.3 mg/kg/day
AUC♂ / Day 0	678 ± 100	1560 ± 250	4538 ± 639
AUC♂ \ Day 30	617 ± 75	1492 ± 221	5133 ± 239
AUC ♀ / Day 0	504 ± 18	1165 ± 140 [1]	3530 ± 944
AUC ♀ \ Day 30	438 ± 24 [1,2]	1240 ± 134	4283 ± 376 [1]

[1]-significantly different ($p < 0.05$) from male rats.
[2]-significantly different ($p < 0.05$) from day 0

The peak plasma level was reached 0.5-1 hr after administration in both male and female rats. Linear pharmacokinetics was indicated from the linearity in the AUC vs dose relationship. The elimination of the drug from the blood was fast with a $t_{1/2}$ range from min.

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(6) G5 Astra Report 802-50 AF 90-2, 1988-9-26. Placental transfer and pharmacokinetics of LEA 103 given subcutaneously to pregnant rats. Halldin M, Lofsson S, Danielson M. Osterlof G., [176/1.32]. Pregnant S-D rats between day 6 -16 of pregnancy received 16, 32 or 81 μmol/kg/day of LEA103 (ropivacaine hydrochloride monohydrate) by subcutaneous injection in the neck. Plasma concentrations of LEA103

were analyzed on days 6 and 15 of pregnancy. Total radioactivity was determined in maternal blood, amniotic fluid and fetus on day 16 of gestation one hour after the administration of ^{14}C-labeled LEA103. GLP/Quality Assurance Statements: None

The absorption from the injection site was rapid, with C_{max} reached between h. The mean plasma clearance decreased after repeated administration as compared to single application. Concentrations of radioactivity in maternal blood, amniotic fluid and fetal tissue (eq. pmol/g of tissue) are given below.

Dose (μmol/kg)	Amniotic fluid	Fetal tissue	Maternal blood
16			
32			
81			

The placental transfer of total radioactivity was linear with a fetal tissue/maternal blood ratio of 45%, 50% and 46% after 16, 32 and 81 μmol/kg, respectively. The corresponding values in the amniotic fluid were 17%, 22% and 21%, respectively.

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(7) G7 Astra Report 802-550 LF 0068-01, 1993-04-01. Comparative study of effects during the peri- and postnatal period in rats of ropivacaine (LEA 103) and bupivacaine (LEA131) given subcutaneously: Evaluation of plasma concentration and protein binding. Lindstrom BE, Halldin M, Brunfelter K., [199/1.32]. Sprague-Dawley rats (8/group) were given subcutaneously daily doses of 16, 43 and 75 μmol/kg LEA103 or 16, 43 and 53 μmol/kg LEA131 from day 15 until day 21 of pregnancy. Blood samples were obtained 0.5, 1.0, 3.0 and 6.0 hours after dosing on day 20 and 0.5 h after dosing on day 21 of pregnancy. GLP/Quality Assurance Statements: Yes

Dose (μmol/kg)	Compound	C_{max} μmol/L	t_{max} h	AUC (μmol/L.h)	$t_{1/2}$ h	F %
16	LEA103	1.09 ± 0.38	0.8 ± 0.3	3.69 ± 0.48	2.31 ± 0.96	93.02 ± 12.22
43	LEA103	1.79 ± 0.46	1.0 ± 0.9	15.01 ± 3.77	6.54 ± 2.58	140.93 ± 35.42
75	LEA103	4.83 ± 1.70	0.6 ± 0.2	18.01 ± 2.27	2.67 ± 0.63	96.94 ± 12.24
16	LEA131	0.66 ± 0.16	0.6 ± 0.2	8.74 ± 5.12	14.99 ± 12.3	-

Dose (μmol/kg)	Compound	C_{max} μmol/L	t_{max} h	AUC (μmol/L.h)	$t_{1/2}$ h	F %
43	LEA131	2.17 ± 0.43	0.8 ± 0.3	10.92 ± 0.87	5.16 ± 0.75	-
53	LEA131	3.97 ± 1.43	0.5	11.25 ± 1.63	2.73 ± 2.19	-

Both LEA103 (C_{max} between 30-60 min) and LEA131 were rapidly absorbed from the site of injection. Significant differences in the C_{max} between LEA103 and LEA131 were seen in the low dose groups. A linear increase in AUC and C_{max} were seen in both drug groups. The protein binding was significantly lower for LEA103 compared with LEA131 in the pregnant rats. At equimolar doses, the free plasma levels of LEA103 in pregnant rats will be about two times higher than that of LEA131.

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(8) G9 Astra Report 802-50 AF 91-2, 1988-09-26. Placental transfer and pharmacokinetics of LEA 103 given subcutaneously to pregnant rabbits. Halldin M, Elofsson S, Danielson M, Osterlof G., [229/1.32]. The drug was administered sc at 32 or 64 μmol/kg/day to New Zealand white rabbits (4/group) during day 6-16 of pregnancy. Blood samples were drawn on days 6, 15 and 16 of pregnancy. GLP/Quality Assurance Statements are not submitted.

Two rabbits in the high dose group were killed on the 10th day of gestation due to heavy convulsions. The absorption from the injection sites was fast in both dose groups. C_{max} was increased on day 15 compared to day 6 in low dose group only. A decrease in the mean plasma clearance and volume of distribution from day 6 to day 15 was observed in both groups after repeated dosings. The placental transfer showed a fetal tissue/maternal blood ratio of 25% and 54% after 32 and 64 μmol/kg administration of LEA103 on the 16th day of gestation, respectively. The corresponding values for the amniotic fluid/maternal blood ratio were 11% and 31%, respectively.

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(9) G10 Astra Report 802-550 LF-0154-02, 1994-05-01. Pharmacokinetics of ropivacaine (LEA103) in male dogs. Halldin M., [265/1.32]. Four dogs were given an intravenous infusion (3.3 mg/kg, 10 μmol/kg for 15 min) and two subcutaneous doses (3.3 and 13.2 mg/kg) of LEA103 with two weeks between the different administrations. ^{3}H-ropivacaine was used in the 3.3 mg/kg (10 μmole/kg) doses (iv & sc) and ^{14}C-ropivacaine in the high sc dose (13.2 mg/kg). Blood, urine and feces were collected up to 96 h after administration.

Dose (umol/kg)	Route	AUC_{∞} (µmol/h/L)	t_{max} h	C_{max} (µmol/L)	$t/_{12}$ h	F
10	iv	7.51 ± o.44	0.25	8.11 ± 1.99	0.65 ± 0.16	-
10	sc	11.84 ± 3.16	0.5	3.22 ± 1.31	9.0 ± 9.8	1.6 ± 0.5
40	sc	35.29 ± 10.72	0.6 ± 0.1	7.01 ± 1.39	6.8 ± 7.3	1.2 ± 0.4
40 (labelled)	sc	474.18 ± 63.43	1.4 ± 0.3	23.29 ± 6.52	33.2 ± 12.5	

The drug was rapidly eliminated from the plasma after iv. Large interindividual differences were seen after sc administration. The elimination half-life for the total radioactivity was estimated to be ≈33 h.

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(10) G11 Astra Report 802-50 AF 71-1, 1986-12-9. Pharmacokinetics of LEA 103 after intravenous and epidural administration in dogs. Arthur GR, Feldman HS, Covino BG., [300/1.32]. Adult male mongrel dogs received either 3 ml epidural injections of 0.25, 0.5, 0.75, and 1.0% of LEA103, both plain and with epinephrine (1:200,000) or 3.0 mg/kg LEA103 by intravenous infusion in 15 minutes. Another group of animals received epidural injections of 0.25, 0.5 and 0.75% bupivacaine, both plain and with epinephrine (1:200,000) . Blood samples were collected before infusion, during the infusion and after the infusion.
No toxic symptoms were observed after iv administration. At equal epidural doses of the drug, LEA103 concentrations were consistently higher than those of bupivacaine with both plain and epinephrine containing solutions. Elimination half life was 26 min after iv administration when compared to 190-202 min after epidural injection. Total body clearance after iv administration was 41 ml/min/kg as compared to 25-30 ml/min/kg after epidural administration.

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(11) Anesth Analg 1988;67:1053-1058 Comparative pharmacokinetics of bupivacaine and ropivacaine, a new amide local anesthetic. Arthur GR, Feldman HS, Covino BG, [321/1.32]. The results of this published pharmacokinetic study showed that after iv infusion of bupivacaine and ropivacaine in dogs, concentration of ropivacaine decreased more rapidly than bupivacaine during the elimination phase. This may result in a greater margin of safety for ropivacaine. However, the pharmacokinetic profile of both drugs were quite similar after epidural administration in dogs.

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(12) G12 Astra Report 802-550 LF 0106-02, 1993-09-01. Pilot/Dose-finding epidural (continuous infusion) tolerance study in the beagle dog of LEA 103 and LEA 131:

Evaluation of the plasma concentration data. Halldin M, [327/1.32]. Beagles (2/sex/group) received 1.51 μmol/kg/h ropivacaine (0.5 mg/kg/h, 6 mg/ml solution) or 0.73 μmol/kg/h bupivacaine (0.25 mg/kg/h, 3 mg/ml solution) as a continuous epidural infusion for 5 consecutive days. Blood samples were collected before dosing and at 1, 12, 24, 48, 72, 96, and 120 h after the start of the treatment. GLP/Quality Assurance Statements: Yes

The peak plasma concentration of ropivacaine (1.64-3.78 μmol/L) and bupivacaine (0.74-1.03 μmol/L) was reached at 48 and 24 h after initiation of dosings, respectively. The plasma clearance for ropivacaine and bupivacaine ranged from 8.2 to 23.2 ml/min/kg and from 14.0 to 20.4 ml/min/kg, respectively.

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(13) G13 Astra Report 802-550 LF-0182-01, 1994-02-17. Pharmacokinetics and excretion of LEA 103 (ropivacaine) in dogs after intravenous, subcutaneous and rectal administration. Ekstrom G, Lindstrom, Boo E, Brunfelter K. [347/1.32]. GLP and QAU statements are present and signed. Four male and two female beagle dogs were given iv (10 μmol/kg), s.c. (10 μmol/kg) and rectal (322 μmol) LEA103. Urine, feces and blood samples were collected for radioactivity analysis. The $t_{1/2}$ after iv, sc and rectal administrations were 0.68 ± 0.22 h, 10.86 ± 11.76 h and 1.43 ± 0.71 h, respectively. No differences between sexes were observed in the pharmacokinetic profiles or the excretion data.

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(14) G14 Astra Report 802-50 AF 10-1, 1986-01-22. Pharmacokinetic considerations of the study: A dose range finding study of LEA 103 and bupivacaine given subcutaneously to dogs for 3 days. Halldin M, Osterlof G, Lundin D. [396/1.32]. Quality assurance statement is present. Six beagle dogs (3 M & 3 F) received LEA103 and bupivacaine by s.c once daily for three days. No significant differences were observed in the plasma concentrations and AUC values of bupivacaine and LEA103 between male and female dogs.

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(15) G15 Astra Report 802-50 AF 19-1, 1986-01-23. Pharmacokinetic evaluation of the study: General toxicity of LEA 103 given subcutaneously to dogs for 1 month. Halldin M, Osterlof G, Lundin D. [1/1.33]

See Study No (17) B4 under TOXICOLOGICAL EFFECTS

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(16) G18 Astra Report 802-24 AF 1-1, 1990-06-18. Dose finding and pilot irritation study in dogs of ropivacaine given rectally for up to 5 days: Evaluation of plasma concentrations of ropivacaine. Halldin M, Boo E, Jonze M. [24/1.33]. GLP/QAU statements are present and signed. One male and one female dog (Kebbel Raahojden, Sweden) weighing ≈15 kg were given single rectal doses of 10, 50, 100, 200 and 400 mg ropivacaine separated by one week. Two additional dogs were administered 400 mg

ropivacaine HCl rectally daily for 5 days. Plasma samples were analyzed for unchanged ropivacaine by gas chromatographic technique with nitrogen detection.

Ropivacaine was rapidly absorbed from the rectum at all doses with peak plasma concentration times of 0.5 - 1 h . C_{max} was not linear in the dose range tested. There were no differences in the plasma concentrations of ropivacaine between day 1 and day 5 of dosing.

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(17) G19 Astra Report 802-24 AF 3-1, 1990-08-31. Local tolerance study in dogs of ropivacaine given rectally for 1 month: Evaluation of plasma concentration data. Halldin M, Boo E, Jonze M. [48/1.33] GLP/QAU statements are present and signed. Dogs (Kennel Raahojden, Sweden: ≈9 - 15 kg body weight) were given rectal doses of 0 mg, 100 mg (322 μmol), 200 mg (643 μmol and 400 mg (1287 μmol) ropivacaine HCl twice daily for one month. Plasma samples were withdrawn at 0, 1, 3, and 6 h after first dose and then 1, 3, 6, and 18 h after the second dose on day 0 and day 21 (male) and 22 (female). Plasma was prepared and analyzed for unchanged ropivacaine.

Pharmacokinetic parameters after repeated rectal administration of ropivacaine to dogs (N = 3) are given below.

Dose (μmol)		322				643				1287			
Day of adm.		Day 0		1 Month		Day 0		1 Month		Day 0		1 Month	
Dose		1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
t_{max} (h) (range)	M	1	1	1	1	1-3	1	1	1	1-6	1	1	1
	Fm												
$t_{½}$ (h)[1]	M	7.9 (6.2)		6.5 (4.9)		5.0 (2.8)		6.4 (0.7)		6.7 (3.1)		5.1 (1.4)[2a]	
	Fm	2.1 (0.9)[a]		4.7 (2.0)		3.6 (2.1)		7.2 (5.0)		8.5 (5.5)		4.6 (1.7)[3a]	
AUC (0→6 h)	M	6.4 (1.9)		5.5 (1.2)		5.6 (1.5)		7.3 (3.1)		16.4 (9.5)		19.4 (15.1)	
(Dose1)	Fm	5.0 (5.1)		7.8 (7.0)		7.8 (8.2)		5.7 (3.1)		12.3 (8.4)		11.5 (6.7)	
(0→18 h) (Dose 2)	M	5.4 (0.5)		9.5 (3.2)		12.6 (9.6)		12.0 (5.3)		40.6 (24.0)		38.0 (22.3)	
	Fm	9.5 (9.9)		11.8 (11.5)		9.3 (3.0)		14.9 (8.7)		27.8 (19.0)		25.1 (17.3)	
(0→24 h)[2]	M	11.8 (1.6)		15.1 (3.7)		18.2 (10.9)		19.3 (8.4)		57.0 (33.5)		57.4 (34.3)	
(μmol/h L)	Fm	15.5 (14.1)		19.5 (13.6)		17.1 (11.1)		20.6 (11.8)		40.1 (27.3)		36.5 (23.9)	
F(%)[3]	M	32.4 (4.2)		41.7 (9.0)		24.4 (13.9)		25.6 (10.1)		35.9 (20.5)		35.4 (20.7)	
	Fm	37.5 (30.2)		46.3 (41.4)		21.0 (9.5)		24.9 (8.9)		27.2 (19.7)		22.2 (12.6)	

M= male; Fm= female; F= estimated bioavailability
[1] obtained from regression analysis of the slope after the second dose
[2] Dose 1 + dose 2
[3] based on AUC (0→24 h)
[a] n=2; dog 911/90 was excluded due to that the last plasma conc. were above the previous conc. and no reliable calculations of $t_{½}$ could be made.
[2a] (n=2) dog 918/90 and [3a] (n=2) dog 932/90 were excluded since the two last plasma conc. did not allow that reliable calculations of $t_{½}$ could be made (374 h and 25 h, respectively)

The absorption of ropivacaine from the rectum was rapid with C_{max} occurring within one

hour after administration. The increase in AUC with doses was not linear in the dose range tested. Large individual variations in PK values were observed. No accumulation of drug in plasma was seen after repeated administration for one month.

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(18) G16 Astra Report 802-524 LF 0005-01, 1991-11-12. General toxicity study of ropivacaine (LEA 103) given subcutaneously and rectally to dogs for six months: Evaluation of the plasma concentration. Halldin M. Boo E. Brunfelter K Arvidsson T. [111/1.33]. GLP/QAU statements are present and signed. Beagle dogs (5/sex/group) were given 0 μmole/kg (physiological saline and vehicle gel; group 1), 10 μmol/kg + 320 μmol (group 2), 20 μmol/kg + 640 μmol (group 3), and 40 μmol/kg + 1300 μmol (group 4) of LEA 103 both subcutaneously and rectally, respectively, daily for six months. Blood samples were collected before dosing and 0.5, 1.0, 2.0, 4.0,, 6.0, and 24 hours after administration on day 0 and 1, 3 and 6 months of dosing. The plasma samples were analyzed for total drug concentration and protein binding.

The absorption of LEA 132 was rapid with C_{max} occurring in 0.5 hour after subcutaneous and rectal administration. The area under the plasma concentration vs time curve (AUC)increased linearly with dose. The AUC values in female dogs were elevated after 6 months administration indicating that LEA 103 could be accumulated over time.

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(19) G17 Astra Report 802-24 AF 2-1, 1990-06-18. Plasma concentrations of LEA 103 (ropivacaine) after rectal administration in dogs. Comparison of different gel vehicles. Halldin M, Boo E, Olsen Sundelin C, Jonze M. [176/1.33]. The absorption was rapid with no difference between the low and high viscosity gels used. The bioavailability was between 24 and 28%.

