

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-533/S-002

**CLINICAL PHARMACOLOGY
BIOPHARMACEUTICS REVIEW**

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880) Tracking/Action Sheet for Formal/Informal Consults		
From: Shinja R. Kim, Ph. D.		To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission		
DATE: 10/3/00	IND No.: Serial No.:	NDA No. 20-533/S-002	DATE OF DOCUMENT 09/28/99	
NAME OF DRUG [Ropivacaine HCl Injection]	PRIORITY CONSIDERATION		Date of informal/Formal Consult: 09/26/00	
NAME OF THE SPONSOR: [Astra]				
TYPE OF SUBMISSION CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE				
<input type="checkbox"/> PRE-IND <input type="checkbox"/> ANIMAL to HUMAN SCALING <input type="checkbox"/> IN-VITRO METABOLISM <input type="checkbox"/> PROTOCOL <input type="checkbox"/> PHASE II PROTOCOL <input type="checkbox"/> PHASE III PROTOCOL <input type="checkbox"/> DOSING REGIMEN CONSULT <input type="checkbox"/> PK/PD- POPPK ISSUES <input type="checkbox"/> PHASE IV RELATED				
<input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST <input type="checkbox"/> SUPAC RELATED <input type="checkbox"/> CMC RELATED <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)				
<input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> ANNUAL REPORTS <input type="checkbox"/> FAX SUBMISSION <input type="checkbox"/> OTHER (SPECIFY BELOW):				
REVIEW ACTION				
<input type="checkbox"/> NAI (No action indicated) <input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail)				
<input type="checkbox"/> Oral communication with Name: [] <input type="checkbox"/> Comments communicated in meeting/Telecon. see meeting minutes dated: []				
<input type="checkbox"/> Formal Review/Memo (attached) <input checked="" type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER (SPECIFY BELOW): []				
REVIEW COMMENT(S)				
<input type="checkbox"/> NEED TO BE COMMUNICATED TO THE SPONSOR <input type="checkbox"/> HAVE BEEN COMMUNICATED TO THE SPONSOR				
COMMENTS/SPECIAL INSTRUCTIONS: [Minimal labeling revision was made at this time since this reviewer did formal review on this NDA (see submission dated 9/24/98 and 6/29/99).]				
SIGNATURE OF REVIEWER: <u>Shinja Kim</u>		Date <u>10/3/00</u>		
SIGNATURE OF acting TEAM LEADER: <u>Tien-Mien Chen</u>		Date <u>10/3/00</u>		
CC.: HFD-170 (Divisional File; ComptomK), HFD-870 (Kim, ChenT, MalinowskiH), CDR (Barbara Murphy)		Project Manager: <u>K. Compton</u> Date _____		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-533, No. SE 002

Submission Date: September 24, 1998; June 29, 1999 (fax)

Drug Name, Dose and Formulation: Naropin™ (Ropivacaine HCl Injection)

Sponsor: ASTRA Pharmaceuticals, L. P. Wayne, PA

Type of Submission: Supplemental NDA

Reviewer: Shinja R. Kim, Ph.D.

SYNOPSIS:

Ropivacaine is commercially available and has been approved for use in surgical anesthesia and acute pain management (postoperative and labor pain), local infiltration and peripheral nerve blocks. Astra pharmaceuticals has submitted this supplemental NDA, in support of labeling revisions that provide for increasing utility of ropivacaine; increasing the dosage for nerve block anesthesia using 7.5 mg/ml (from current 5 mg/ml) and for extending the duration of treatment for postoperative analgesia up to 72 hours (from up to 24 hours) using ropivacaine 2 mg/ml.

Eight clinical/pharmacokinetic studies, involving 119 subjects and patients ranging from 19 to 80 years of age, were conducted to support the submitted supplement. It consists of three postoperative pain management studies, epidural anesthesia for cesarean delivery, brachial plexus block in patients undergoing surgery of the upper limb and *in vivo* study of metabolic drug interaction with CYP1A2 (fluvoxamine) and CYP3A4 (ketoconazole) inhibitors. Two studies included in this section were not reviewed, because these studies did not look at pharmacokinetics of ropivacaine (one study involves investigating the efficacy of ropivacaine gel and the other study is a clinical study comparing bupivacaine and ropivacaine in terms of efficacy).

No significant issues have been found from a pharmacokinetics's point of view as to make this submission unapprovable. However, ropivacaine plasma concentrations in some patients may approach the threshold for CNS toxicity, after 300 and 375-mg infiltration (though, dosage recommendation for the infiltration procedure is 2-200 mg) or 300mg brachial block.