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(20) G31 (F33) Astra Report 802-50 AF 48-1, 1986-02-19. Systemic hemodynamics and myocardial kinetics following intravenous administration of LEA 103, bupivacaine and lidocaine to pentobarbital anesthetized pigs. Reiz S, Haggmark S, Johansson G, Nath S. [188/1.33]

See Study No (30) F33 under PHARMACOLOGICAL ACTIONS

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(21) G20 Astra Report 802-550 LF-0147-01, 1993-12-23. Pharmacokinetic evaluation of the study: Effects of ropivacaine on uterine blood flow in pregnant sheep. Halldin M, Arthur GR. [230/1.33]. Nine pregnant sheep (124-131 days of gestation, term 148 days) were administered ropivacaine (≈6 mg/kg) by iv. The same animals were also administered bupivacaine (≈4.2 mg/kg) as comparison. Results from arterial blood samples are given on the next page.

Animal	Drug	AUC mg/min/l	C_{max} mg/l	t_{max} min	$t_{1/2}$ min	AUC_{fetal}/AUC_{ewe}
Pregnant sheep	Ropivacaine	354.6 ± 194.8	3.15 ± 1.04	15	126.0	
Fetal sheep	Ropivacaine	57.4 ± 19.3	0,60	33.0 ± 25	91.1 ± 46.4	0.23 ± 0.08
Pregnant sheep	Bupivacaine	272.4 ± 102.0	2.05 ± 0.63	31.7 ± 21.8	161.3 ± 49.6	
Fetal sheep	Bupivacaine	52.1 ± 26.2	0.36 ± 0.11	49 ± 21	105.3 ± 40.2	0.23 ± 0.09

Large interindividual variations in pharmacokinetic data of both drugs were observed for both ewes and fetuses. The PK values may be similar for ropivacaine and bupivacaine.

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(22) G21 Astra Report 802-50 AF 125-1, 1992-07-02. Pharmacokinetics and serum protein binding in pregnant, fetal and nonpregnant sheep: Systemic toxicity and pharmacokinetics of ropivacaine in pregnant and nonpregnant ewes. Arthur GR. [261/1.33].GLP/QAU statements are present and signed. Pregnant (131 ± 3 days of gestation) and nonpregnant (41.5-69 kg body weight) sheep were given 180 mg ropivacaine by 4 min. iv infusion. Peak plasma concentration at the end of infusion were 5.93 ± 2.06 μg/ml in pregnant and 4.18 ± 1.11 μg/ml in nonpregnant animals Total body clearance was greater in nonpregnant sheep (45.1 ± 6.7 ml/min/kg) as compared with pregnant animals (21.6 ± 4.5 ml/min/kg). The elimination half-life was 74.7 ± 10.76 min in the pregnant and 64.4 ± 7.4 min in the nonpregnant animals. The placental transfer was rapid with fetal plasma concentration being observed in min after the end of maternal infusion. The protein binding in fetal detected was ~38%.

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(23) Anesth Analg. 1990;70:262-266. Pharmacokinetics of ropivacaine in nonpregnant and pregnant ewes. Santos CA, Pederson H, Sallusto JA, Johnson HV, Morishima HO, Finster M, Arthur GR, Covino BG. [320/1.33].

This paper reports on the data in the above study

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(24) G22 Astra Report 802-550 LF-0175-01 Pharmacokinetics, protein binding and systemic toxicity of ropivacaine and bupivacaine in pregnant and nonpregnant ewes. A pharmacokinetic evaluation. Halldin M, Arthur GR. [1/1.34].

Fourteen non-pregnant and pregnant sheep (approximately 135 days of gestation) were administered an iv infusion of about 2 mg/Kg of ropivacaine or bupivacaine over 15 minutes. Arterial blood and urine samples were taken up to 300 minutes after the infusion. The metabolites are reported in Study (25) G42 below. GLP/QAU statements

were present and signed. These studies were conducted at

RESULTS

• PK data:	ropivacaine		bupivacaine	
:	pregnant	nonpregnant	pregnant	nonpregnant
• C_{max} (mg/L):	2.79 ± 0.73	2.16 ± 0.46	2.85 ± 0.74	2.18 ± 0.60
• t½ (minutes):	83.2 ± 23.9	89.4 ± 35.2	117.9 ± 44.9	141.9 ± 51.3
• CL (mL/min·Kg):	20.0 ± 9.6	28.1 ± 10.2	16.7 ± 7.9	23.2 ± 8.4
• Vss (L/Kg):	1.6 ± 0.7	2.3 ± 0.9	1.9 ± 0.8	3.1 ± 1.4
• protein binding (%):	87.6	80.8	91.3	87.7

• serum concentrations were higher in pregnant sheep-
• the C_{max} values were significant between pregnant and nonpregnant ewes-

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(25) G42 Astra Report 802-550 LF-0176-01 Pharmacokinetics, protein binding and systemic toxicity of ropivacaine and bupivacaine in pregnant and nonpregnant ewes. Biotransformation of ropivacaine. Halldin M, Askemark Y, Brunfelter K. [52/1.34].

This study reports on the biotransformation of ropivacaine in pregnant and nonpregnant sheep that were reported in Study (24) G22 (see immediately above). Urine was collected and analyzed for ropivacaine and its metabolites.

RESULTS

Mean 5¼ Hour Cumulative Recovery From Hydrolyzed Urine

	nonpregnant	pregnant
	Percent	Percent
• ropivacaine:	0.38 ± 0.40	1.40 ± 1.72
• 3-hydroxy-PPX (LEA 140):	1.56 ± 0.49	1.77 ± 0.27
• 3-hydroxy ropivacaine (LEA 145):	7.98 ± 3.85	8.44 ± 2.19
• 4-hydroxy ropivacaine (LEA 144):	0	0
• 2-hydroxymethyl ropivacaine (LEA 166):	0	0

• the major metabolite was 3-hydroxy-ropivacaine (LEA 145)

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(26) F37 Astra Report 802-550 LF-0219-01 Pharmacokinetics, protein binding and systemic toxicity of ropivacaine and bupivacaine in pregnant and non pregnant ewes; systemic toxicity evaluation. [96/1.34].

The objective of this study was to compare the systemic toxicity of ropivacaine and bupivacaine in pregnant and nonpregnant mixed breed sheep 1-4 years old. There

were 12 pregnant and 12 nonpregnant ewes administered ropivacaine and bupivacaine. Pregnant sheep had a body weight of 43.5-86.0 Kg; the body weight of nonpregnant sheep was 38.8-59.6 Kg. The gestation range was 131-140 days. The animals were iv infused with 5 mg/mL at 0.1 mL/Kg (0.5 mg/Kg/minute) of ropivacaine and bupivacaine until circulatory collapse. BP, heart rate, arterial blood gas tensions, pH, and serum concentrations of the drugs were determined corresponding to the onset of convulsions, hypotension, respiratory arrest, and circulatory collapse. These studies were done in the

GLP/QAU statements

were present with signatures.

RESULTS

- toxic signs: tonic/clonic convulsions associated with hypertension/tachycardia, hypotension, respiratory arrest, circulatory collapse-

	Ropivacaine		Bupivacaine	
	nonpregnant	pregnant	nonpregnant	pregnant
• convulsant dose (mg/Kg):	6.1 ± [illegible].2	7.5 ± 1.8	5.0 ± 2.2	4.6 ± 1.1
• heart rate at convulsion (beats/min):	228 ± [illegible].2	162 ± 49.9	195 ± 48.3	138 ± 44.4
• circulatory collapse (mg/Kg):	11.6 ± [illegible].3	12.9 ± 2.6	8.9 ± 2.2	8.5 ± 4.3
• ventricular fibrillation-terminal:	3/12	5/11	2/10	3/12
• protein binding at convulsion(%):	60.4 ± 6.1	61.8 ± 13.0	71.3 ± 10.1	71.4 ± 11.3
• serum conc at convulsant dose:	5.8 ± 1.2	6.6 ± 2.7	6.2 ± 1.6	6.8 ± 2.4
• serum conc at circulatory collapse:	9.9 ± 2.2	10.6 ± 3.3	8.6 ± 2.6	8.6 ± 2.4

- mean arterial pressure increased at convulsions then decreased to respiratory arrest-
- ↑ pCO_2 at onset of hypotension up to circulatory collapse-
- protein binding ↓ from control values through to circulatory collapse-
- free concentration of ropivacaine and bupivacaine increased at the onset of each toxic manifestation in both pregnant and nonpregnant animals-

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(27) G23 Astra Report 802-550 LF-0204-01. Comparative efficacy of epidurally administered ropivacaine and bupivacaine in the sheep. Evaluation of the pharmacokinetics. Halldin M. [145/1.34].

The pharmacokinetics of ropivacaine and bupivacaine were compared after epidural administration to female Dorset sheep (12/group). Both drugs were administered at 5.0 mg/mL and 7.5 mg/mL. The volume of injection was 5.0 mL over 60 seconds. Blood samples were collected up to 360 minutes after drug administration. The animal study was done at

Astra, Sweden did the PK analytical work. GLP/QAU statements were present and signed.

RESULTS

The PK data is from Table 4 p. 172 and Table 5 p. 172

	Low Dose (μmol/Kg)	C_{max} (μmol/L)	t_{max} (h)	AUC_{tot} (μmol·h/L)	$t_{½}$ (h)
Ropivacaine					
mean	1.70	0.40	0.23	1.99	3.45
max-min	2.01-1.34	0.79-0.14	0.50-0.05	7.45-0.77	5.76-2.01
	High Dose				
mean	2.48	0.63	0.14	3.15	4.0
max-min	2.80-1.98	1.12-0.41	0.25-0.05	8.76-1.24	7.59-1.51
Bupivacaine					
	Low Dose				
mean	1.67	0.44	0.14	2.08	6.13
max-min	1.94-1.30	0.72-0.23	0.25-0.10	3.90-0.93	11.44-2.24
	High Dose				
mean	2.45	0.61	0.14	2.94	6.16
max-min	2.86-1.91	0.86-0.24	0.20-0.10	6.29-0.74	10.62-1.23

• significant differences occurred in the $t_{½}$ in both groups and in the C_{max}.

B. Protein binding

1. In Vivo

(28) G28 Astra Report. 802-550 AF 129-1, 1991-01-07. Plasma protein binding of LEA 132 (ropivacaine) and LEA 112 (bupivacaine) in rats after repeated subcutaneous administration . Halldin M. Boo E. Elofsson S. Eklund E. [192/1.34].

GLP/QAU statements are submitted with signatures. Male, pregnant, and non-pregnant rats were subcutaneously administered 30 μmol/kg (10 mg/kg) or 79 μmol/kg (26 mg/kg) ropivacaine (LEA 132: the base form of LEA 103) or bupivacaine (LEA 112: the base form of LEA 131: 44 μmol/kg (15 mg/kg) or 87 μmol/kg (30 mg/kg)) for six days. Ropivacaine and bupivacaine were administered on days 15 to 20 of pregnancy. Males and non-pregnant females were treated during the same time interval. The animals were sacrificed on the last day of administration. Plasma samples were collected and analyzed for free and total drug concentrations by a gas chromatographic technique with nitrogen detection.

RESULTS

One low dose and four high dose deaths occurred in the male bupivacaine group, (one after the first dose, two after the third dose, two after the fourth dose), five non-pregnant and one pregnant female bupivacaine animals were sacrificed after the fifth dose due to respiratory difficulties, two pregnant high dose bupivacaine animals died (one

after the second dose and one after the fourth dose), and one animal in the high dose ropivacaine group was sacrificed after the fifth dose due to respiratory difficulties. Animals in the LEA 131 high dose group could not tolerate 87 μmol/Kg and was reduced to 58.33 μmol/kg. The mean total plasma concentrations of ropivacaine in the low dose group were higher in male rats (3.1 ± 0.7 μmol/l) compared to both pregnant (1.6 ± 0.6 μmol/l) and non-pregnant (1.5 ± 0.6 μmol) rats. There were no differences in the total and free plasma concentrations in the high dose group. Total and free plasma concentrations of bupivacaine were not different in the different groups. The mean percentage plasma protein binding was lower in the animals receiving ropivacaine compared to those receiving bupivacaine.

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2 In Vitro

(29) G32 Astra Report 802-50 AF 20-2, 1996-02-28. Blood/plasma concentration ratio of ^{3}H-LEA 103 and binding to serum protein from man, dog and rat. Elofsson S, Jostell KG, Halldin M. [211/1.34].

^{3}H-LEA 103 and ^{3}H-bupivacaine binding to serum protein and plasma concentrations were determined in dogs, rats, and humans. Protein binding experiments were determined by ultrafiltration. The study was done by Astra, Sweden. The date on the study was 2/28/94. The data is taken from Tables 1-3, pp. 218-219.

RESULTS

Percent Binding of ^{3}H-LEA 103 and ^{3}H-Bupivacaine in Human Serum Albumin (HSA) and α1 acid Glycoprotein (AGP)

^{3}H-LEA 103 (μmol/L)	0.35	1.7	3.5	6.9	17.3	34.7	69.3	173.4
HSA:	23.0	22.0	21.6	19.4	17.3	18.0	16.6	16.9
AGP:	68.9	72.6	67.3	62.9	45.6	32.1	21.4	13.3
^{3}H-Bupivacaine (μmol/L)								
HSA:	57.4	69.0	62.7	67.4	67.8	63.7	57.9	62.6
AGP:	71.0	63.4	67.3	65.3	49.6	37.7	26.3	27.4

Blood/Plasma Concentration Ratio of ^{3}H-LEA 103

^{3}H-LEA 103 (μmol/L)	0.35	1.7	3.5	6.9	17.3	34.7	69.3	173.4
Man:								
Dog:								
Rat:								

Percent Serum Protein Binding

^{3}H-LEA 103 (μmol/L)

	0.35	1.7	3.5	6.9	17.3	34.7	69.3	173.4
Man:	90.3	88.9	89.1	86.9	78.4	62.3	45.6	52.7
Dog:	92.4	90.8	89.3	78.0	64.2	57.9	54.9	51.7
Rat:	70.5	68.6	63.2	63.6	59.9	58.1	50.9	55.1

- LEA 103 is 90% bound to serum protein up to 3.5 μmol/L, then decreases-

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(30) G33 Astra Report 802-50 AF 66-1, 1986-10-15. Effect of sex and pregnancy on the in vitro binding of ropivacaine (LEA 103) to human serum proteins. Halldin M, Elofsson S. [224/1.34].

This study measured the blood/plasma concentration ratio in male and female (pregnant and nonpregnant) subjects by ultrafiltration. The study was done by Astra, Sweden in May-June 1986.

RESULTS

	male	nonpregnant	pregnant
• protein binding (%): at 0.35-6.9 μmol/L	94.3 - 91.3	93.2 - 89.5	93.2 - 86.5
• blood/plasma ratio:	0.60 - 0.64	0.66 - 0.70	0.68 - 0.74

- protein binding decreased at higher concentrations-
- blood/plasma concentration ratio increased with increasing blood concentrations-
- a decrease in the pH increased in the unbound fraction by 14%-24%-

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C. Tissue distribution/accumulation

(31) G25 Astra Report 802-50 T1732, 1986-01-30. Whole-body autoradiographic study on the distribution of radioactivity in mice after single intravenous injection of LEA 103-^{3}H. Astra Toxicology Laboratories, Sodertalje, Sweden. [245/1.34].

This study looked at the whole body distribution of radioactivity in male albino and pigmented mice after administration of 26 μmol/Kg (8.4 mg/Kg) to male mice and 17 μmol/Kg (5.5 mg/Kg) to 17 day pregnant mice. The study was conducted by Astra, Sweden in July-August 1985. Both QAU and GLP statements are present and signed.

RESULTS

- high levels of radioactivity (1 minute) in the brown fat, nasal mucosa, gastric mucosa, eyeball wall, adrenals, islets of Langerhans, and the kidney-
- concentrations ↓ (5 min) but was still high in liver, spleen, eye lens, and pituitary-
- moderate/low levels of radioactivity found in the brain and spinal cord at 1 hr but not detected at 4 hr-
- low levels detected in the heart up to 1 hr-
- moderate/low levels in fetal liver and body - high levels in fetal intestinal content-

- low levels at 16 hr in amnion fluid and in fetal brain, liver, intestinal content, and kidney pelvis-
- levels detected in urinary bladder, gallbladder/bile ducts and ovaries at 16 hrs--
- very high levels at 2 days and high levels up to 32 days in the melanin containing layer in the retina-

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(32) G24 Astra Report 802-50 AF 98-1, 1987-11-11. Retention of LEA 103 (Ropivacaine hydrochloride monohydrate) in melanin containing tissues of pigmented mice after single subcutaneous administration. Halldin M, Elofsson S. [267/1.34].

In an earlier study, radioactivity was found to be distributed and retained in melanin tissues. This report further evaluates the retention of radioactivity from 14C-LEA 103 in melanin tissue of pigmented mice of the CBA strain. The dose was 25.2 μmol/Kg (8.29 mg/Kg) sq in 0.2 mL. Blood and tissue samples (eyes, brain heart kidney, liver, tail skin) were collected for radioactive determination. Astra, Sweden conducted the study in April-September 1987. QAU/GLP statements were present and signed.

Results

- concentrations were found in decreasing levels in eyes, liver, kidneys, tail skin, blood, heart, and brain-
- radioactivity present at 120 days in eyes ($t_{½}$ = 141 days) and tail skin ($t_{½}$ = 31 days)-
- most of the radioactivity extracted from eyes cochromatographed with LEA 103-
- small amounts (14%) of 3-hydroxy-LEA 103 were extracted from eyes-
- two unidentified metabolites were seen in the eyes-

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(33) G26 Astra Report 802-550 LF 047-01, 1993-10-10. Tissue distribution of ropivacaine (LEA 103) after single intravenous administration to male rats. Elofsson S, Halldin M, Boo E, Neidenstrom P. [286/1.34].

This tissue distribution study was done in the Astra Pain Control AB Lab, Sweden in March-December 1990.Both GLP and QAU statements were present and signed.

After a single iv dose of ^{14}C-LEA 103, about 10 μmol/Kg (3.3 mg/Kg), ropivacaine was administered to male rats, eight groups of four per group. The brain, heart, liver, lungs, spleen, kidney, stomach, testes, and samples of small intestine, muscle, and fat were collected and analyzed for radioactive distribution of ropivacaine and metabolism. GC analysis was used to determine parent drug and metabolites. Elimination half-life ($t_{½}$) was estimated for the various tissue samples.

The results showed a rapid distribution of ropivacaine in all tissues. Metabolism of ropivacaine was rapid in the liver. No rapid metabolism was seen in the brain, heart, or lung. The elimination half-life for ropivacaine in the various tissues ranges from 0.57

hr in the heart to 1.27 hr in the kidney. On the other hand, the half-life for the total radioactivity (LEA and its metabolites in these tissues ranged from 2.9 hr to 19.1 hr in the spleen; $t_{\frac{1}{2}}$ in the heart was 15.1 hr.

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(34) G29 Astra Report 802-550 LF-0151-01, 1994-02-04. Tissue distribution of ^{14}C-ropivacaine (LEA 103) after subcutaneous administration to male dogs. Halldin M. Elofsson S, Lindstrom Boo E. [322/1.34].

The study was conducted to determine the distribution of radioactivity in three male dogs after a single sq dose of 11 μmol/Kg (3.6 mg/Kg) of ^{14}C-LEA. Blood was collected up to 30 days after drug administration. Urine and feces were also collected. Tissues from the brain, eyes, heart, kidneys, liver, lungs, spleen, stomach, intestine, pancreas, adrenals, muscle, fat, and pigmented and nonpigmented skin were collected and analyzed for total radioactivity.

Results

Radioactivity was distributed throughout the body tissues. The estimated terminal half-life of total radioactivity in the eyes and pigmented skin was 7.0 days and 17.6 days, respectively. Other tissues with a long $t_{\frac{1}{2}}$ were the lungs (12.2 d), heart (11.9 d), kidneys (10.7 d), spleen (12.3 d), stomach (10.2 d),fat (10.9 d), and white skin (16.7 d). Peak plasma concentrations of ropivacaine occurred at 15 to 30 minutes in the three dogs; this is the same time frame as the appearance of radioactivity. Estimated terminal half-life of the total radioactivity in the various tissues ranged from 5.8 days in the pancreas to about 17 days in white or pigmented skin. The highest radioactivity was seen in the liver at all times, followed by the kidney and spleen. By the end of 30 days, the cumulative recovery of radioactivity was 72% in the urine and 27% in the feces. The amount of ropivacaine excreted in the urine was only 0.3% of the administered over the first 24 hours. These results indicate ropivacaine is extensively distributed throughout the various tissues of the body.

D. Metabolism Characteristics, Metabolites, and Excretion

1. In Vivo

(35) G34 Astra Report 802-50 AF 99-1, 1987-11-11. Biotransformation of LEA 103 (ropivacaine hydrochloride monohydrate) in pigmented mice after single subcutaneous administration. Halldin M. Elofsson S. [1/1.35]

^{14}C-LEA 103 (77.3 kBq·μmol^{-1} spec. activity, >97% radiopurity) in physiologic saline was administered sq in the neck region (25.2 μmol/Kg, 8.29 mg/Kg) to pigmented male mice of the CBA strain, 16-22 g body weight. Urine and feces were collected at 24 hr intervals for 96 hours and the radioactive metabolites isolated and identified. The study was done by Astra, Sweden in April - September 1987. GLP/QAU were present

with signatures.

RESULTS

At the 24 hour collection, 27.9% of the radioactivity was in the urine and 45.1% in the feces. The total recovered was 33.9% in the urine and 52.5 % in the feces (total = 86.4%). An additional 0.4% was recovered in the cage washings. Five radioactive compounds were identified in the 24 hour urine fraction, one of which was LEA 103 (4.5%). The other four metabolites were 2',6'-pipecoloxylidide or PPX (4.7%), 3'-OH-LEA 103 (2.8% unconjugated and 6.8% conjugated), 6-oxo-PPX (3%), and 3'-OH-PPX (1%). An additional 10% to 11% radioactivity appeared in two additional peaks in the HPLC tracings. These were not identified. Fecal excretion was the major route for excretion in this species. Other species, including humans, formed the 4'-hydroxy LEA 103; however, none was detected in this mouse species.

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(36) G35 Astra Report 802-550 LF-0165-01, 1994-02-20. Biotransformation and excretion of ^{14}C-ropivacaine (LEA 103) in male rats following single intravenous and subcutaneous administration. Elofsson S, Halldin M. [16/1.35].

Two groups of three male SD rats (12-13 weeks old, 230-250 g body weight) were given either a single iv or sq dose of ^{14}C-LEA 103 (330 kBq, 10 μmol/Kg). Labeling was on the aromatic methyl group. Urine and feces were collected over seven days and the major metabolites determined. Urine from this study was also used in study (42) G37 to look at the racemization question. Astra, Sweden conducted this study in March 1993-February 1994. GLP/QAU statements were present and signed.

In 168 hours of collection, about 94% to 95% of the total radioactivity was recovered from in the urine and feces of the iv and sq administration. The breakdown in the urine and feces corresponded to 42% and 52% in the iv and 44% and 51% in the sq administration. After 48 hours, about 85% of the total radioactivity was collected from the iv or sq administration. Only 1% (iv) and 3% (sq) was unchanged LEA 103 in the urine and about 1% was detected in the feces from either route of administration. Identified urinary metabolites from the 24 hour iv administration and their percent of the radioactivity excreted were LEA 145 (37.9%), LEA 144 (1%), LEA 140 (4.8%), and LEA 142 (6.2%). LEA 145 (11.5%) was also found in feces. There were several unidentified urinary metabolites designated as M1 (1.3%), M2 (1.8%), M3 (2.2%), and M4 (2.1%). A fifth unidentified metabolite (M5, 4.4%) was seen in the feces. These metabolites were also observed with similar percentages in the urine of sq treated animals. The major metabolite in urine was 3-hydroxy-ropivacaine (LEA 145).

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(37) G36 Astra Report 802-50 AF 18-1, 1986-01-23. Biotransformation of LEA 103 in rats. Erixson E, Halldin M. [43/1.35]

This study is similar to the above iv and sq metabolism study in rats. Two groups

of 6 male SD rats (290-320 g body weight) were administered 10 μmol/Kg (3.3 mg/Kg) of ^{14}C-LEA 103 in a saline solution, one by iv and one by sq injection. The label was on the aromatic methyl group. Astra, Sweden did the study in October 1985. No GLP/QAU statements were present.

RESULTS

Excretion data was similar to that seen in Study (36) G35. The accumulated urinary excretion of radioactivity over 96 hours was 45.3% from the iv administration and 45.6% from the sq administration; 47.6% iv and 52.8% sq were recovered in the feces. Less than 0.1% was excreted in the exhaled air. Four metabolites were identified in the urine: 1) 10% 3'-hydroxy LEA 103 (LEA 145)
2) 19% glucuronide of 3'-hydroxy LEA 103
3) 2% 4'-hydroxy LEA 103 (LEA 144)
4) 3% glucuronide of 4'-hydroxide
No differences were seen in the metabolic pattern between the iv and sq administration.

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(38) G27 Astra Report 802-550 LF-0178-01, 1994-05-01. Distribution of ^{14}C-ropivacaine to milk of lactating rats. Floby E, Elofsson S, Halldin M. [60/1.35].

This study was done to evaluate the excretion of radioactive LEA 103 in milk of lactating rats. One ml iv or sq bolus of 10 μmol/Kg of 14C LEA 103 (batch F141) was administered to SD rats on days 8-10 of lactation. Blood samples were collected prior to milk collection at various times after drug administration. Radioactivity was determined in milk, blood, and plasma by liquid scintillation. The study was done in September - November 1993 by Astra, Sweden. Both QAU and GLP statements were present with signatures.

RESULTS

The following PK data is taken from Table 4, p. 80.

	C_{max} (nmol/g)	t_{max} (hr)	AUC (nmol·h/g)	$AUC_{(tot)}$ (nmol·h/g)	$t_{½}$ (h)
Intravenous					
Blood:	3.74	0.08	12.11	15.16	10.72
Plasma:	4.97	0.08	17.79	20.43	8.38
Milk:	3.38	0.08	10.21	30.25	52.31
Subcutaneous					
Blood:	0.60	0.5	9.52	15.11	16.58
Plasma:	0.80	0.5	13.80	19.77	13.83
Milk:	0.78	1.0	8.82	18.79	27.38

C_{max} was reached about 5 minutes after iv administration. Four hours after dosing the rats, a second radioactive peak appeared in the blood and plasma but not in the milk. The first appearance of radioactivity in the milk was assumed to be from

ropivacaine, while the second peak in the blood and plasma was assumed to be metabolites that did not diffuse into the milk.

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(39) G38 Astra Report 802-50 AF 92-2, 1988-09-26. Biotransformation of LEA 103 given subcutaneously to pregnant rabbits Halldin M, Elofsson S, Danielson M, Osterlof G, Thorin H. [92/1.35].

NZW rabbits (> 6 months old, 3.0-4.6 Kg body weight) were dosed with 2 ml/Kg sq with 32 or 64 μmol/Kg of LEA 103 on Days 6-16 of pregnancy. On Day 6 they received a radioactive dose of ^{14}C-LEA 103. Urine and feces were collected every 24 hours for 96 hours. HPLC-GC-MS was used to analyze the urine extracts. Renal clearance (Clr, ml/min/Kg) was calculated by dividing the unchanged LEA 103 in the urine by the AUC in plasma. The animal part of the study was done in October-November 1986; the bioanalysis was done in January-March 1987 by Astra, Sweden. GLP/QAU statements were not present.

Results

There were five metabolites identified in the urine: 1) 3'-hydroxy LEA 103 , this is the major metabolite and appears after acid hydrolysis, 2) pipecolo-2',6'-xylidide (PPX) found only before acid hydrolysis, 3) 4'-hydroxy LEA 103 found after acid hydrolysis, 4) (S)-N-(2,6-dimethylphenyl)-piperidine-6-one-2-carboxamide (6-oxo-PPX) found before hydrolysis, and 5) 3'-hydroxy-PPX. In addition, LEA 103 was also identified in the urine (1.4%-2.9%). Six other unidentified peaks were seen in the HPLC chromatogram after hydrolysis. On Day 6 the renal clearance was 0.67 and 0.82 ml/min/Kg for the 32 and 64 μmol/Kg dose, respectively. When corrected for the protein bound fraction, then Clr was calculated at 3.2 and 3.5 ml/min/Kg for the low and high dose, respectively.

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(40) G39 Astra Report 802-550 LF-177-01, 1994-06-01. Biotransformation of ^{14}C-ropivacaine (LEA 103) in male and female dogs, following single intravenous, subcutaneous and rectal administration. Elofsson S, Lindstrom Boo E, Halldin M. [114/1.35]

The metabolic profile of LEA 103 in four male and two female beagle dogs (11-15 Kg, 17-18 months old) was studied following a single iv, sq, and rectal administration of 10-25 μmol/Kg ^{14}C-LEA 103. Each dog received one dose by each route, with a two week rest period before the next administration. Radioactivity was measured only in the urine at 24 hours every seven days. Urine samples from this study were used to look at the question of racemization in dogs [see Study (42) G37]. The animal part of this study was done by Astra, Sweden in October 1992. Metabolic analysis was done in May-November of 1993. Both GLP and QAU statements were present and signed.

RESULTS

As in rats and rabbits, LEA 103 was also extensively metabolized in this dog study. At 48 hours the radioactivity excreted in the urine was 61% (iv), 57% (sq), and 60% (rectal). The following metabolites were isolated in the urine: 1) 3'-hydroxy LEA 103 (LEA 145), the major metabolite from all routs of administration, 2) 3'-hydroxy-PPX (LEA 140), the second most abundant metabolite, 3) M2, the third most abundant metabolite and found only after hydrolysis - structure not elucidated, 4) 4'-hydroxy LEA 103, 5) 4'-hydroxy-PPX (LEA 142) was found only after iv and sc administration, 5) 2'-hydroxy-methyl LEA 103 (LEA 166) was seen prior to hydrolysis. These were assumed to be conjugated with glucuronide. At least 6 additional metabolites were seen in the HPLC trace. 2,6-xylidine was not observed.

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(41) G40 Astra Report 802 [illegible] AF 17-1, 1986-01-23. Biotransformation of LEA 103 in dogs. Elofsson S. Halldin M. [illegible]rin H. [140/1.35].

This study evaluated the excretion and metabolic pattern from a 15 minute iv (cephalic) infusion and sq (lower back) administration of ^{14}C-LEA 103 (batch OA 309/19) and ^{3}H-LEA 103 (batch OA 287/23) in four male beagle dogs (11.5-15.5 Kg body weight, age not indicated). Each dog received 10 μmol/Kg (3.3 mg/Kg) in the iv part of the study. In the sq evaluation, one dose of 10 μmol/Kg (3.3 mg/Kg) and one dose of 40 μmol/Kg (13.2 mg/Kg) were evaluated. A two week period separated each administration. The study was done by Astra, Sweden during September-October 1985. GLP/QAU statements were not present.

RESULTS

The accumulated mean percent of the dose excreted in the urine is indicated in the following table (from Tables 2-4, pp. 11-13):

	10 μmol/Kg IV			10 μmol/Kg SQ			40 μmol/Kg SQ		
Time	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total
24	47,5	9.7	57.2	35.3	3.5	38.8	47.4	10.3	57.7
48	52.2	13.9	66.1	46.9	11.3	58.2	65.2	23.1	88.3
72	54.4	14.6	69.0	50.2	13.2	63.4	66.8	24.2	91.0
96	56.1	14.8	70.9	51.6	16.6	68.2	67.7	25.7	93.4

Four metabolites plus unchanged LEA 103 (4%) were identified in the urine.

1) 3'-hydroxy LEA 103 (2% free, 11% conjugated)
2) 4'-hydroxy LEA 103 (2% free, 7% conjugated)
3) pipecolo-2',6'-xylidine (trace, tentative identification)
4) 6-oxopipecolo-2',6'-xylidide (4% free)

Most of the radioactivity was excreted within 48 hours following the iv and low dose sq administration. The high dose sq was 93% eliminated by 96 hours. In dogs the major route of elimination is by the urine.

(42) G37 Astra Report 802-550 LF-0212-01, 1994-03-01. Lack of metabolic racemization of ropivacaine in urine samples of man, dog, rat and sheep. Arvidsson T, Bredberg E, Forsmo Bruce H, Halldin M. [158/1.35].

This study looked at the interconversion of (S)-(-) LEA 103 in the rat, dog, sheep, and human (man) after iv, sq, or rectal administration. Enantiomers in urine samples were extracted, separated on a Chiral-AGP column, and detected at 210 nm. The urine samples were obtained from the following studies (Table 1, p.164):

	Astra	Test Substance		Formulation	
Species	Study N°	Batch N°	Ropivacaine	Type	Batch
Man	91Ro42 pt I	121/90	<0.2%	gel (10.2 mg/g)	1070-1-1
Man	90Ro27	112/89 OA614/10*	<0.2%	parenteral soln 2.5 mg/ml	470-22-2
Dog	LF9205	200/91 OA755/21*	<0.2%	gel 1%	100-7-1
Dog	LF9205	203/91 OA755/21*	<0.2%	parenteral soln	
Rat	LF9302	203/91 OA755/23*	<0.2%	parenteral soln	
Sheep	USLF9101	200/91	<0.2%	parenteral soln 4.78 mg/ml	1110-1-1

* ^{14}C labeled

a) (36) G35, male rats, iv administration
b) (40) G39, male and female dogs, iv administration
c) (25) G42, pregnant and nonpregnant ewes, iv administration
d) Astra report: 802-550-LC-0102-01, Study code 90Ro27, man iv administration

Racemization of ropivacaine has been shown to occur at pH 5.5 and 100°C but not below pH 3 [Fyhr P, Högström C, Acta Pharm Suec 1988, 25:121-132]. (R)-(+) ropivacaine hydrochloride monohydrate (LEA 104, batch OA 283/08) and (S)-(-)-ropivacaine hydrochloride monohydrate (LEA 103, batch 114/91 were the standards used in the study. Urine standards, containing 5-12 μmol/L (S)-(-) ropivacaine and 0.6% (R)-(+) ropivacaine, were treated the same as the urine samples. Conditions giving suitable resolution of the R and S isomers were pH 3 - 7.4, temperature 22°C to 55°C, 5%-6% v/v acetonitrile in the mobile phase, and 2-3 nmol of the S isomer in the sample. It was possible to determine < 0.2% of the R form under these conditions.

RESULTS

All of the samples assayed from the urine of the rat (iv and sq), dog (IVs, and rectal), sheep (iv), or human (iv) has less than 0.2%-0.3% (R)-(+)-ropivacaine. There was no evidence for the interconversion of the S-isomer of ropivacaine in this study.