Comment to sponsor: No information has been submitted by the sponsor, regarding 'PK characterization in Special populations' as requested in the filing memorandum. We remind you of your phase IV commitment to evaluate the ropivacaine PK in hepatic impairment and pediatric patients. Additionally, please submit the information to justify that verapamil is a (strong) CYP1A2 inhibitor.

Recommendation: The NDA 20-533 is acceptable from the Clinical Pharmacology and the Biopharmaceutics perspective provided the Comment is addressed satisfactorily. Please forward the Comment, above to the sponsor.

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Shinja R. Kim, Ph.D.

Division of Pharmaceutical Evaluation II

RD

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11/07/06/99

Ramana Uppoor, Ph.D.

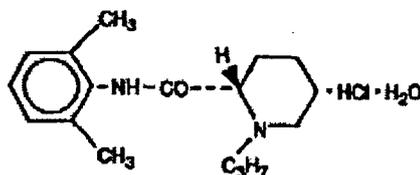
TABLE OF CONTENTS

Background.....	3
Summary of PK characteristics.....	4
Proposed labeling.....	10
Comments (to the medical officer).....	12
 <u>Appendix I (Study summaries)</u>	
94R083-01 72 hour continuous infusion with 20 and 30 mg/h ropivacaine 2 and 3 mg/ml for postoperative pain relief following major orthopedic surgery.....	14
94R084 Continuous 72 Hour epidural infusion of ropivacaine for pain management after orthopedic surgery.....	19
94R080 An open study using 150 mg and 187.5 mg of ropivacaine 7.5 mg/mL in epidural anesthesia for caesarean delivery.....	23
94R086 An open study using 300 mg, 375 mg and 450 mg of ropivacaine for postoperative pain relief after hernia repair.....	27
95R088 An open pharmacokinetic and tolerability study of ropivacaine 7.5 mg/mL, used for brachial plexus block in patients undergoing surgery of the upper limb.....	30
96R099 Effect of fluvoxamine and ketoconazole on the pharmacokinetics of single dose intravenous ropivacaine in healthy volunteers	34
Bioavailability.....	37
 <u>Appendix II (Attachment from NDA 20533-1S)</u>	
Formulation.....	39
Analytical Methodology.....	40

I. BACKGROUND

Naropin™ is the newest of the amide based local anesthetics. Its pharmacodynamic properties of producing minimal motor blockade while producing good sensory blockade at low concentrations has made it widely accepted in clinical practice for obstetrical labor pain control and for postoperative pain control. This drug chemically is closely related to mepivacaine and bupivacaine. It is marketed as a single isomer drug.

Naropin™ contains ropivacaine HCl which is chemically described as S-(-)-1-propyl-2', 6'-pipecoloxylidide hydrochloride monohydrate. The drug substance is a white crystalline powder, with a chemical formula of $C_{17}H_{26}N_2O \cdot HCl \cdot H_2O$, molecular weight of 328.89 and the following structural formula:



Ropivacaine has a distribution ratio between n-octanol and phosphate buffer at pH 7.4 of 141 and a pK_a of 8.07 in 0.1 M KCl solution. Ropivacaine injection is preservative free and is available in single dose containers in 2.0, 5.0, 7.5 and 10.0 mg/ml concentrations.

Ropivacaine is indicated for the production of local or regional anesthesia for surgery and pain management: (1) surgical anesthesia (epidural block for surgery including cesarean section; major nerve block; local infiltration), (2) pain management (epidural continuous infusion or intermittent bolus e.g., postoperative or labor; local infiltration). The doses administered depend on several factors: anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient.

Although ropivacaine is not dependent on the general circulation for exerting the local anesthesia, it is absorbed from epidural or local infiltration administration into systemic circulation where the secondary pharmacological effects such as CNS and cardiovascular toxicity occur. Edvardsson *et al.* reported that the threshold for CNS toxicity was at mean free arterial concentrations of approximately 0.6 mg/L (range 0.3-0.9 mg/L).

The study, submitted in NDA 20-533-1S, has shown that ropivacaine is extensively metabolized with about 1% excreted unchanged in urine. The major metabolite found in urine was 3-OH-ropivacaine (3-OH_R) (37%). Minor amounts of 4-OH-ropivacaine, N-despropyl ropivacaine (PPX) and 3-OH-N-despropyl ropivacaine (3-OH-PPX) were also found in urine. *In vitro*, ropivacaine is metabolized to 3-OH-ropivacaine by the CYP1A isozyme. The formation of 4-OH-ropivacaine; 2-OH-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 are not expected to impair the metabolism of ropivacaine. The proposed metabolic pathway is shown in Figure 1.

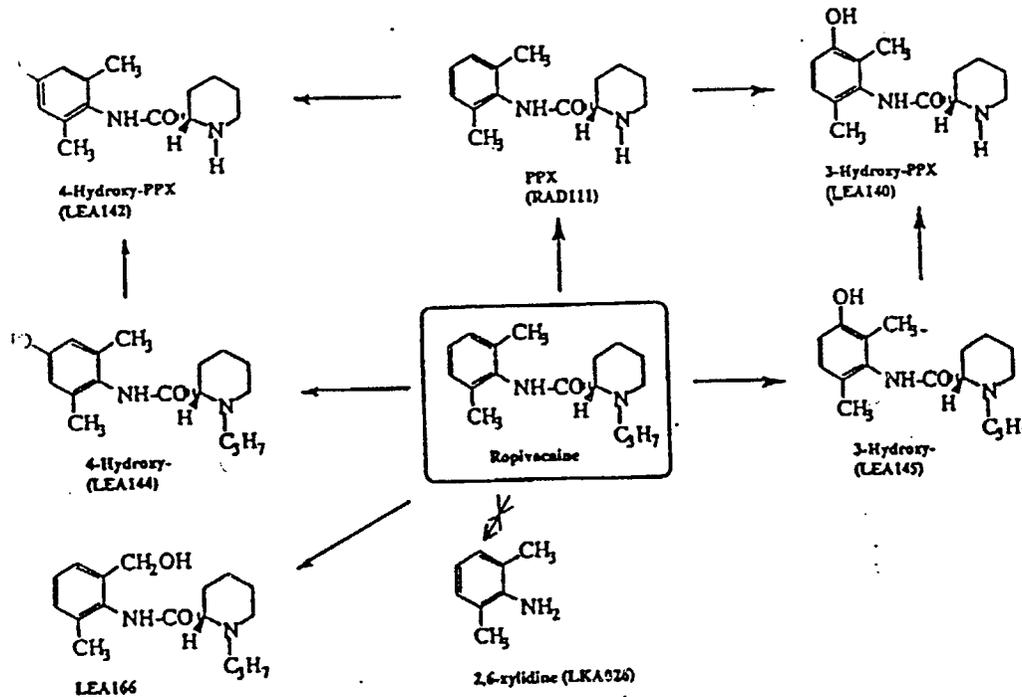


Figure 1. Proposed metabolic scheme of ropivacaine

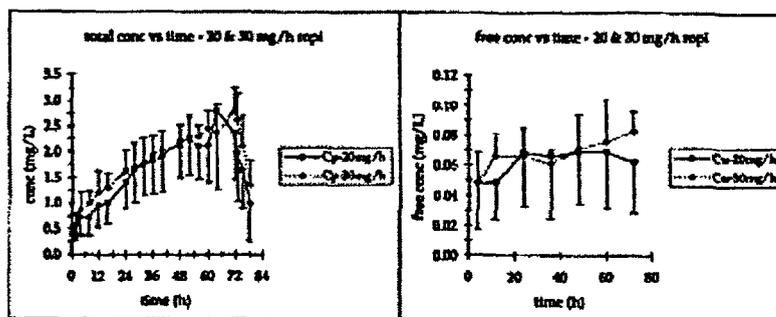
Pharmacological activity of metabolites: The effects of the main ropivacaine metabolites (PPX, 3-OH-PPX, 3-OH-ropivacaine and 4-OH-ropivacaine) were investigated in guinea pigs. The results indicated that all metabolites of ropivacaine tested, except 3-OH-PPX, produced local anesthetic effect. Also, it was found that activity of unbound PPX was about one twelfth of that of unbound ropivacaine in mice.

II. EPIDURAL INFUSION (Pain management)

Study 94RO83 was designed as double blind, randomized study with two parallel treatment groups, conducted in 12 patients in each group for total knee or total hip surgery. An epidural bolus injection of 50 or 75 mg ropivacaine 5 mg/ml was given prior to surgery and the infusion pump was then immediately started with epidural infusion rates of 20 mg/h (2 mg/ml) or 30 mg/h (3 mg/ml) ropivacaine for 72-h. If the postoperative degree of motor block exceeded one (according to the Bromage scale) or if the sensory block exceeded T4, the infusion rate could be reduced by 2 ml/h. The results are summarized here: (1) The mean (\pm SD) dose of ropivacaine administered during the 72-h treatment for 20 and 30 mg/h group are 1493.92 ± 9.9 mg and 2020.8 ± 206.2 , respectively. (2) The total plasma concentrations (*i.e.*, bound and unbound ropivacaine) increased with time throughout the treatment period, however, the free concentrations leveled off at around 24-36 hours after the start of infusion with mean unbound steady state concentrations ($C_{ss, u}$) of about 0.06 mg/L and 0.07 mg/L for ropivacaine 20 mg/h and 30 mg/h, respectively (Figure 2). This unbound ropivacaine is below the levels that may result in CNS toxicity. (3) Large variability was seen in AUC in both treatment groups. The increase in mean AUC (and AUC_u) after the epidural infusion of 30 mg/h compared to 20 mg/h was only about 10%. (4) The terminal half-life was estimated to be