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2. In Vitro

(43) G43 Astra Report 802-550 LF 0117-01, 1993-08-13. In Vitro metabolism of LEA 103 (ropivacaine) in liver microsomes prepared from male animals and man. Ekstrom G, Gunnarsson U-B. [174/1.35]

The object of this study was to determine the metabolic pattern of ^{14}C-LEA 103 in liver microsomal preparations from male NMRI mice, SD rats, NZW rabbits, beagle dogs, and from a 56 year old deceased male human renal transplant donor. After a 30 minute incubation, the preparations were extracted and analyzed by HPLC and UV detection. The isolated metabolites were analyzed by mass spectrometry.

RESULTS

There were four ^{14}C containing metabolites isolated from the human microsomal preparation. They were 1) LEA 145 (3'-hydroxy-LEA 103, 1%), 2) RAD 111 (PPX, pipicolo-2',6'-xylidide, 88%), 3) metabolite A, unknown structure, unstable, 5%, 4) B the hydroxyl or N-oxide of LEA 103, 6%. The mouse, rat, rabbit, and dog contained the above four metabolites plus LEA 144 (3'-hydroxy-LEA 103), metabolite C (unknown structure), and metabolite E (an unknown hydroxylated compound). Metabolite D was seen only in the rabbit preparation and was assumed to contain a keto group. PPX was the major metabolite in all preparations, followed by 3'-hydroxy-LEA 103. The quantitative picture of these metabolites was variable in these species. When compared to the in vivo data, 3'-hydroxy-LEA 103, 4'-hydroxy-LEA 103, and PPX were identified in this in vitro study.

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(44) G44 Astra Report 802-550 LF-0118-01, 1993-12-02. In vitro metabolism of LEA 103 (ropivacaine) in liver microsomes prepared from female animals, including the pregnant rat and man. Ekstrom G, Gunnarsson U-B. [195/1.35].

The purpose of this study was to evaluate the in vitro metabolism of ^{14}C-LEA 103 in liver microsome preparations from female mice, rats, pregnant rats, rabbits, dogs, and humans. Liver microsomes were obtained from female mice, rats, pregnant rats, rabbits, and from three female renal transplant donors. The incubation mixture contained 1 mg of protein, 1 mM LEA 103 containing $1x10^6$ dpm, and 0.75 mg NADPH in 50 mM Tris-HCl at pH 7.5 in a final volume of 1 ml.

RESULTS

The following table indicates the six to eight metabolites observed in the various species. In all species, the major metabolite was RAD111 (PPX, the depropylated LEA 103). LEA 145 was also a major metabolite in the rat, mouse, rabbit, and dog.

Metabolites of LEA 103 in Liver Microsomes (from Table 2, p.211)
(area expressed percent of total UV area)

Compound	Rat (n = 5)	Rat (n = 1) pregnant	Mouse (n = 5)	Rabbit (n = 5)	Dog (n = 1)	Human (n = 3)
	%	%	%	%	%	%
LEA 144	4	2	4	2	2	1

Compound	Rat (n = 5)	Rat (n = 1) pregnant	Mouse (n = 5)	Rabbit (n = 5)	Dog (n = 1)	Human (n = 3)
LEA 145	56	58	23	15	9	1
RAD 111	21	22	50	60	38	88
A	1	6	5	4	3	3
B	9	6	6	5	41	5
C	3	3	8	8	6	
D	4		2	2		
E	2	2	1	4	2	2
SUM	100	99	99	100	101	100

When the HPLC separation was run at temperatures higher than 45° C, metabolite E was not observed. This metabolite was identified in study G47 as being hydroxylated at one of the methyl groups on the aromatic ring.

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(45) G45 Astra Report 802-550 LF-0183-01, 1994-02-17. In Vitro metabolism of LEA 103 (ropivacaine) in microsomes prepared from lung and kidney of male and female rats. Ekstrom G, Gunnarsson U-B . [217/1.35].

The object of the study was to determine the metabolic pattern of LEA 103 in microsomal preparations from the lungs and kidneys of male and female rats.

Microsomes were prepared from the kidneys and lungs of male and female Sprague-Dawley rats. Incubations were carried out with 1 mmol LEA 103 (batch F13) containing $1x10^6$ dpm ^{14}C-LEA 103 (LRB002) for 30 minutes at 37°C and pH 7.5 in the presence of 1 to 6 mg of microsomal protein and 0.75 mg NADPH in 50 mmol Tris-HCl pH 7.5. After extraction of the incubation mixtures, the metabolites were isolated and detected by HPLC-UV. The study was done by Astra, Sweden during September-December 1993. GLP/QAU statements were present and signed.

RESULTS

Eleven metabolites were found in the lung and kidney, eight of which have been seen in the rat liver microsomal preparations of earlier studies. Three new metabolites (F, G, and H) were seen in the lung and kidney preparations. The following table indicates the amount of each metabolite, expressed as percent of the total area of all metabolites (from Table 1, p. 230).

Metabolite	Kidney Male Percent	Kidney Female Percent	Lung Male Percent	Lung Female Percent
LEA 144	-	-	0.2	-
LEA 145	18.4	12.3	3.6	6.6
RAD 111	12.2	11.6	14.5	12.2
LEA 166	15.9	14.2	18.2	21.1
A	1.1	1.7	10.6	10.3
B	10.5	11.3	32.3	30.1
C	3.6	4.3	9.4	7.4
D	11.7	9.9	3.5	2.6
F	14.5	27.5	7.5	9.6
G	11.9	7.3	-	-
H	-	-	-	-
Total:	100.0	100.1	100.0	99.9

Metabolite H was not possible to separate, due to other metabolites in the chromatogram. In addition to the above metabolites, LEA 103 was also seen as the largest peak in the HPLC tracings. This study found identical metabolites in kidney and lung microsomal preparations as were seen in liver, but quantitative differences were obvious.

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(46) G46 Astra Report 502-550 LF-0173-01, 1993-12-20. Evaluation of the contribution of cytochrome P4502D to the metabolism of LEA 103 (ropivacaine). Ekstrom G. [234/1.35].

This study looked at the involvement of cytochrome P4502D (CYP2D) in the metabolism of LEA 103. The drug was incubated with liver microsomal preparations from male and female Dark Agouti rats, as they have an impaired ability to metabolize debrisoquinone [Al-Dabbagh SG,, et al., J Pharm Pharmacol 1981;33:161-164]. Sprague-Dawley rats were also used in the study. The incubation conditions used in study G46 were followed. An isocratic HPLC system was used to isolate parent drug and metabolites. The study was done by Astra, Sweden and dated 12/20/1993. GLP/QAU statements were not present.

RESULTS

A significant reduction occurred in the amount of 3'-hydroxy-LEA 103 (LEA 145) obtained from Dark Agouti rat preparations, as compared to the hydroxylation seen in the SD rat preparation. This 3'-hydroxylation was inhibited by 50 to 100 μmol of propranolol added to the incubation mixture. No reduction occurred in the amount of hydroxylation of LEA 144 (4'-hydroxy-LEA 103) or hydroxylation at the aromatic methyl group. No decrease occurred in the amount of RAD 111 (PPX) produced. The amount of observed LEA 145 and PPX was sex dependent, with higher levels occurring in females. The sponsor concluded the 3'-hydroxylation was probably catalyzed by CYP2D.

(47) G47 Astra Report 802-550 LF-0172-01, 1993-12-06. Identification of a new metabolite formed from LEA 103 (ropivacaine) that is hydroxylated in the ortho methyl group (LEA 166). Ekstrom G. 248/1.35].

This study was undertaken to determine the structure of metabolite E seen earlier in vitro and in vivo metabolism studies of LEA 103. $^{2}H_{3}$-LEA 103 and $^{2}H_{7}$-LEA 103 were incubated with liver microsomal preparations from NZW rabbits. Incubation conditions described in G45 were followed. An isocratic HPLC with a GC-UV-MS-NMR system was used to separate and detect metabolites. Astra, Sweden did the study in 12/6/93. GLP/QAU statements were not present.

RESULTS

Metabolite E was identified as LEA 103 hydroxylated on the aromatic methyl group. It has been designated as LEA 166 in the above metabolism studies. In addition, Metabolites A, B, and C were also observed.

Summary and Evaluation of Pharmacology

LEA103 [S-(-)-1-Propyl-2', 6'-pipecoloxylidide HCl H_2O; ropivacaine] is a new, long acting, local anesthetic agent of the amide type. The pharmacological and toxicological activity of ropivacaine [S-(-)-ropivacaine hydrochloride monohydrate] parallels that of bupivacaine. Its primary pharmacological applications include epidural anesthesia for the management of postoperative pain, labor pain, and surgical anesthesia. The local anesthetic block of ropivacaine, as with other structurally related local anesthetics, is presumably due to its ability to increase the threshold for electrical excitation in the nerve, by reducing the rate of rise of the action potential, and by slowing the propagation of the nerve impulse.

In studies comparing ropivacaine and bupivacaine in sensory and motor sciatic nerve block in guinea pigs, the mean onset of sensory blocks were similar between ropivacaine and bupivacaine over a 2.5-10 mg/ml dose range. The R-(+) isomer had a similar onset time. The duration of the motor block was also similar, with bupivacaine showing a significantly longer duration at the lower doses. With the addition of 5 µg/ml of epinephrine to these dosages, prolongation of the block duration occurred with both ropivacaine and bupivacaine. R-(+)-ropivacaine also had a shorter duration of block than ropivacaine. 3-Hydroxy-ropivacaine and 4-hydroxy-ropivacaine, the metabolites, were shown to have some local anesthetic activity.

In sensory and motor brachial plexus block, no significant differences were seen in block onset, sensory block, or motor block with 5 or 7.5 mg/Kg doses of either ropivacaine or bupivacaine. The addition of 5 µg/ml of epinephrin significantly prolonged the motor block with 7.5 mg/Kg of ropivacaine or bupivacaine. Lidocaine had a much

shorter block duration.

Lumbar spinal anesthesia block in mice following a single injection was significantly prolonged with bupivacaine when compared at the same concentrations (2.5 - 10 mg/ml) to ropivacaine. In dogs, the time to onset was greater with ropivacaine than bupivacaine at 7.5 mg/ml. At higher doses, changes were not equivalent. With repeated intrathecal doses administered to rats, rapid absorption occurred, followed by rapid elimination. The systemic availability was estimated to be 72% and 102% after single and multiple injections, respectively.

Epidural anesthesia was studied in guinea pigs, dogs, sheep and monkeys. The duration of sensory and motor block in guinea pigs without and with 10 μg/ml adrenaline were significantly longer with bupivacaine than with ropivacaine at equal mg/ml doses. In dogs, no significant differences were seen between ropivacaine (10 mg/ml) and bupivacaine (7.5 mg/ml) in the incidence, time to onset, duration of block, or time to recovery. Complete recovery was less with ropivacaine than with bupivacaine at all concentrations, with or without epinephrine. In sheep, no significant differences occurred between ropivacaine and bupivacaine in the onset of sensory or motor block; however, the time to complete recovery from the motor block was significantly longer for bupivacaine at 5 and 7.5 mg/ml. The results with monkeys were similar to those in the dog.

The data from the infiltration anesthesia study in guinea pigs showed the duration of complete block to be longer with ropivacaine than with bupivacaine at % concentrations, without and with 5 μg/ml epinephrine. The time to complete recovery was also longer and significant with ropivacaine.

Corneal anesthesia in rabbits indicated no differences with % concentrations in the duration or time of onset of block with ropivacaine and bupivacaine.

In studies comparing R-(+)-ropivacaine, S-(-)-ropivacaine, and RS-(±)-ropivacaine, the S enantiomer produced a longer duration in local anesthesia than the racemate or the R enantiomer, and when compared with bupivacaine, ropivacaine produced a longer block, although not always significant at the equivalent molar dose. In the spinal anesthesia studies (mice, rats, and dogs), the duration of motor block was significantly greater with bupivacaine than with ropivacaine at the same mg/ml dose.

In vitro conduction block studies were run with frog sciatic nerves, rat vagus and phrenic nerves, and rabbit vagus nerves. The action potential blocking activity of ropivacaine and bupivacaine were equal in the frog sciatic nerve from 1 μM to 50 μM. All blocks were reversible within 2 hours. The action potential amplitudes of rat vagus and phrenic nerves were reduced with concentrations of μM. Conduction block in rabbit vagus nerves (A fibers) with ropivacaine was somewhat less with ropivacaine, compared to equal concentrations of bupivacaine. No differences were found between ropivacaine and bupivacaine on C fibers. The ED_{50} values were larger for ropivacaine

than bupivacaine; lidocaine values were two to four times larger than ropivacaine ED_{50} values.

To conclude, the above studies indicated that ropivacaine is similar to bupivacaine in its pharmacological activity as a local anesthetic. Ropivacaine was not comparable to lidocaine in many of the preclinical studies.

Summary and Evaluation of Acute, Subchronic, and Chronic Toxicity Studies.

Intravenous and subcutaneous acute studies in mice and rats produced decreased motor activity, irregular breathing, piloerection, tremors, ataxia, clonic convulsions, and death, which occurred during or following shortly after ropivacaine administration. When comparing ropivacaine, bupivacaine, or lidocaine in iv or sq lethality studies, mortality was of the order bupivacaine > ropivacaine > lidocaine. All mortality was due to convulsions, but all convulsions did not lead to mortality. Further, the duration of convulsions were not changed with the addition of 1-2.5 μmol/Kg epinephrine. There appeared to be little difference in mortality between each enantiomer and racemic ropivacaine. The estimated fifty percent mortality range seen in mice was μmol/Kg sq and μmol/Kg iv. In rats these values were μmol/Kg sq and μmol/Kg iv.

Repeat sq studies were conducted in rats for 2 weeks and 1 month. Ropivacaine produced small ulcerations and incrustations with all sq doses (10-90 μmol/Kg sq x 2 weeks). Mortality occurred at 90 μmol/Kg (30 mg/Kg). The one month sq study in rats (10-80 μmol/Kg, 3.3-26 mg/Kg) produced short clonic convulsions and cyanosis at 80 μmol/Kg. Other changes were increases in cholesterol and calcium and decreases in potassium and magnesium. No gross pathology was reported, and no histopathologic lesions were seen in the heart.

Repeat sq studies in dogs were conducted for 3 days and 1 month. A 6 month sq concomitant rectal administration was also evaluated. The 3 day study (5-50 μmol/Kg, 1.6-16.4 mg/Kg) reported neurologic signs - muscular tonus, rigid movements, mild body tremors, ataxia, and urinary incontinence, and periodic clonic convulsions. No arrhythmias were reported; however, irregular or occasional changes in PR and QRS deviations were seen but were said to be within the normal range. Periodic clonic convulsions occurred in one dog dosed at 50 μmol/kg. These same dogs were doses with bupivacaine (5-50 μmol/Kg, 1.6-16.2 mg/Kg) following a 5 day dose free washout. Severe body tremors occurred at the high dose. Irregular/occasional changes in PR and QRS that occurred were said to be within the normal range. Severe convulsions occurred in two dogs dosed at 50 μmol/kg bupivacaine. The one month sq study (10-40 μmol/Kg, 3.3-13.2 mg/Kg LEA103) produced most of the same toxic signs. The EKGs picked up deviations in the QRS axis in 1 or 2 dogs at 20 and 40 μmol/Kg, but all were said to show normal sinus rhythms. The ropivacaine no effect dose was 20 μmol/Kg (6.6 mg/Kg). The sq/rectal administration (10-40 μmol/Kg sq plus 320-1300 μmol/Kg LEA103

rectal) resulted in a dose related increase in feces and itching at the sq site. Hb, RBCs, and PCV was decreased at 20 and 40 μmol/Kg. There were some changes in the lungs (inflammatory changes), urinary bladder (inflammatory changes and focal hemorrhage), pyelitis in all drug groups in the kidneys, liver (inflammatory changes and foci of mononuclear cells), and inflammatory changes in the anal canal. Individual variables were recorded in the EKGs, but not presumably related to the treatment.

Cardiovascular Toxicity Summary

In study (19) F20, the addition of 1.4 μg/Kg of epinephrine to 2.5 mg/Kg ropivacaine iv increased the mean arterial pressure, the PQ/QT/ QRS values, and decreased the heart rate above those values reported for 2.5 mg/Kg ropivacaine without added epinephrine. Singular ectopic beats and 2° AV blocks were present in both groups. Sustained complex arrhythmias, pulmonary edema, convulsions, and deaths were present in the ropivacaine only group. With added epinephrine, convulsions, pulmonary edema, complex arrhythmias, and mortality resulted. The toxicity increased further with increasing amounts of added epinephrine. Deaths were attributed to pulmonary edema and or ventricular arrhythmias.

In study (20) F29, iv doses required to cause convulsions in six conscious nonsedated dogs - 14.64 μg/Kg (4.88 mg/Kg) for ropivacaine, 13.69 μg/Kg (4.31 mg/Kg) for bupivacaine, and 82.59 μmol/Kg (20.84 mg/Kg) for lidocaine- indicated that bupivacaine was more cardiotoxic than ropivacaine. There were no deaths in any group with convulsive doses. Ventricular arrhythmias were of a greater frequency with bupivacaine than with ropivacaine; no ventricular arrhythmias occurred with lidocaine. Seizure duration was somewhat longer with bupivacaine than with ropivacaine or lidocaine. At 2x the convulsive dose, 1/6 of the ropivacaine and 5/6 of the bupivacaine animals died. There was a greater occurrence of ventricular arrhythmias in the bupivacaine group, with one dog progressing to ventricular fibrillation. No arrhythmias occurred at this dosage in the ropivacaine or lidocaine animals.