about 5 h, with CL of 11-14 L/h. (5) The α_1 -acid glycoprotein (AAG; protein to which ropivacaine is bound to extensively) plasma concentration decreased slightly during the first few hours of infusion but then increased throughout the treatment period. The f_u -time curve of AAG appears to be identical with C_u ropivacaine-time curve. (6) Plasma concentrations of PPX were on average about half of those of ropivacaine, however, the mean unbound PPX (PPX_u) was 7 times higher than that of ropivacaine. Since PPX_u is 12 times less 'active' than that of ropivacaine, about 39% of the 'CNS activity' could be due to PPX_u . In addition, plasma concentrations of 3-OH-ropivacaine were minimal (*i.e.*, below LOQ level). (7) 3-OH-ropivacaine and PPX are the major metabolites excreted in urine during 72-h epidural infusion; about 2% is excreted as unchanged ropivacaine, and about 19% and 10% as 3-OH-ropivacaine and PPX. (8) It appears that there is no significant difference in pain scores (VAS) between the two doses.

Figure 2: The mean (\pm SD) total and unbound plasma concentrations after continuous 72-h epidural infusion of ropivacaine 20 mg/h and 30 mg/h for post-operative pain relief after surgery.



Study 94RO84 was a single center, open-labeled, uncontrolled study, conducted in eleven patients. Within one hour of the end of surgery an epidural infusion of ropivacaine 2 mg/ml was started at 6 ml/h. The infusion was then adjusted during the 72 hours infusion period according to pain scores rated by the patient on a Visual Analogue Scale (VAS). The results can be summarized as follows: (1) Total individual doses given during the treatment varied between 690 and 1559 mg. (2) The total plasma concentrations increased with time throughout the treatment period but the free concentrations leveled off more. The highest individual total plasma concentration (C_{high}) of ropivacaine was determined to be 5.2 mg/L, while the individual free plasma concentrations ($C_{high,u}$) ranged from _____ . The plasma C_{max} (equivalent to C_{high}) at 21 hours, from previous study NDA 20533-1S, ranged from _____ whose value is similar to this study. (3) The mean terminal half-life was estimated to 6 h (*flip-flop* kinetics; $t_{1/2} \cong 2$ hr after iv dose). (4) The AAG plasma concentration increased during the course of the study, with a trend towards a decreasing free fraction of ropivacaine with time. (5) The urinary recovery of ropivacaine, 3-OH-R (conjugated and unconjugated) and PPX during the treatment and within 10 h of the end of infusion was in total 20-39% of the given dose with mean 1.6% excreted as unchanged ropivacaine and about 18% and 10% excreted as 3-OH-R and PPX.

III. EPIDURAL ANESTHESIA

Study 94RO80 was a single center, open, non-randomized, rising dose design clinical trial for which 3 consecutive dose groups were planned; eight women scheduled for elective Cesarean section each received 150 mg (20 ml) ropivacaine 7.5 mg/ml and another 8 women received 187.5 mg (25 ml). The third dose group (225 mg) was never entered into the trial due to the results from the first two groups (the decision was mainly based on excessive sensory blocks and more frequent events of hypotension in the 187.5 mg than in the 150 mg group). The patients received ropivacaine epidurally

as a single dose injected in 5 minutes with a motorized syringe. In order to characterize PK, peripheral maternal venous (MV) blood samples and umbilical venous (UV) and arterial (UA) blood samples from the umbilical cord (at the time of delivery) were collected for ropivacaine (total and free). AAG was also analyzed. The results show the following: (1) Unbound ropivacaine appears to increase dose-proportionally (*i.e.*, $C_{max,u}$, MV_u , UV_u and UA_u) between 150 and 187.5 mg doses. (2) The estimated apparent CL ranged from _____ 3) The estimated terminal $t_{1/2}$ was 6-7 hours after the two doses (flip-flop situation). (4) The free concentrations at the time of delivery were higher in the mothers than in the neonates with ratios between the maternal vein and the umbilical vein (UV_u/MV_u) of about 0.8 at both doses (Figure 4). (5) The MV_u is below the threshold for CNS toxicity (*e.g.*, 0.1-0.12 mg/L). (6) The plasma concentrations of both total and free ropivacaine in the blood leaving the fetus (UA) were lower than in the blood entering the fetus (UV), with ratios of about 0.8 for both UA/UV and UA_u/UV_u (Figure 5). This can be due to elimination and distribution from the fetus itself. The total plasma concentration-time profile of ropivacaine following an epidural injection of 150 mg and 187.5 mg ropivacaine is shown in Figure 3 below.