Study F30 (Astra Report 802-50 AF 118-1, 1992-09-02; P 186, Vol 1.25) reports on the treatment of the acute toxicity produced from rapid iv administration of ropivacaine or bupivacaine in conscious dogs. No ventricular arrhythmias were observed with 4.9 mg/Kg ropivacaine or 4.3 mg/Kg bupivacaine, both of which are doses producing convulsions. At 2x the convulsive dose, all 5/6 developing convulsions in the ropivacaine group survived, while two of the 4/6 that developed convulsions in the bupivacaine group could not be saved by intervention. Cardiovascular toxicity and resuscitation was further evaluated in anesthetized dogs (study F 34, Astra Report 802-50 AF 67-1, 1987-01-08; P 92, Vol 1.26). Resuscitation was initiated when the systolic BP was <45 mm Hg. The results indicated no great differences in cardiovascular toxicity, mortality, or resuscitation results. Resuscitation required rapid control of the hemodynamic changes and acidosis.

No significant difference in the convulsive dose was seen in the iv infusion study conducted in pregnant and nonpregnant sheep. Doses producing hypotension,

respiratory arrest, or circulatory collapse were similar in both groups. Mean concentration of ropivacaine in the heart and brain were also not significantly different between the two groups, although the mean values were somewhat higher in the pregnant animals. An earlier study (Morishima, HO, et al, Anesthesiology 1985;63:134-139) reported that doses of bupivacaine required to produce equivalent toxic signs in pregnant sheep were greater than in nonpregnant sheep.

Summary and Evaluation of Reproductive Toxicology Studies

Reproduction studies were performed in rats and rabbits. The daily subcutaneous administration of LEA103 (up to 23 mg/kg) to male Sprague-Dawley rats for 9 weeks before mating and during the mating period, and to female rats for 2 weeks before mating and 42 days post coitus did not effect the mating rate, the conception rate and the length of gestation. An increased number of pups (~25%) were found dead within 3 days post parturition in the high dose group (28→23 mg/kg - 84→71 μmol/kg). There was no significant pup loss after day 3 in any group. Similar results have been obtained with a pharmacologically closely related compound, bupivacaine, at 30 mg/kg (25% loss in pups when compared with controls).

The increase in pup loss in this segment I reproductive study, but not in segment III (peri-and postnatal) study may be due to a longer period of dosing before delivery in segment I (~35 days compared with 6-7 days). As it is also mentioned in the Pharmacokinetic section, subcutaneous administration of 26 mg/kg LEA103 for 10 days showed 25-35% increased plasma concentration compared with single administration in both pregnant and nonpregnant rats (Astra Report 802-50-AF90-2, 1988-09-26). There were no differences in body weight gain or food consumption between pups in the control and treated groups. The reproduction capacity of the F1-generation was the same in all the groups. The F2-generation did not show intergroup differences in body weights, litter size and pup loss in this multigeneration (segment I) study in rats. Therefore, this increase in pup loss may be due to impaired maternal care of the pups caused by an increased plasma concentration of LEA103 in the high dose group.

During the teratology study, daily doses of 16, 32 and 81 μmol/kg (5.3, 11.0 and 26.0 mg/kg) of LEA103 given subcutaneously on days 6-15 of pregnancy in rats did not effect body weight gain, food consumption, preimplantation loss, fetal loss and fetal weights. Plasma half-life was similar in all three groups, about 1.7 hours on day 6 and about 2.4 hours on day 15. The placental transfer of labelled LEA103 was linear with a fetal tissue/maternal blood ratio of 45%, 50% and 46% after 16, 32 and 81 μmol/kg administration, respectively. The corresponding values in the amniotic fluid were 17%, 22% and 21%, respectively. LEA103 at dose levels of 16, 32 and 81 μmol/kg/day during days 6-15 of pregnancy did not effect organogenesis and early fetal development in Sprague-Dawley rats.

LEA 103, similar to other local anesthetic agents such as lidocaine, mepivacaine

and bupivacaine, crossed the placenta and reached the fetal circulation in pregnant rabbits during the dose range finding teratology study. Daily doses of 1.3, 4.2, and 13 mg/kg/day (corresponding to 4, 13 and 39 μmol/kg) in rabbits on days 6-18 of pregnancy did not produce any mortality but produced lack of one kidney in two animals in the high dose group. Major skeletal defects (unossified vertebral arches and skull) were found in one pup in the low dose group, two pups in the medium dose group and two pups in the high dose group.

Daily doses of LEA up to 11 mg/kg (32 μmol/kg) from day 15 of pregnancy to day 21 post parturition did not cause adverse effects on the dams or on the litters during peri- and postnatal development in rats. However, two mortalities seen at 26 mg/kg (81 μmol/kg) might be due to test compound. The high dose did not effect the delivery, lactation or litters.

During a comparative peri- and postnatal study in S-D rats, daily administration of LEA131 (bupivacaine) at 43 or 53 μmol/kg from day 15 of gestation until day 21 post parturition produced piloerection, increased salivation, chewing, irregular breathing and clonic convulsions. The onset of these signs was ~10 minutes after dosing and continued up to 5 hours. No toxicological signs were noticed in any animal receiving LEA103 (ropivacaine) up to 75 μmol/kg/day (25 mg/kg). There were no intergroup differences in litter size, litter weight, mean pup weight, and physical development (pinna unfolding, tooth eruption, eye opening). The peak plasma concentration (C_{max}) after the administration of LEA103 or LEA131 was reached within the first sampling interval (30 min). The AUC and C_{max} values on day 20 showed a tendency to increase linearly with dose for both drugs. Equimolar doses of LEA103 and LEA131 gave similar PK values. This indicates that LEA103 was less toxic in the pregnant rats than LEA131.

Summary and Evaluation of Genotoxicology Studies

Mutagenicity studies were conducted in the following tests: 1) Ames Salmonella/mammalian microsome mutagenicity test, 2) mouse lymphoma test, 3) E. coli differential DNA repair test *in vitro*, 4) analysis of structural chromosome aberration in human lymphocytes, 5) mouse micronucleus test, 6) E. coli host-mediated DNA repair test in mice, and 7) somatic mutation and recombination test in Drosophila melanogaster. Of the above tests, the mouse lymphoma test was positive in the presence of S9 metabolic activation. When the test was repeated using Fisher's medium as the solvent, rather than DMSO as in the first one, the study was positive in the presence of metabolic activator. Hence, it is concluded that ropivacaine is mutagenic in the mouse lymphoma assay. All other test conducted to evaluate mutagenicity were negative.

Summary and Evaluation of ADME Studies

In pregnant and nonpregnant sheep, the PK data resulting from iv administration of ropivacaine followed the trends seen with bupivacaine in pregnant and nonpregnant sheep; however, with all parameters that were compared, the values for ropivacaine were lower. Serum concentrations of ropivacaine were higher in pregnant sheep and protein binding was slightly higher. After epidural administration of ropivacaine and bupivacaine to female sheep, the AUC and $t_{\frac{1}{2}}$ values were lower with ropivacaine.

Ropivacaine was rapidly distributed in rats to the tissues following iv administration. The elimination half-life for ropivacaine in the various tissues ranged from 0.57 hours in the heart to 1.27 hours in the kidney. The radioactivity half-life, however, was 2.9 to 19.1 hours ; the $t_{\frac{1}{2}}$ in the heart was 15 hours. Radioactivity was also detected in the milk of lactating rats. Ropivacaine was 90% bound to serum protein in the rat. In mice, high levels of radioactivity were in the brown fat, nasal mucosa, gastric mucosa, wall of the eyeball (melanin tissue), adrenals, islets of Langerhans, and kidney. High levels of radioactivity could be detected in the melanin containing layer in the retina of mice even after 32 days. In dogs, radioactivity was distributed throughout the body following sq administration. The highest radioactivity was seen in the liver, followed by the kidney and spleen. Tissue half-life for radioactivity was longest in the eyes and pigmented skin (17 days). Pharmacokinetic data for amide-type local anesthetics in dogs after iv infusion (Anesth Analg 1988:67:1053-8) are given below..

	Ropivacaine	Bupivacaine	Mepivacaine	Lidocaine	Etidocaine
$t_{1/2\beta}$ (min)	26	39	45	46	60
V_{ss} (L/kg)	1.1	1.2	1.9	2.3	3.4
Cl (ml/min/kg)	41	32	39	56	58

Urine and feces recovery of administered radioactive ropivacaine in dogs by the end of 30 days was 72% and 27%, respectively. In pigmented mice the urine and feces distribution was 34% and 53%, respectively. The distribution in rats was 42% in the urine and 52% in the feces.

Ropivacaine's metabolic profile has been studied in mice, rats, rabbits, dogs, and sheep. Urinary metabolites that have been isolated are the 3-hydroxy-ropivacaine and its glucuronide, 4-hydroxy-ropivacaine and its glucuronide, N-despropyl-ropivacaine (PPX), 6-oxo-PPX, and 3-hydroxy-PPX. In addition to the *in vivo* metabolite studies, *in vitro* studies were also evaluated with liver microsomes from animals and humans. Metabolic activity is rapid in the liver. Only small amounts (1-3%) of ropivacaine are excreted unmetabolized following iv or sq administration to male rats There was no evidence for the interconversion of the S-(-) to the R-(+) isomer of ropivacaine in the rat, dog, sheep or human.

Overall Summary and Evaluation

LEA-103 (ropivacaine HCl monohydrate, Naropin™) is a new, long-acting, amide-type, local anesthetic agent with pharmacological properties similar to those of bupivacaine (Marcaine) and mepivacaine (Carbocaine). Unlike these agents, which are racemic mixture, ropivacaine is exclusively the S-(-) enantiomer. The S-(-) form is less toxic and/or has a longer duration of action than the R-(+) form.

Ropivacaine has been shown to be a local anesthetic agent similar in activity to bupivacaine in conduction, infiltration, and topical anesthesia. It is active in peripheral neural block and as a central neural blocker. At equivalent or near equivalent doses, ropivacaine produced longer blockade. Toxicity in general is less with ropivacaine than with equivalent doses of bupivacaine. Of concern is cardiotoxicity, as this drug is of the same class as bupivacaine. The submitted studies reported less cardiotoxicity with LEA103 compared to bupivacaine. However, with high iv doses this drug will produce cardiovascular toxicity similar to that reported for bupivacaine. Of additional interest is the toxic effect of the drug during pregnancy. Those studies comparing ropivacaine toxicity in pregnant and nonpregnant sheep indicated no increase in toxicity in pregnant ewes.

Ropivacaine at dose levels up to 26 mg/kg/day subcutaneously did not effect fertility, general reproductive performance, teratology, perinatal and postnatal development in S-D rats. Teratogenicity studies in rabbits did not effect organogeneris or early fetal development at dose level up to 13 mg/kg. Ropivacaine was positive in the mouse lymphoma test in the presence of metabolic activation, but other mutagenicity assays were negative.

Ropivacaine rapidly distributes to most organs, particularly to the liver, heart, brain, and lungs. High concentrations of radioactivity remain in the pigmented tissues after administration of labeled drug. Radioactivity passes the blood brain and placental barriers and is found in the milk of lactating rats and in fetal tissue. There is little unmetabolized ropivacaine excreted. It is extensively metabolized and excreted in the urine and feces, the proportion varies with the species. Ropivacaine's principal metabolite is 3-hydroxy-ropivacaine, which is excreted mainly as the glucuronide. Other metabolites include 4-hydroxy-ropivacaine, the N-despropyl-ropivacaine, 2-hydroxy-methyl-ropivacaine, and several other minor metabolites. 3-hydroxy-and 4-hydroxy-ropivacaine have shown some local anesthetic activity. Ropivacaine is not interconverted to the R-(+) enantiomer.

Recommendations

This NDA is approvable from the pharmacology/toxicology point of view with the following changes in the labeling under:

Anwar Goheer

Will Coulter

Concur by peer reviewer:

Lucy Jean Nov. 8, 1995

Statistical Review

Statistical Review and Evaluation—Addendum

NDA 20-533
Name of drug: Naropin (ropivacaine HCl monohydrate)
Applicant: Astra USA
Indication: Local anesthetic for epidural injection for surgery, labor, and postoperative pain; local infiltration for postoperative pain; peripheral nerve block
Documents reviewed: volume 4.2, 25 August 1995
medical officer review by R. Bedford, 16 November 1995
fax correspondence (draft labeling), 12 July 1996
Reviewer: Thomas Permutt
Date review completed: 17 July 1996

This is a review of a study report submitted as part of a safety update but used to substantiate a labeling claim. The proposed labeling is as follows:

Pooled analysis of studies in labor and delivery was prospectively specified, and the six studies were of similar design. Mantel-Haenszel tests for categorical outcomes and stratified

Wilcoxon tests for continuous outcomes were specified, stratified by study and by parity of the mother. These methods are appropriate.

Twelve different measures were proposed in the protocol, including those in the table and several measures of neonatal status (Apgar and NACS scores). None were described as primary. Insofar as this analysis is directed at safety, it is appropriate to cast a broad net. On the other hand, a comparative claim raises concerns about multiplicity.

No statistically significant differences were found in the neonatal status measures. The first sentence quoted above accurately represents this finding. On the other hand, a significant difference was found with respect to modes of delivery, which is presented in the table. The particular comparison pointed out as statistically significant was one chosen from many. However, the p-value is small enough to allay concerns of spurious significance. Furthermore, the presentation of the table makes it reasonably clear that the comparison is a selected one. Also, the reviewing medical officer found the effect plausible: "It is possible that better motor strength in the mothers receiving ropivacaine improves their chances of delivering spontaneously."

The labeling in question fairly reports a finding of potential significance to practitioners. I recommend it be accepted.

Thomas Permutt

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concur:
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archival: NDA 20-533
cc:
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HFD-720/S. Moore (file copy, chron. copy)
HFD-170/D. Morgan
HFD-170/B. Palmisano
HFD-170/L. Landow
HFD-170/T. Permutt
HFD-170/division file

Statistical Review and Evaluation

NDA 20-533
Name of drug: Naropin (ropivacaine HCl monohydrate)
Applicant: Astra USA
Indication: Local anesthetic for epidural injection for surgery, labor, and postoperative pain; local infiltration for postoperative pain; peripheral nerve block
Documents reviewed: volumes 1.1, 1.85, 1.87, 1.106, 1.118, 1.130-1.134, 1.142-1.149, 1.165, 1.185, 29 March 1995; electronic data sets; correspondence dated 19 September 1995
Reviewer: Thomas Permutt
Date review completed: 11 October 1995

Introduction

Ropivacaine is a new local anesthetic chemically and pharmacologically similar to the widely used drug bupivacaine. The draft labelling proposes the same indications as bupivacaine: epidural administration for surgery and labor and peripheral nerve block. In addition, a new indication for postoperative pain management by epidural administration or local infiltration is proposed.

The NDA lists 49 controlled clinical trials. For some indications the effectiveness of ropivacaine is clearly demonstrated in a single study. In these cases one such study is reviewed in detail, even though there may not be any clear reason to prefer one study to another. These single studies in different indications are also mutually supportive insofar as the action of the drug is similar, so that the requirement for adequate and well-controlled studies is amply met. In other indications a clearer picture of the action of ropivacaine emerges from an overview of several studies.

In most of the indications, placebo-controlled trials would be impracticable or unethical. In these cases ropivacaine was appropriately compared to a standard drug, bupivacaine. In some studies additional evidence of efficacy emerges from the dose response to ropivacaine. In the postoperative pain indication, placebo-controlled designs with effective rescue medications were appropriately used.

Ropivacaine was an effective local anesthetic for the indications studied, with a qualification for peripheral nerve block. In peripheral nerve block it was still approximately as effective as bupivacaine, but the results were unsatisfactory in more than a quarter of patients in all but one study.

Some statistical aspects of safety are addressed in this review. In particular, a potential claim of less toxicity than bupivacaine does not appear to be justified by the clinical data. Other safety considerations pose no special statistical problems and are addressed in the medical officer's review.

Orthopedic Surgery--Study K9

The NDA lists nine studies of epidural anesthesia for orthopedic surgery. The largest of these studies (K9) compared three different doses of ropivacaine to bupivacaine, so that evidence of effectiveness comes from the dose response as well as from the comparison to a standard drug. Study K9 was a randomized, double-blind, parallel-group comparison of ropivacaine (20 ml×0.5, 0.75, or 1.0%) and bupivacaine (20 ml×0.5%) for elective hip surgery. Three centers in the Netherlands and Denmark enrolled 126 patients aged 22 to 80 (median 65). Women numbered 58 percent of the patients. Race appears not to have been recorded.

Ropivacaine or bupivacaine was injected into the epidural space through a catheter. At intervals thereafter, patients were pricked with a needle in various places, and it was recorded whether they felt pain. Different regions of the skin, called dermatomes, are associated with different parts of the spine and named for the associated vertebrae. For example, the primary criteria of efficacy (according to the protocol) involved analgesia at the level of the ninth thoracic vertebra (T9). In particular, efficacy criteria were whether analgesia at this level was achieved on both sides of the body and, if so, when it began and how long it lasted. There was also a global assessment by the physician of the acceptability of anesthesia and muscle relaxation.