Figure 3

Figure 4

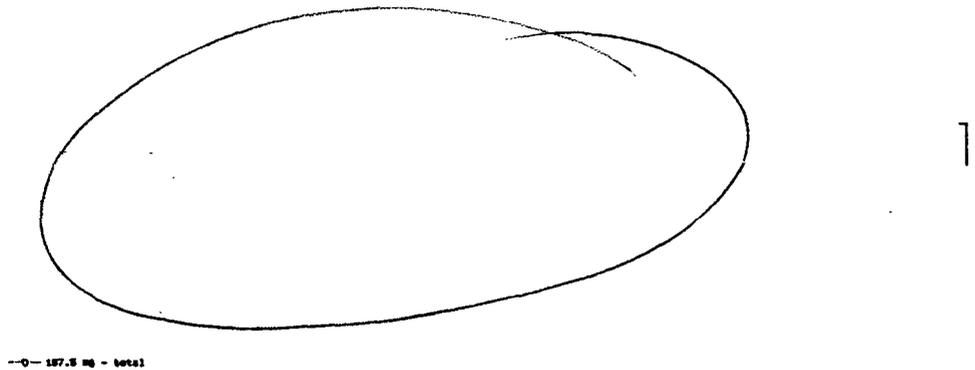
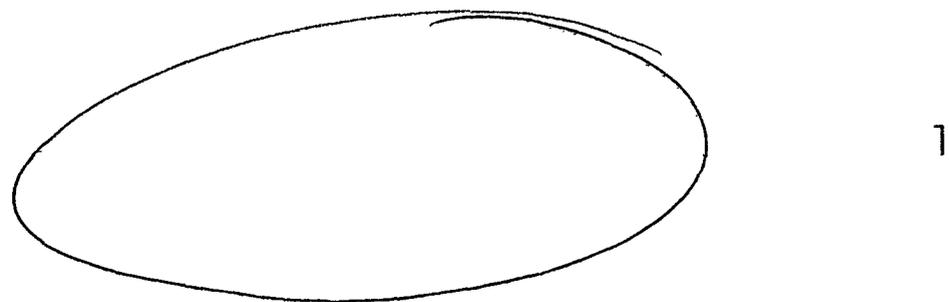


Figure 5

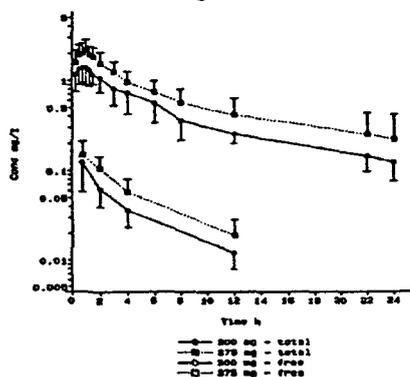


INFILTRATION

Study 94RO86 was a single center, open-labeled, non-randomized, rising dose design clinical trial for which 3 consecutive dose groups were planned; ten male patients scheduled for elective, primary,

unilateral, inguinal hernia repair each received 300 mg ropivacaine 7.5 mg/ml. Another 10 patients received 375 mg. The third dose group (450 mg) was never entered into the trial. Summarized results are as follows: (1) $C_{max,u}$ in some patients after 300 and 375 mg for infiltration may approach the threshold for CNS toxicity (e.g., 0.234 and 0.227 mg/L). (2) The analysis of dose-proportionality in the present study was inconclusive. (3) The estimated terminal $t_{1/2}$ of 5-33 h is longer than that reported after intravenous administration, about 2 h, indicating absorption-dependent elimination. (4) Caution is needed in repeated infiltration with ropivacaine when used at these high doses, because a very long $t_{1/2}$ were evidenced in a few patients. (5) Analgesia represented as pain at mobilization seems to be inversely correlated with the terminal $t_{1/2}$ (i.e. increased analgesia was seen in the patients where ropivacaine was slowly removed from the site of administration, long absorption $t_{1/2}$). (6) The sponsor stated that the planned 3rd group never entered into the trial since there was no increase in clinical effect with the 375-mg dose and an increased variation in plasma concentrations with the increased dose. The mean plasma concentrations of ropivacaine after the infiltration of 300 mg and 375 mg ropivacaine 7.5 mg/ml at the end of surgery is shown below (Figure 6).

Figure 6



V. BRACHIAL PLEXUS BLOCK

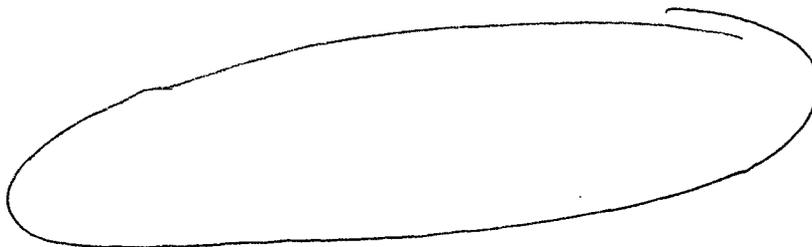
Study 95RO88 was an open label pilot study conducted in fourteen patients (2 females and 12 males; 21-66 years age) who were undergoing elective reconstructive or plastic surgery in the hand and forearm. The brachial plexus block was performed via the axillary approach. There were 3 dose groups: 30-ml (225-mg) in 2 patients, 35 ml (262.5 mg) in 2 patients and 40-ml (300-mg) in 10 patients using ropivacaine 7.5 mg/ml. Conclusions are as follows: (1) It is difficult to determine dose-proportionality due to only 2 subjects in two lower dose groups. (2) f_u is calculated to be about 5-9%, based on the one-point estimate $C_{u,45}$ (unbound ropivacaine concentration at 45 minutes, first sample time-point) and C_{max} . (3) Rather than stating that 'no correlation' was found regarding the relationship between f_u and C_{total} , it should be interpreted as ' f_u was constant through out the study time' (i.e., unbound concentration (C_u) was maintained at about 5% of total concentration, C_{total}). (4) The plasma levels of AAG were not changed between the samples taken before the dose administration and the 24-h samples. (5) Some patients in the 300 mg group may approach the threshold for CNS toxicity (e.g., $C_{u,45} = 0.264$ mg/L).

VI. DRUG-DRUG INTERACTION

Study 96RO99 was an open label, randomized, balanced crossover study design of three periods, each separated by a washout period of 7-15 days in 12 healthy volunteers, males and females.

Subjects received either ropivacaine 40 mg iv infusion alone or co-administered oral fluvoxamine (dosed with 100mg total; CYP1A2 inhibitor) or ketoconazole (400 mg total dose; CYP3A4 inhibitor): the oral drugs (inhibitors) were given as two daily doses (8AM & 8PM) for two days with the first day being the day before administration of ropivacaine, altogether 4 doses. On the second day of inhibitor administration, 1 h after the morning dose, the infusion of ropivacaine started. Figure 7 shows the total plasma concentrations of ropivacaine after 40 mg ropivacaine given as a 20-min iv infusion alone (left), during coadministration of ketoconazole (middle) and during coadministration of fluvoxamine (right) to 12 healthy subjects.

Figure 7



The results from the study are as follows: (1) Co-administration of fluvoxamine resulted in a 70% reduction in clearance of ropivacaine, the magnitude of reduction was similar to the change in the fraction of the dose excreted as 3-OH- ropivacaine. This indicates that the observed reduction in CL arises mainly from a reduction of 3-OH formation, most likely through the inhibition of CYP1A2. (2) When fluvoxamine was co-administered, there was an increase in PPX formation, indicating an increase in the amount of metabolite formed via CYP3A4. The K_m values *in vitro* for the formation of 3-OH-ropivacaine by CYP1A2 and PPX by CYP3A4 are 16 μ M and 400 μ M respectively. When metabolism via CYP1A2 is inhibited, the concentration of ropivacaine increases and thus more PPX can be formed via CYP3A4 despite the higher K_m . (3) The results of this study verify the previous results of *in vitro* studies, showing that CYP1A2 and CYP3A4 are important enzymes for the metabolism of ropivacaine. CYP1A2 is the quantitatively most important enzyme since the plasma clearance of ropivacaine is reduced by 70% during co-administration of a selective and potent CYP1A2 inhibitor (fluvoxamine). This reduction could be of clinical importance during long-term administration. A selective and potent inhibitor of CYP3A4 (ketoconazole) slightly reduces (about 15% decrease) the clearance of ropivacaine, therefore, this reduction may not likely be of clinical relevance.