A "per protocol" and an "all patients treated" analysis were specified in the protocol. These analyses actually differed in respect of only one patient, who was treated but was afterward found not to have met the inclusion criteria of the protocol, being 1 kg underweight. There being no material difference, discussion will focus on the "per protocol" analysis. Both these analyses, however, excluded 10 patients classified as "technical failures." These were cases in which no analgesia was achieved because, in the investigator's judgment, the epidural catheter was incorrectly placed (and one additional case in which no drug was given because a dural puncture was noted before injection). Technical failures were to be excluded from analysis and replaced by new recruits assigned the same treatment. Theoretically, this is not a very sound design. It is possible that a drug that was ineffective in some patients would have those patients replaced, so that it would appear quite effective in all patients analyzed. Furthermore, the assignment of additional patients to the same treatment as the withdrawn patients can raise some doubts about effective blinding. Practically, however, these considerations raise no concerns about the interpretation of this study. Technical failures are

inescapable in epidural anesthesia; they were not numerous; they were evenly distributed across treatment groups; and there is no reason to believe ropivacaine would be completely ineffective in some patients.

No measurements were recorded at the dermatome T9 specified in the protocol, so the sponsor considered the measurements at T10 to be the primary measures of efficacy. Bilateral analgesia was achieved at this level in almost all patients ("per protocol" analysis):

	analgesia at T10	no analgesia at T10
Ropivacaine 0.5%	28	1
Ropivacaine 0.75%	29	0
Ropivacaine 1.0%	28	1
Bupivacaine 0.5%	25	3

Measurements were also made at several other dermatomes. The frequency of analgesia was highest at dermatomes associated with the lumbar region, where the drug was injected, and lowest far away in either direction. There were no consistent differences between treatment groups with respect to this primary measure of outcome. The median time to onset of analgesia at T10 was approximately 10 minutes in each treatment group.

There was a statistically significant dose response ($p < 0.0001$, analysis of variance with center and center-by-treatment interaction terms) to ropivacaine with respect to the duration of analgesia at T10. The median duration was 5.8 hours with ropivacaine 1.0%, 4.2 hours with ropivacaine 0.75%, and 3.8 hours with ropivacaine 0.5%. The median duration for bupivacaine (which was not included in the dose-response analysis of variance) was 4.3 hours. In pairwise comparisons between bupivacaine and each dose of ropivacaine (unadjusted for multiple comparisons), only ropivacaine 1.0% was significantly different ($p = 0.02$, rank-sum test) from bupivacaine.

At least some motor block was also achieved in most patients:

	degree		
Motor block of at least . . .	1	2	3
Ropivacaine 0.5%	21/28	7/26	3/25
Ropivacaine 0.75%	24/29	13/28	7/28
Ropivacaine 1.0%	25/29	21/29	16/28
Bupivacaine 0.5%	22/28	14/27	8/27

The sponsor reported no significant dose response for motor block and no significant differences between ropivacaine and bupivacaine, based on preplanned comparisons at degree 1. However, there was a clear difference between doses of ropivacaine, and between ropivacaine 1.0% and bupivacaine, with respect to more profound motor block. Some difference in duration was also noted: motor block of any degree, among patients who had it, lasted about 1 hour longer with ropivacaine 1.0% than with bupivacaine.

The overall quality of anesthesia was rated satisfactory in most cases in all treatment groups. The following table classifies as "satisfactory" all cases where the rating was simply "satisfactory" as well as cases judged "satisfactory until . . ." provided that the satisfactory period was at least 2 hours.

	satisfactory	unsatisfactory	not applicable
Ropivacaine 0.5%	19	6	4
Ropivacaine 0.75%	23	6	0
Ropivacaine 1.0%	26	1	2
Bupivacaine 0.5%	20	7	1

There was a statistically significant dose response for ropivacaine ($p = 0.05$, Mantel-Haenszel test for trend) and a significant difference between bupivacaine and the highest dose of ropivacaine ($p = 0.05$, Fisher's exact test, unadjusted for multiple comparisons). As the

sponsor points out, these tests ignored the "not applicable" category, which in fact consisted of patients in whom analgesia was so unsatisfactory that other anesthetics were given, so that they would more appropriately be considered "unsatisfactory"; this would slightly strengthen the dose-response relationship, but slightly weaken the comparison with bupivacaine. Muscle relaxation was also generally satisfactory, but no differences among treatment groups were detected.

There is some indication from animal studies that the toxic dose of ropivacaine may be about 30% higher than that of bupivacaine. I have not reviewed those studies, and I do not comment on the validity of this finding. If it is true, the question remains whether ropivacaine in use is likely to be less toxic than bupivacaine. This would depend on the relative potency of the two compounds. This study shows that ropivacaine and bupivacaine at equal doses have roughly similar effects, and allows rough estimation of the dose response for ropivacaine. However, the relationship of response to dose in the region tested is rather flat, so that even small uncertainties in the response at a given dose translate into large uncertainties in the dose for a given response. In particular, only at 1.0% was ropivacaine confidently found to be more effective than bupivacaine 0.5% on any criterion (duration of analgesia). Thus, it can be stated with confidence that the equivalent dose of ropivacaine is no more than twice that of bupivacaine; but if the toxic dose is only 30% more, the question of relative toxicity in use remains unanswered.

This study provides substantial evidence of the safety and efficacy of ropivacaine as an epidural anesthetic.

Cesarean Section—Study M2

The NDA lists five studies comparing ropivacaine and bupivacaine as epidural anesthetics for cesarean section. All these studies appear to be mutually supportive, and there is no clear reason to think of any one of them as pivotal. Nevertheless, one study (M2) will be reviewed in detail. An earlier part of this study was an open-label, uncontrolled study. This review refers to "Part B," a randomized, double-blind, single-center (U.S.) comparison of ropivacaine and bupivacaine, each at concentration 0.5% and volume 30ml.

Of the 69 women enrolled, 4 were excluded from analysis as technical failures and 2 as protocol violations. The patients ranged in age from 19 to 41 (median 34). Whites comprised 80 percent, blacks 11 percent, and others 9 percent.

Measures of efficacy were similar to those in orthopedic surgery. Sensory block was achieved at dermatomes from T6 to L5 in all patients in both groups. The mean time to onset varied

in both groups from about 4 minutes at T12 to about 13 minutes at T6. Mean duration in both groups was about 6 hours at T12. The majority of patients in both groups reported zero pain on a visual analog scale during and after the procedure. Motor block was somewhat less with ropivacaine:

	degree		
Motor block of at least . . .	1	2	3
Ropivacaine 0.5%	24/29	17/29	6/25
Bupivacaine 0.5%	30/31	23/30	12/30

This difference was not statistically significant ($p = 0.07$, rank-sum test).

Apgar scores were at least 7 at 5 minutes in all neonates and at 1 minute in all but one, who was in the ropivacaine group. A variety of neurological assessments of the newborns failed to detect any differences between the groups, nor were there any differences in fetal heart rates or neonatal capillary blood pH. Almost all mothers in both groups experienced hypotension, and about half in each group experienced paresthesia.

This study provides substantial evidence that epidural ropivacaine is an effective and safe anesthetic for cesarean section.

Labor Pain—Study N4

The NDA lists eight studies comparing ropivacaine and bupivacaine for the management of labor pain. Again, all these studies appear to be mutually supportive, and there is no clear reason to think of any one of them as pivotal. Nevertheless, one study (N4) will be reviewed in detail. This was a three-center (Canada), randomized, double-blind comparison of epidural administration of ropivacaine and bupivacaine, both at concentrations of 0.25%. A test dose of 5 ml was followed by a main dose of an additional 5 ml after 2 minutes, and a further 5 ml after 10 additional methods if deemed necessary by the investigator. Up to eight additional ("top-up") doses of 10 ml could be given on the patient's request at the investigator's discretion. Sixty-five patients were enrolled, but 5 were excluded from analysis because of technical failure. Ninety percent of the patients were white, and 10% were Asian; ages ranged from 16 to 38 (mean 28).

Pain during contractions was assessed by the patient on a 100 mm visual analog scale. The mean values before treatment were 77 and 74 in the ropivacaine and bupivacaine groups, respectively. After treatment but before the first additional dose if any, the means were 23 and 24. Over the whole course of treatment, the means were 31 and 30. The median time to onset of "a lot" or "complete" relief was 10 minutes in each group. Analgesia was judged good or excellent by 33 of 34 patients on ropivacaine and all 26 patients on bupivacaine. The investigator judged overall quality good or excellent in 32 of 34 ropivacaine patients and in all 26 bupivacaine patients.

Spontaneous delivery occurred in 53 percent and 62 percent of patients in the ropivacaine and bupivacaine groups, respectively. Apgar scores were at least 7 in 91 and 92 percent of neonates in the ropivacaine and bupivacaine groups at 1 minute, and in all neonates at 5 minutes. NACS scores were at least 35 in 74 percent (ropivacaine) and 73 percent (bupivacaine) at 2 hours, and 91 and 96 percent at 24 hours.

No statistically significant differences were found between groups in any efficacy or safety measure. However, the lack of statistical significance in this active-controlled trial is of little importance. What is important is the magnitude of any differences and whether differences of these magnitudes could be of any clinical importance. While this is ultimately a matter of medical judgment, the differences all appear to be quite small.

Some motor block was experienced by 7 of 34 ropivacaine patients and 11 of 26 bupivacaine patients. This apparently lesser motor block with ropivacaine was also observed in some other studies (compare study K9 above), but has not been clearly demonstrated in any one study. A formal pooled analysis might show a difference between equal doses of ropivacaine and bupivacaine with respect to motor block, but no such analysis has been submitted.

A study such as this one, with top-up doses as needed, may offer the possibility of detecting a dose response more sensitively than fixed-dose studies. The distribution of patients by number of top-up doses is shown below:

top-ups	0	1	2	3	4	5	6	7	8
rop.	4	5	12	6	0	4	3	0	0
bup.	2	11	6	1	3	1	1	0	1

The groups were not statistically significantly different (rank-sum test). On the other hand, if the dose of bupivacaine were multiplied by 1.3, the groups would still not be significantly

different. Thus, the possibility that a 30 percent higher dose is needed of ropivacaine than of bupivacaine cannot confidently be excluded. Therefore, it is not clear that the putatively lower toxicity of ropivacaine milligram for milligram would translate into less toxicity in use.

Epidural administration of ropivacaine was clearly effective in alleviating labor pain. Ropivacaine apparently had properties very similar to those of bupivacaine, but it was not demonstrated to be equivalent to bupivacaine.

Local Infiltration

Three studies compared ropivacaine to saline when infiltrated at the wound site before surgery for the purpose of controlling postoperative pain. One of the three studies (Q4) is described in the NDA as a Phase III study. Its protocol was fairly specific about endpoints and statistical methods for showing efficacy. The other two studies (Q2 and Q7) are described as Phase II studies, and the statistical methods were exploratory, making an unequivocal demonstration of efficacy difficult.

Study Q4

This was a randomized, double-blind, two-center comparison of three different concentrations of ropivacaine (0.125%, 0.25%, or 0.5%×30ml) to saline, infiltrated before hernia repair. Of 110 men enrolled, 10 were excluded from analysis, 8 of whom received no study drug and 2 of whom had general anesthesia. The patients ranged in age from 19 to 75 (median 50), and 93 percent were white.

The protocol's specification of the statistical analysis was ambiguous. It stated, for example, "If the assumptions for a parametric analysis are violated, nonparametric methods will be considered"; it did not state how it would be determined whether assumptions were violated, what nonparametric methods would be used, nor the circumstances under which the nonparametric analysis would be considered primary. Nevertheless, the preferred analysis was fairly clearly described, is reasonable, and was carried out. Three primary endpoints were given: the time from end of infiltration until the patient first asked for an analgesic, and the consumption of analgesics over 24 hours and over 6 days.

Time to rescue was analyzed by linear regression on the dose of ropivacaine, treating saline as a zero dose, yielding a p-value of 0.0009. The main potential difficulties with this approach are censoring and skewness. In fact, six observations were censored, in the sense that the patients left the recovery room without ever requesting an analgesic. These patients were analyzed as though they had requested an analgesic at the time they left the recovery room.

The usual parametric survival methods would assign them a longer time (e.g., censoring time plus mean time for uncensored patients). However, since censoring increased with increasing dose (0, 1, 2 and 3 patients on saline and ropivacaine 0.125%, 0.25%, and 0.5%, respectively), the analysis as carried out is conservative. As regards skewness, the distribution in each treatment group does appear somewhat skewed to the right, but the conclusions of the linear analysis are borne out by the medians. These median times to rescue were 1.3, 1.4, 1.9 and 2.3 hours, from lowest dose (saline) to highest; and only two of 24 patients in the saline group had times longer than the median for the highest-dose group.

Two analgesics were used in the recovery room, Vicodin (acetaminophen and codeine) and fentanyl. The protocol specified a "total dose of analgesics" to be computed as the number of Vicodin tablets plus 100 times the dose of fentanyl in micrograms. This measure is numerically meaningless, but a nonparametric analysis was specified (Jonckheere-Terpstra test for trend with respect to dose). The effect was to rank patients by their consumption of fentanyl, if any, and to rank those who had no fentanyl by their consumption of Vicodin. This procedure is sound, and the p-value was 0.009, indicating that at higher doses of ropivacaine, patients consumed less fentanyl or less Vicodin or both (but possibly less fentanyl and more Vicodin). In fact 12, 9, 6 and 7 patients (in order of increasing dose of ropivacaine) had fentanyl, with no clear differences between groups in the amount of fentanyl; and almost all patients had Vicodin, again with no differences in amount.

In the six days after discharge from the recovery room, there were no significant differences between groups in the consumption of Vicodin (Jonckheere-Terpstra test). The saline group was numerically lowest.

This study provides substantial evidence that local infiltration of ropivacaine reduces the need for other analgesics for the first few hours after surgery.

Other studies

Two other placebo-controlled studies (Q2 and Q7) produced a smattering of statistically significant results among a large number of possible measures of efficacy. Because of the multiplicity of endpoints, the evidence of efficacy from these two studies must be considered weak, but they clearly add to rather than take away from the evidence from study Q4.

There was a noteworthy dose response in an adverse event in study Q7. Hematomas occurred in 3, 7, and 12 (of 44, 43 and 43) patients in the saline, ropivacaine 0.25%, and ropivacaine 0.5% groups, respectively. The investigators judged these events unlikely to be related to the study drug. The sponsor suggests that they might be related to the use of an

algometer. This is a device that exerts increasing pressure on the wound until the patient signals that the pain is intolerable. The ropivacaine patients tolerated more pressure; so, if patients were injured by the algometer, it is plausible that the rate would increase with the pressure and so also with the dose of ropivacaine.

Peripheral Nerve Block

Six trials studied ropivacaine injected at the brachial plexus by a subclavian or axillary route to produce anesthesia for surgery on the arm. The proportions of patients in whom anesthesia was judged satisfactory for surgery are shown below.

Approach	Study	Rop. 0.5%	Bup. 0.5%	Rop. 0.25%	Bup. 0.25%
Subclavian	P2	22/24	21/23		
	P3			14/22	12/21
Axillary	P6	19/30		11/31	
	P8	21/29	18/29		
	P5	18/29	20/31		
	P7	0/2	1/4		

It is noteworthy that the investigator was the same in studies P2 and P7. Dr. Ramamurthy, the only investigator to achieve a success rate above 75 percent with ropivacaine (with subclavian administration), terminated the later study (with axillary administration) on grounds of ineffectiveness. In the terminated study P7, the investigator deviated from the protocol in assessing success 30 minutes after injection, rather than at the end of surgery.

Ropivacaine appeared to be about as effective as bupivacaine, which is labelled for peripheral nerve block. However, the results were unsatisfactory in about a third of all patients, except in one study of subclavian administration at the 0.5% concentration.

Epidural Infusion for Postoperative Pain

The draft labelling proposes an indication for the management postoperative pain by epidural infusion. This use is not specifically indicated in the labelling for other drugs of this class, but has become common since they were approved. The NDA lists seven studies in this

indication. One study (O7) compared ropivacaine 2 mg/ml at five different rates of infusion (6–14 ml/h). The other six studies (O1–O6) all compared three concentrations of ropivacaine (1, 2 and 3 mg/ml × 10 ml/h) to saline. Each of these six studies had from 9 to 12 evaluable patients per treatment group. Because of the small numbers and the variability of the measures of efficacy, no one study gives unequivocal evidence of the effects of ropivacaine. The clearest picture emerges from an overview of the six similarly designed concentration-controlled studies.

The six studies O1–O6 had essentially identical protocols except for the type of surgery involved: studies O1 and O6 were in upper abdominal surgery, studies O4 and O5 were in lower abdominal surgery, and studies O2 and O3 were in orthopedic surgery. A total of 12 centers in Canada, New Zealand, Australia, the United Kingdom and Sweden enrolled 282 patients, of whom 37 were excluded from analysis for technical failures, withdrawal or major violations of protocol. Between 9 and 12 patients were evaluable in each treatment group in each study (24 groups). Most of the patients were white (93 percent); only 1 percent were black. About half were female, and elderly patients were well-represented, the mean age being 56 (range 18-80).

After surgery with epidural ropivacaine used as anesthetic in all groups, a continuous infusion of saline or one of three concentrations of ropivacaine was given for 21 hours. Patients had access to morphine through a patient-controlled pump (1 mg doses with 5 minute lockout). Patients who did not tolerate morphine were given pethidine instead, with one 10 mg dose of pethidine considered equivalent to 1 mg of morphine. Efficacy measures were the consumption of morphine, visual analog ratings of pain at rest and, in the abdominal studies, on coughing, and a global assessment by the patient.

Median consumption of morphine (mg)

surgery	study	drug	N	0-4h	4-8h	8-21h
upper	O1	saline	10	16	16	36
abdominal		rop. 0.1%	10	16	9	27
		rop. 0.2%	10	3	2	14
		rop. 0.3%	10	14	4	21
	O6	saline	9	24	13	40
		rop. 0.1%	9	7	8	18
		rop. 0.2%	9	14	5	15
		rop. 0.3%	9	0	0	9
lower	O4	saline	10	10	12	22
abdominal		rop. 0.1%	10	2	4	9
		rop. 0.2%	9	1	2	23
		rop. 0.3%	10	0	0	12
	O5	saline	10	6	13	22
		rop. 0.1%	10	2	4	12
		rop. 0.2%	10	0	1	8
		rop. 0.3%	10	4	0	12
orthopedic	O2	saline	10	7	15	36
		rop. 0.1%	12	0	2	15
		rop. 0.2%	11	0	0	11
		rop. 0.3%	11	0	1	7
	O3	saline	12	9	10	18
		rop. 0.1%	11	2	3	13
		rop. 0.2%	12	0	2	26
		rop. 0.3%	11	0	0	4
pooled		saline	61	B	C	C
		rop. 0.1%	61	A	B	B
		rop. 0.2%	60	A	A	A
		rop. 0.3%	59	A	A	A

Considering the studies and the time periods separately, in very few cases was the response monotonic in dose. In most but not all cases, all three ropivacaine doses were better than saline. In two studies (O4 and O3) ropivacaine 0.2% was worse than saline in the last period, but in two other studies (O1 and O5) it was best of all for the same period (and most other periods). The treatment groups were small, and the morphine requirements within groups were highly variable, possibly reflecting varying amounts of pain, varying response to morphine, and varying response to the study drug. The asystematic variation of the medians probably is mostly random noise. The sponsor reported some differences between groups to be statistically significant

(some in the expected direction and some in the opposite sense), but in this context of multiplicity and incoherence these individual tests have little meaning.

At the reviewer's request, the sponsor conducted a pooled analysis of these data. The statistical technique was the same one used in the NDA for the separate studies: rank-sum tests stratified by center. (Center being nested within study, no additional stratification by study or type of surgery was needed.) The sponsor expressed some reservations about the appropriateness of pooling, especially across different kinds of surgery. I believe these reservations were well founded. Certainly there is no sufficiently powerful test to conclude that the data being pooled are homogeneous. In fact, their apparent inhomogeneity, which I think is most likely random, is the reason I think the pooled analysis is helpful in describing a common pattern obscured by considerable noise.

In the table above, different letters mark treatments significantly different at level 0.05, two-sided, with the letter A marking the most favorable outcome. No adjustment for multiple comparisons was made, but the *largest* of the nine p-values for comparisons involving placebo (3 other treatments × 3 periods) was 0.005. All three concentrations of ropivacaine were statistically significantly better than placebo in all periods. Furthermore, there was some evidence of dose response, in that ropivacaine 0.2% and 0.3% were statistically significantly better than ropivacaine 0.1% for the last two periods.

Quality of treatment good or excellent (percent)

surgery	study	drug	N	0-4h	4-8h	8-21h
upper abdominal	O1	saline	10	60	80	90
		rop. 0.1%	10	80	80	80
		rop. 0.2%	10	100	89	89
		rop. 0.3%	10	90	90	100
	O6	saline	9	11	67	100
		rop. 0.1%	9	89	89	89
		rop 0.2%	9	78	89	100
		rop. 0.3%	9	100	100	100
lower abdominal	O4	saline	10	30	50	50
		rop. 0.1%	10	80	80	80
		rop. 0.2%	9	100	89	100
		rop. 0.3%	10	89	90	90
	O5	saline	10	50	30	60
		rop. 0.1%	10	80	80	90
		rop. 0.2%	10	90	80	80
		rop. 0.3%	10	100	80	80
orthopedic	O2	saline	10	90	90	100
		rop. 0.1%	12	100	100	100
		rop. 0.2%	11	91	100	91
		rop. 0.3%	11	100	100	100
	O3	saline	12	33	67	67
		rop. 0.1%	11	82	73	73
		rop. 0.2%	12	92	92	83
		rop. 0.3%	11	89	100	80

Overall satisfaction was not a very sensitive measure, inasmuch as the great majority of patients in all groups were satisfied. In only four (underlined) groups (of 24 groups × 3 periods), fewer than half the patients called the treatment good or excellent in one period. All four of these groups had saline, and in all four such cases, satisfaction with any dose of ropivacaine was at least 80 percent. Thus, treatment with ropivacaine was judged satisfactory in some instances where morphine alone was not.

Median VAS pain at rest (100 mm scale)

surgery	study	drug	N	0-4h	4-8h	8-21h
upper	O1	saline	10	44	29	14
abdominal		rop. 0.1%	10	29	16	11
		rop. 0.2%	10	7	14	26
		rop. 0.3%	10	25	12	28
	O6	saline	9	45	31	11
		rop. 0.1%	9	15	4	0
		rop. 0.2%	9	12	5	9
		rop. 0.3%	9	0	0	8
lower	O4	saline	10	63	36	21
abdominal		rop. 0.1%	10	11	14	6
		rop. 0.2%	9	0	6	10
		rop. 0.3%	10	9	2	6
	O5	saline	10	49	43	18
		rop. 0.1%	10	15	30	15
		rop. 0.2%	10	0	10	8
		rop. 0.3%	10	0	0	6
orthopedic	O2	saline	10	38	41	25
		rop. 0.1%	12	0	8	10
		rop. 0.2%	11	0	0	24
		rop. 0.3%	11	0	0	5
	O3	saline	12	33	21	29
		rop. 0.1%	11	0	2	0
		rop. 0.2%	12	0	0	7
		rop. 0.3%	11	0	0	10

Patients treated with ropivacaine at any of the three concentrations experienced less pain than patients treated with saline. The differences were largest in the 4 or 8 hours after surgery. No differences between ropivacaine doses were apparent.

Median VAS pain coughing (100 mm scale)

surgery	study	drug	N	0-4h	4-8h	8-21h
upper	O1	saline	10	50	58	34
abdominal		rop. 0.1%	10	42	45	19
		rop. 0.2%	10	28	32	22
		rop. 0.3%	10	27	21	42
	O6	saline	9	67	45	31
		rop. 0.1%	9	44	42	34
		rop. 0.2%	9	33	20	12
		rop. 0.3%	9	0	0	12
lower	O4	saline	10	67	66	66
abdominal		rop. 0.1%	10	28	40	28
		rop. 0.2%	9	16	12	28
		rop. 0.3%	10	12	8	27
	O5	saline	10	59	69	53
		rop. 0.1%	10	25	48	31
		rop. 0.2%	10	8	20	24
		rop. 0.3%	10	9	9	16

Abdominal surgery patients also evaluated pain upon coughing. In this case ropivacaine 0.2% or 0.3% appeared more effective than 0.1% in the first 8 hours.

Motor block (frequency (percent) of block of degree 2 or 3/frequency of block of any degree)

surgery	study	drug	N	0-4h	4-8h	8-21h
upper abdominal	O1	saline	10	0/10	0	0
		rop. 0.1%	10	0	0	0
		rop. 0.2%	10	10/30	10/20	10/20
		rop. 0.3%	10	0	0/10	0
	O6	saline	9	0	0	0
		rop. 0.1%	9	0	0	0
		rop. 0.2%	9	0/11	0/11	0/11
		rop. 0.3%	9	11/11	11/11	11/11
lower abdominal	O4	saline	10	0/10	0	0
		rop. 0.1%	10	0/30	0/20	0
		rop. 0.2%	9	33/67	0/22	0/11
		rop. 0.3%	10	40/90	20/80	0/60
	O5	saline	10	0/20	0/10	0/10
		rop. 0.1%	10	0	0	0
		rop. 0.2%	10	10/30	10/20	0/20
		rop. 0.3%	10	40/70	30/70	20/30
orthopedic	O2	saline	10	10/10	0/20	0
		rop. 0.1%	12	33/42	17/33	8/17
		rop. 0.2%	11	18/64	9/55	27/45
		rop. 0.3%	11	64/82	55/91	0/36
	O3	saline	12	8/33	0/8	0
		rop. 0.1%	11	9/36	0/18	0/18
		rop. 0.2%	12	58/75	50/58	17/58
		rop. 0.3%	11	45/64	45/55	36/55

In upper abdominal surgery, motor block in the legs occurred only occasionally and was slight. In lower abdominal and orthopedic surgery, where the affected region and accordingly the site of injection were lower, it was seen more frequently and was more likely to be profound. There was a dose response: ropivacaine 0.1% produced less motor block. The block was gone or slight in most cases by 21 hours after surgery, but most of the effectiveness was also seen in the earlier time periods.

Considering the six parallel studies together, ropivacaine was effective in alleviating pain and reducing the need for morphine in the first 8 hours after surgery. Concentrations of 0.1% to 0.3% were all effective. The higher concentrations were marginally more effective, particularly with pain upon coughing after abdominal surgery, but also produced more motor block.

The evidence from such a combined analysis falls short of the usual standard for demonstrating efficacy. No single study clearly demonstrated an effect with respect to a prospectively defined endpoint. Nevertheless, information on the effectiveness and safety of the tested doses in this indication is substantial enough to be useful to physicians and should be included in the label for this drug, whose efficacy with the same mode of action has been demonstrated in other indications.

Summary Conclusions

Ropivacaine was shown to be a safe and effective epidural anesthetic in orthopedic surgery and cesarian section, and to alleviate labor pain. It appeared to have properties similar to bupivacaine at similar doses. Equivalency of dose was not established, however, with sufficient precision to justify a claim of lower toxicity at equipotent doses.

In peripheral nerve block ropivacaine demonstrated efficacy similar to that of bupivacaine, but in all studies except one, anesthesia was judged unsatisfactory in more than a quarter of patients.

Substantial evidence of efficacy and safety was also presented in a new indication for this class of drugs, control of postoperative pain by local infiltration or epidural infusion. This was not based on a comparison with other drugs, and is therefore not the basis for any comparative claim. However, information on the experience in this indication would be useful to physicians and should appear in the label.

Thomas Permutt, Ph.D.
Mathematical Statistician

Hoi M. Leung 10/12/95
Hoi M. Leung, Ph.D., Peer Reviewer

original: NDA 20-533
cc:
HFD-007/Morgan
HFD-007/Bedford
HFD-007/Tyler
HFD-007/Permutt
HFD-713/Dubey
HFD-007/Division file
HFD-007/Morgan
R/D Init. by: HLeung/10-12-95
F/T by: sl/10-12-95

Chemist Review

DIVISION OF ANESTHETIC, CRITICAL CARE AND ABUSE DRUGS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20 - 533

REVIEW # 2 **DATE REVIEWED:** Mar. 22, 1996

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	29 - 03 - 95	31 - 03 - 95	07 - 04 - 95
AMENDMENT	20 - 02 - 96	22 - 02 - 96	23 - 02 - 96

NAME & ADDRESS OF APPLICANT:

Astra USA, Inc.
50 Otis Street
Westborough, MA 01571 - 4500

DRUG PRODUCT NAME

Proprietary:	NAROPIN Injection
Established:	Ropivacaine Hydrochloride
Code Name/#:	LEA - 103
Chem.Type/Ther.Class:	1S

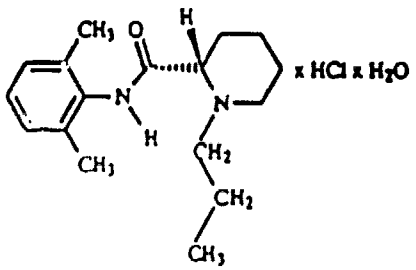
PHARMACOL. CATEGORY: Anesthetic

DOSAGE FORM: Injection
STRENGTHS: 2.0, 2.5, 5.0, 7.5 and 10.0 mg/ml
ROUTE OF ADMINISTRATION:
DISPENSED: X Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Chemical name[1]: (S)-(-)-1-Propyl-2',6'-pipecoloxylidide hydrochloride monohydrate

Structural formula:



Molecular formula: $C_{17}H_{26}N_2O \times HCl \times H_2$

Molecular weight: 328.89

REMARKS:

The firm has responded in this amendment dated Feb. 20,1996 to our fax dated Dec. 5,1995.

The responses were satisfactory.

1. Naropin Injection is manufactured by Astra, USA,Inc. in Westborough, Massachusetts. Its sterile paks are sterilized by
One of its inactive ingredients, namely sodium chloride is tested by

2. The drug substance, ropivacaine hydrochloride, is synthesized by Astra Production Chemicals AB, in Sweden. The starting material, 2',6'-pipecoloxylidide is synthesized by

3. Naropin Injection is filled into glass vials, anpuls and bottles, with stoppers and aluminum seals. The concentrations, which are all preservative free, range from 2.0mg/mL, 5.0 mg/mL, 7,5 mg/mL to 10.0 mg/mL. in sizes of 10 mL,20 mL, 30 mL,and in some potencies, 100 mL and 200 mL bottles(2 mg/mL).

4. All drug masters files have been reviewed and are acceptable.

5. The establishment inspections have been completed and were found acceptable.

6. The Environmental Assessment Review has been completed. Certain deficiencies have been identified and have been sent to the applicant. The Applicant has responded and their responses have been sent to Nancy Sager for consult review.

7. The microbiology review has been completed and found acceptable as per HFD-160.

8. The methods have were sent to the district laboratories. on Mar. 22,1996.

9. The expiration dating period is 18 months.

CONCLUSIONS & RECOMMENDATIONS:

From a chemist viewpoint the application is approvable, provided the Environmental Assessment deficiencies have been addressed adequately.

cc:

Orig. NDA 20-533
HFD-170/Division File
HFD-170/JMRoss
HFD-170/DMorgan
HFD-120/Dr. Y. Y. Chiu
F/T by JMRoss/ 03-15-96

Juanita Ross
Juanita Ross, M.Sc.
Review Chemist

filename:WPFiles\N20533.AMD

/s/ Theodorakis
Michael Theodorakis, Ph.D.
Team Leader (Acting)

DIVISION OF ANESTHETIC, CRITICAL CARE AND ABUSE DRUGS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20 - 533

REVIEW # 1 DATE REVIEWED:

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	29 - 03 - 95	31 - 03 - 95	07 - 04 - 95
AMENDMENT	04 - 10 - 95	05 - 10 - 95	11 - 10 - 95

NAME & ADDRESS OF APPLICANT:

Astra USA, Inc.
50 Otis Street
Westborough, MA 01571 - 4500

DRUG PRODUCT NAME

Proprietary: NAROPIN (ropivacaine hydrochloride) Injection
Established: Ropivacaine Hydrochloride
Code Name/#: LEA - 103
Chem. Type/Ther. Class: 1S

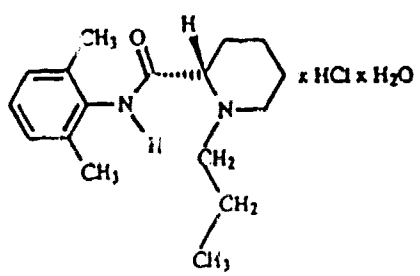
PHARMACOL. CATEGORY: Anesthetic

DOSAGE FORM: Injection
STRENGTHS: 2.0, 2.5, 5.0, 7.5 and 10.0 mg/ml
ROUTE OF ADMINISTRATION:
DISPENSED: X Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Chemical name[1]: (S)-(-)-1-Propyl-2',6'-pipecoloxylidide hydrochloride monohydrate

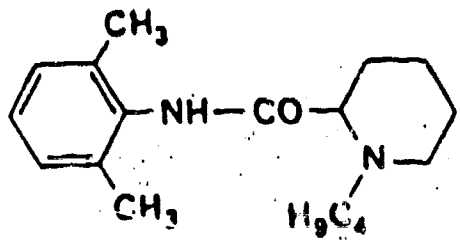
Structural formula:



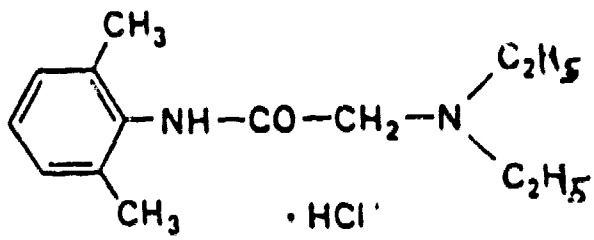
Molecular formula: $C_{17}H_{26}N_2O \times HCl \times H_2O$

Molecular weight: 328.89

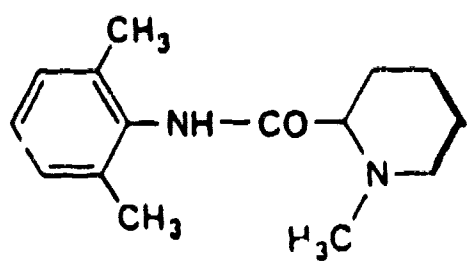
STRUCTURAL FORMULAS OF RELATED COMPOUNDS



BUPIVACAINE (*Marcaine*).



LIDOCAINE HYDROCHLORIDE (*Xylocaine*)



MEPIVACAINE (*Carbocaine*).

SUPPORTING DOCUMENTS:

1. IND

Astra USA, Inc.
50 Otis Street
Westborough, MA 01581

The firms investigational drug application was submitted and reviewed for ropivacaine hydrogen chloride monohydrate and found to be acceptable for further processing to the NDA stage.