VII. BIOAVAILABILITY

Bioavailability was compared between 5 mg/ml (from the study submitted in NDA 20533-1S, I18) and 7.5 mg/ml (from study 94R080 and a study submitted in NDA 20533-1S, I19) formulations following 150 mg ropivacaine via epidural anesthesia in cesarean section patients. The mean total C_{max} in the mother using 5 mg/ml was 1.3 mg/L and with 7.5 mg/ml, 1.5 mg/L (I19) and 1.1 mg/L (94R080). The mean MV_u concentration using 5 mg/ml was 0.099 mg/L and the corresponding concentrations using 7.5 mg/ml were 0.089 mg/L and 0.1 mg/L. Similarly, the mean UV_u concentrations at delivery were 0.072 mg/L using 5 mg/ml and 0.06 mg/L and 0.08 mg/L using 7.5 mg/ml. In summary, the 5 and 7.5 mg/ml strengths appear to be equally bioavailable when used in epidural nerve block cesarean patients.

VIII. ANALYTICAL METHODOLOGY

IX. CONCLUSIONS

- The total plasma ropivacaine concentrations increased with time throughout the treatment period, however, the free concentrations leveled off, with f_u of 3.5%, at around 24-36 hours after the start of continuous epidural infusion of 72-h. Similarly, AAG plasma concentration increased throughout the treatment period after a 72-h continuous infusion. On the other hand, AAG level in plasma did not change following a brachial block (f_u was calculated to be 5-9%).
- The terminal half-life was estimated to be about 5-7 h following an epidural infusion or local nerve block, which is longer than that reported after intravenous administration, about 2 h, indicating absorption-dependent elimination (or flip-flop). Especially, a very long $t_{1/2}$ (> 30 h) was evidenced in a few patients, therefore, caution is needed in repeated infiltration with ropivacaine when used at these high doses (*i.e.*, 300 or 375 mg).
- Plasma concentrations of PPX were on average about half of those of ropivacaine, however unbound PPX was about 7 times higher than that of ropivacaine after a continuous epidural infusion of 72-h.
- The plasma C_{max} at 21 hours, from previous study NDA 20533-1S, ranged from _____ whose value is similar to this study following a 21hr-epidural continuous infusion.
- Unbound ropivacaine appears to increase dose-proportionally between 150 and 187.5-mg doses administered in epidural anesthesia for cesarean delivery.
- Bioavailability appears to be comparable between 5 and 7.5 mg/ml, used in epidural nerve block cesarean patients.
- The plasma concentration ratio of UA/UV or UA_u/UV_u was about 0.8. Therefore, ropivacaine is distributed to the fetus (the medical officer, M. Roberts, M.D. confirms that it should not be a problem for the baby).
- Some patients, after 300 and 375-mg infiltration or 300mg brachial block, may approach the threshold for CNS toxicity. Following a continuous 72-h infusion in orthopedic patients, the unbound ropivacaine was below the threshold for CNS toxicity.
- 3-OH-ropivacaine and PPX are the major metabolites excreted in urine during 72-h epidural infusion; about 2% is excreted as unchanged ropivacaine, and about 19% and 10% as 3-OH-R and PPX.
- Co-administration of fluvoxamine or ketoconazole with ropivacaine verified the previous results of *in vitro* studies, showing that CYP1A2 (quantitatively most important enzyme) and CYP3A4 are important enzymes for the metabolism of ropivacaine.
- Information regarding characterization of PK in 'Special populations' (hepatic/renal failure, gender, geriatric, etc) is not included in the package insert/NDA submission even though the sponsor was requested in the filing memorandum. However, the sponsor previously made phase IV commitments to conduct a study to characterize PK in hepatic failure patients and pediatric patients.

X. PRELIMINARY COMMENTS ON PROPOSED PACKAGE INSERT

Note: Strikeouts and underlined text indicate the sponsor's deletions and additions respectively. Italics are the reviewer's suggested additions and strikeouts over underlined text indicate the reviewer's suggested deletions.

PHARMACOKINETICS

Absorption

The systemic concentration of ropivacaine is dependent on the total dose and concentration of drug administered, the route of administration, the patient's hemodynamic/circulatory condition and the vascularity of the administration site. From the epidural space, ropivacaine shows complete and biphasic absorption. The half-lives of the two phases, (mean ± SD) are 14 ± 7 minutes and 4.2 ± 0.9 h, respectively. The slow absorption is the rate limiting factor in the elimination of ropivacaine which explains why the terminal half-life is longer after epidural than after intravenous administration. Ropivacaine shows dose-proportionality up to the highest intravenous dose studied, 80 mg, corresponding to a mean ± SD peak plasma concentration of 1.9 ± 0.3 µg/mL.