2. DMF

This drug master file contains information on the USP Glass which is the type of glass used in the ampoules, vials and bottles. The information submitted was satisfactory.

3. DMF

This drug master file contains information on the stoppers and the Flip-Off or E-Z-Off seals. The information submitted is satisfactory.

4. DMF

This drug master file contains satisfactory information on the Glass used for the ampoules, vials and bottles.

5. DMF

The information submitted in this drug master file concerns the polyvinylchloride, the material from which the sterile - pak trays are made. The information is in conformance with FDA regulations.

6. DMF

The information submmitted in this drug master file describes the components of the sterile-pak lid and its adhesive. The information does conform to FDA regulations.

RELATED DOCUMENTS:

Basically the literature references cited by the applicant provided valuable information in understanding more about the chemistry of the compound.

CONSULTS:

The Environmental Assessment Information was sent to our Environmental Assessment consultants. This review is still pending.

The microbiology information was sent to HFD-160, Division of Medical Imaging, Surgical and Dental Drug Products for consultation. From the perspective of sterility assurance the application was recommended for approval.

REMARKS\COMMENTS:

The application was reviewed for chemistry, manufacturing and control information. Some deficiencies were noted and are cited under COMMENTS in each section of the Review Notes.

Inspection requests have been sent to Compliance and they have responded that inspections are being arranged.

The methods have not been sent out for validation.

REMARKS:

CONCLUSIONS & RECOMMENDATIONS:

After reviewing the application, there were portions where additional information was needed, namely (a) clarification in some portions of the synthesis of the drug substance, (b) clarification in the description of some of the analytical methods, (c) justification for some of the wide specification limits, and (d.) submission of additional stability data to support their proposed expiration date.

From a chemist's viewpoint, this application is not approvable See attached " Draft Chemistry Deficiency Letter"

cc:
Orig. NDA 20-533
HFD-170/Division File
HFD-170/JMRoss
HFD-170/DMorgan
HFD-120/Dr. Y. Y. Chiu
F/T by JMRoss/ 10-30-95

Juanita Ross 10/30/95
Juanita Ross, M.Sc.
Review Chemist

filename:WPFiles\N20.533

MTheodorakis 11/1/95
Michael Theodorakis, Ph.D.
Team Leader (Acting)

Micro

CONSULTATIVE REVIEW TO HFD-007

AUG 21 1995

DIVISION OF MEDICAL IMAGING, SURGICAL, and DENTAL DRUG PRODUCTS; HFD-160

Microbiologist's Review #1
18 August 1995

A. 1. NDA 20-533

SPONSOR Astra USA, Inc.
Westborough, MA
01581

2. PRODUCT NAMES: Naropin®-MPF (methylparaben free) at 2 mg/mL, 2.5 mg/mL,5 mg/mL, 7.5 mg/mL and 10 mg/mL Ropivacaine product strengths, and Naropin® (preserved) at 2.5 and 5 mg/mL

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Single dose vials of 10 mL, 20 mL and 30 mL; ampules of 20 mL and 30 mL; Infusion bottles of 100 mL and 200 mL; and multiple dose, preserved vials of 20 and 30 mL. Vials are packaged individually in cartons or in "Sterile-Paks". Sterile-Paks are in cartons containing 5 vials which are sterilized by ETO to provide sterile vial outer surfaces. Ampules are packaged in cartons of 5. Infusion bottles are packaged individually in cartons.

Solution may be administered by epidural catheter in doses which infuse to 250 mg having analgesic duration of 5 to 8 hours (when used as a major nerve block). Additional doses may be required for up to 24 hours at an infusion rate of 12 to 20 mg per hour.

4. METHOD(S) OF STERILIZATION: Aseptic fill and terminal moist heat. Trays sealed with and containing vials (Sterile-Pak), are sterilized by ETO to provide sterile outer surfaces for use in sterile clinical environments.

5. PHARMACOLOGICAL CATEGORY: Anesthetic

B. 1. DATE OF INITIAL SUBMISSION: 29 March 1995

2. DATE OF AMENDMENT: none

3. RELATED DOCUMENTS: DMF (Astra USA, Inc.)

4. ASSIGNED FOR REVIEW: 9 June 1995

C. REMARKS: DMF was reviewed as part of Microbiologist's Review #1 of 22 March 1993. That review addressed aseptic filling at the facility in Westborough, Massachusetts.

NDA documents for consultative review include volumes 1.3 (ETO process sterilization information and drug product CMC information, pages 1 - 85 and 280 - 353), 1.4 (aseptic processing validation), 1.13 (pages 194 - 220 describing release test methods), 1.14 (pages 41 - 91 providing microbiology release test validation) and 1.15 (labelling).

D. CONCLUSIONS: The submission is recommended for approval from the perspective of sterility assurance.

8-18-95

David Hussong, Ph.D.

Date 8/21/95

cc:

Original NDA 20-533
HFD-160/Consult File
HFD-007/CSO/D. Morgan
HFD-007/Chemist/J. Ross
drafted by: D. Hussong, 08/18/95
R/D initialed by: P. Cooney, 08/ /95

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-533

NAROPIN™

(ropivacaine hydrochloride injection)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS (HFD-170)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-533

NAROPIN™

(ropivacaine hydrochloride injection)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **NAROPIN™, Astra USA, Inc.** has prepared an abbreviated environmental assessment in accordance with 21 CFR 25.31a(b)(3) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Ropivacaine is a synthetic drug which will be administered epidurally as a local anesthetic for surgery and acute pain management, infiltration for surgery and postoperative pain management, and peripheral nerve blocks for surgery and postoperative pain management. The drug substance will be manufactured by Astra Production Chemicals AB, Sweden and the drug product will be manufactured by Astra USA, Inc., Westborough, MA. The finished drug product will be used in hospitals and practitioner's offices.

Disposal may result from production waste such as out of specification lots, returned goods and user disposal of empty or partly used product and packaging. Information regarding disposal of production waste and returned goods is included in environmental assessment. At U.S. hospitals and practitioner's

offices, empty or partially empty packages will be disposed of as according to hospital/clinic procedures.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

3/28/96
DATE

PREPARED BY
Nancy B. Sager
Acting Supervisor
Environmental Assessment Team
Center for Drug Evaluation and Research

3/29/96
DATE

CONCURRED
Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

c.c. original NDA 20-533/DMorgan copy to NDA/HFD-170
HFD-357/EA File NDA #20-533
HFD-357/Docket File
HFD-205/FOI COPY

NON-CONFIDENTIAL

ATTACHMENT 1

Material Safety Data Sheet

Ropivacaine Hydrochloride Monohydrate

MATERIAL SAFETY DATA SHEET
Ropivacaine Hydrochloride Monohydrate (Raw Material)

CHEMTREC® Emergency Telephone Numbers (24 - Hours)
United States: 800-424-9300
International: 202-483-7616 (collect)

These CHEMTREC® numbers are to be used ONLY IN THE EVENT OF A CHEMICAL EMERGENCY INVOLVING A SPILL, LEAK, FIRE, EXPLOSION OR ACCIDENT

MSDS: 67

ISSUE DATE: 3/20/96
Revision Date: 3/20/96

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Astra USA, Inc.
50 Otis Street
Westborough, Massachusetts 01581

General Information Phone Numbers:
800-225-6333
508-366-1100

Product Name: Ropivacaine Hydrochloride Monohydrate
Chemical Name: (S)-(-)-1-Propyl-2', 6'-pipecoloxylidide hydrochloride monohydrate
Therapeutic Category: Local anesthetic

2. COMPOSITION/INFORMATION ON INGREDIENTS

COMPONENT	CAS REGISTRY	EINECS	PERCENT	MOL. WT.
Ropivacaine Hydrochloride Monohydrate	132112-35-7		100%	328.89

$C_{17}H_{26}N_2O \bullet HCl \bullet H_2O$

(See Section 8 for exposure guidelines)

3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW

POTENTIAL HEALTH EFFECTS

Ropivacaine Hydrochloride Monohydrate is used in the manufacture of Ropivacaine Hydrochloride Injection. Ropivacaine is a long-acting aminoamide local anesthetic. The formulated product is intended for epidural anesthesia, local infiltration and peripheral nerve block. Local anesthetics block nerve conduction where they are administered locally. They cause both a sensory and a motor paralysis. When high systemic concentrations are reached through an incorrect injection or overdose, adverse effects

occur in the form of central nervous system and/or cardiovascular toxicity. No information was found regarding occupational exposure to this material. Potential routes of exposure include inhalation of dust or powder, and skin and eye contact. Symptoms of overexposure include light-headedness, restlessness, anxiety, numbness and tingling of the mouth and lips, ringing in the ears, dizziness, blurred vision, nausea, vomiting, tremors and twitching. Convulsions may occur if the dose is high enough. Central nervous system depression follows the initial stimulation phase and can lead to respiratory failure and circulatory collapse. Effects on the heart include decreases in the heart's conduction rate and force of contraction. Exposure to high concentrations of dust may cause eye and respiratory tract irritation. Ropivacaine is not irritating to the skin but may cause local vasoconstriction resulting in paleness or blanching of the skin.

4. FIRST AID MEASURES

EYE: First check victim for contact lenses and remove if present. Flush victim's eyes with large quantities of water and contact a physician immediately.
SKIN: Wash with soap and water while removing all contaminated clothing. If rash or irritation develop, contact a physician.
INGESTION: If victim is conscious, use activated charcoal or cathartics. Gut decontamination may be useful within the first several hours post-ingestion. Do not give anything by mouth if victim is convulsing or unconscious. Immediately transport the victim to a hospital.
INHALATION: Remove to fresh air. If not breathing, use artificial respiration.
NOTE TO PHYSICIAN: In case of accidental overexposure in a worker, ascertain airway breathing, and ensure oxygenation and ventilation. Equipment for emergency resuscitation should be readily available. Monitor cardiac functioning.

5. FIRE FIGHTING MEASURES

FLAMMABLE PROPERTIES
FLASH POINT: NA
FLAMMABLE LIMITS:
LOWER FLAMMABLE LIMIT: NA
UPPER FLAMMABLE LIMIT: NA
EXTINGUISHING MEDIA: Use extinguishing media suitable for surrounding materials. Drug powder may be combustible.
UNUSUAL FIRE OR EXPLOSION HAZARDS: None known. Organic dusts at sufficient concentrations can form explosive mixtures with air.
FIRE-FIGHTING INSTRUCTIONS: Firefighters should use self-contained breathing equipment and protective clothing.

HAZARDOUS COMBUSTION PRODUCTS: Oxides of carbon and nitrogen, chlorides.

6 ACCIDENTAL RELEASE MEASURES

SPILLS: Use caution when handling spilled material using appropriate protective equipment. Eliminate all ignition sources. Carefully collect, avoiding dust, and place in a suitable, properly labeled container for disposal. Wash area with soap and water.
DECONTAMINATION PROCEDURES: Water based detergents are expected to be effective in cleanup and decontamination operations.

7 HANDLING AND STORAGE

HANDLING: This substance is a potent local anesthetic. Use extreme caution. Avoid breathing dust. Avoid contact with eyes, skin and clothing. Do not smell or taste chemicals. Do not eat, drink, or smoke in areas where chemicals are present. Wash thoroughly after handling. Wash contaminated clothing before reuse.
STORAGE: Protect from light and extreme heat. Store at controlled room temperature: 15°-30° C (59-86° F).

8 EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE GUIDELINES: No exposure guidelines established by ACGIH or OSHA.
ENGINEERING CONTROLS: Good general ventilation should be sufficient for most conditions. Local exhaust ventilation may be needed in weighing area.
RESPIRATORY PROTECTION: For operations where exposure to dust is possible, such as weighing and mixing operations, wear a NIOSH-approved half-face respirator equipped with a dust/mist HEPA filter.
SKIN PROTECTION: Rubber gloves.
EYE PROTECTION: Chemical safety goggles to prevent contact with eyes.
OTHER: A laboratory coat or apron appropriate for the work situation.

9 PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE: White, crystalline powder
ODOR: ND
PHYSICAL STATE: Solid
BOILING POINT: NA
VAPOR PRESSURE: NA

VAPOR DENSITY: NA
SOLUBILITY IN WATER: 53.8 mg/mL at 25° C
SPECIFIC GRAVITY: NA
pH: NA
MELTING POINT: 269.5° - 270.6° C
OCTANOL/PHOSPHATE BUFFER (pH 7.4): 141 at 25° C

[redacted]

STABILITY: Stable from a safety point of view.
INCOMPATIBILITY: Alkaline solutions, disinfecting agents containing heavy metals.
HAZARDOUS DECOMPOSITION PRODUCTS: When heated to decomposition, product may emit toxic oxides of carbon and nitrogen, and chlorides.
HAZARDOUS POLYMERIZATION: Will not occur.

[redacted]

ORAL TOXICITY: ND. Probably not very toxic by the oral route because of large first pass hepatic filtration.
PARENTERAL TOXICITY: Rat, Subcutaneous LD_{50}: 58 - 76 mg/kg; Intravenous LD_{50}: 9.9 - 12 mg/kg. Clinical signs included decreased motor activity, piloerection, tremor, ataxia, and convulsions. Mean IV seizure dose in dogs: 4.9 mg/kg. The most common adverse effects noted after large overdoses of local anesthetics are convulsions and effects on the cardiovascular system. Signs of toxicity may include lightheadedness, numbness of the mouth, tinnitus, restlessness and anxiety. Tremors may progress to convulsions. After the initial stimulation phase, large overdoses cause CNS depression, manifested as hypotension, failure to breath, and circulatory collapse. Death usually results from respiratory failure. Effects noted on the cardiovascular system include decreases in the heart's conduction rate and force of contraction.
INHALATION TOXICITY: ND. Exposure to high concentrations of dust or powder may cause respiratory tract irritation.
EYE: ND. Direct contact with the dust or powder may cause slight eye irritation.
SKIN: Ropivacaine hydrochloride was not irritating to rabbit skin after 4 or 24 hour exposures. Ropivacaine can cause some local vasoconstriction resulting in paleness or blanching of the skin.
SENSITIZATION: ND. Allergic type reactions are rare. These reactions are characterized by signs such as hives, itching, redness, edema, rapid heart rate, sneezing, nausea, vomiting, dizziness, fainting, excessive sweating, elevated temperature, and possible, anaphylactoid symptoms. Cross sensitivity among members of the amide-type local anesthetic group has been reported.

SUBCHRONIC/CHRONIC/CARCINOGENICITY: Clinical signs noted in parenteral repeat-dosing studies (1 and 6 months) in dogs included tremors, vomiting, and convulsions (high doses). Long-term studies in animals to evaluate the carcinogenic potential of ropivacaine have not been conducted. Ropivacaine hydrochloride is not listed as a carcinogen by NTP, IARC, or OSHA.
MUTAGENICITY: No mutagenic effect was found in three *in vivo* systems or in three of four *in vitro* systems. Ropivacaine was weakly mutagenic in the mouse lymphoma test with metabolic activation.
REPRODUCTIVE/DEVELOPMENTAL EFFECTS: Classified as a **Pregnancy Category B Drug**. No effects on fertility or general reproductive performance were noted in rats over two generations. The highest dose level caused increased pup loss during the first three days postpartum probably due to impaired maternal care of the newborn. Ropivacaine did not cause any teratologic effects in rats or rabbits. No adverse effects were noted on late fetal development, labor delivery, lactation, neonatal viability or growth in a peri-/postnatal study in rats. There are no adequate and well-controlled studies in pregnant women of the effects of ropivacaine on the developing fetus. Ropivacaine crosses the placental barrier and can be detected in fetal tissue and amniotic fluid. No information was available regarding ropivacaine distribution into human milk.
DRUG INTERACTIONS: Other local anesthetics, amide-type anesthetics.
MEDICAL CONDITIONS ENHANCING TOXICITY: Known hypersensitivity to ropivacaine or any anesthetic of the amide type, hepatic disease, impaired cardiovascular function, severe renal dysfunction.

[redacted]

ECOTOXICOLOGICAL INFORMATION: ND.
CHEMICAL FATE: ND.

[redacted]

Return rejected batches to the Astra facility in Sweden. Dispose of waste material on-site in a licensed chemical incinerator, if allowed by the incinerator license or permit. Rinse water should be sent to a NPDES permitted municipal sewage treatment plant. Disposal should be conducted in accordance with local, state and federal environmental regulations.

[redacted]

TRANSPORTATION AND HAZARDOUS MATERIALS DESCRIPTION:
Not a hazardous material by DOT.

ND = No Data

NA = Not Applicable

[redacted]

OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200). Labeling regulated by FDA.
CERCLA/SUPERFUND: Contains no Reportable Quantity (RQ) substances.
SARA SECTION 302: Contains no extremely hazardous substances.
SARA HAZARD CATEGORY (311/312): Immediate health hazard. Exempted from reporting since material is regulated by FDA.
SARA 313 INFORMATION: Contains no chemical subject to the reporting requirements of SARA 313.
TSCA: Drugs exempted from TSCA Chemical Substance Inventory.
CALIFORNIA PROPOSITION 65: Contains no material known to the State of California to cause cancer, birth defects or reproductive toxicity.

[redacted]

PACKAGING DESCRIPTION: NA
ADDITIONAL INFORMATION: Refer to manufacturer's package insert.
HAZARD LABEL TEXT:
NFPA RATING: Health = 1 Fire = 1 Reactivity = 0

DISCLAIMER

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END

BT

J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011