Pharmacokinetic (plasma concentration-time) data from clinical trials

Route	Infusion ^a		Epidural ^b		Block ^c	Infusion ^d	
Dose received (mg)	[redacted]		150	187.5	300	40	
n	12	12	11	8	8	10	
C _{max} (mg/L)	2.4±1 ^e	[redacted]	2.3±1.1 ^e	1.1±0.2	1.6±0.6	2.3±0.8	1.2±0.2 ^f
T _{max} (min)	[redacted]		43±14	34±9	54±22	[redacted]	
AUC _{0-∞} (mg·h/L)	[redacted]		161±90	7.2±2	11.3±4	13±3.3	1.8±0.6
CL (L/h)	11.03	13.7	[redacted]	5.5±2	5±2.6	[redacted]	21.2±7
t _{1/2} (hr)	5±2.5	5.7±3	6.0±3	5.7±2	7.1±3	6.8±3.2	1.9±0.5 ^g

^aBrachial plexus block with 7.5 mg/ml ropivacaine.

^cC_{ma} measured at the end of infusion (i.e., at 72 hr).

^fC_{ma} measured at the end of infusion (i.e., at 20 minutes).

^gt_{1/2} is the true terminal half-life. On the other hand, t_{1/2} follows absorption-dependent elimination (flip-flop) after non intravenous administrations.

Distribution

After intravascular infusion, ropivacaine has a steady state volume of distribution of 41 ± 7 liters. Ropivacaine is 94% protein bound, mainly to α₁-acid glycoprotein. An increase in total plasma concentrations during continuous epidural infusion has been observed, related to a postoperative increase of α₁-acid glycoprotein. Variations in unbound, i.e. pharmacologically active, concentrations have been less than in total plasma concentration. Ropivacaine readily crosses the placenta and equilibrium in regard to unbound concentration will be rapidly reached (see PRECAUTIONS, Labor and Delivery).

Metabolism

Ropivacaine is extensively metabolized in the liver, predominantly by aromatic hydroxylation mediated by cytochrome P4501A2 to 3-hydroxy ropivacaine. Approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy ropivacaine. Low concentrations of 3-hydroxy ropivacaine have been found in the plasma. Urinary excretion of the 4-hydroxy, the N-dealkylated (PPX) and both the 3-hydroxy and 4-hydroxy N-dealkylated metabolites accounts for less than 3% of dose. An additional metabolite, 2-hydroxy-methyl- ropivacaine, has been identified but not quantified in the urine. PPX and 3-OH- ropivacaine are the major metabolites excreted in the urine during epidural infusion.

Total PPX concentration in the plasma was about half as that of total ropivacaine, however, than that of unbound ropivacaine following continuous epidural infusion up to 72 hours. Unbound PPX 3-hydroxy and 4-hydroxy ropivacaine have a pharmacological activity in animal models less than that of ropivacaine. There is no evidence of *in vivo* racemization in urine of ropivacaine.

Elimination

The kidney is the main excretory organ for most local anesthetic metabolites. In total, 86% of the ropivacaine dose is excreted in the urine after intravenous administration of which only 1% relates to unchanged drug. Ropivacaine has a mean \pm SD total plasma clearance of 387 ± 107 mL/min, an unbound plasma clearance of 7.2 ± 1.6 L/min, and a renal clearance of 1 mL/min. The mean \pm SD terminal half-life is 1.8 ± 0.7 h after intravascular administration and 4.2 ± 1.0 h after epidural administration (see Absorption).

Clinically Significant Drug-Drug Interactions

Naropin should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive.

Cytochrome P4501A2 is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. *In vivo* the plasma clearance of ropivacaine was reduced by 70% during coadministration of fluvoxamine (25 mg bid for 2 days), a selective and potent CYP1A2 inhibitor. Thus strong inhibitors of cytochrome P4501A2, such as fluvoxamine

given concomitantly during administration of Naropin, can interact with Naropin leading to increased ropivacaine plasma levels. Caution should be exercised when CYP1A2 inhibitors are coadministered. Possible interactions with drugs known to be metabolized by CYP1A2 via competitive inhibition such as theophylline and imipramine may also occur.

coadministration of a selective and potent inhibitor of CYP3A4, Ketoconazole (100 mg bid for 2 days with ropivacaine infusion administered 1 hour after ketoconazole) caused a 15% reduction in *in vivo* plasma clearance of ropivacaine.

XI. COMMENTS TO THE MEDICAL OFFICER:

- Some patients, after 300 and 375-mg infiltration (however, in the package insert, dosage recommendation for the infiltration procedure is 2-200 mg) or 300mg brachial block, may approach the threshold for CNS toxicity as indicated by high unbound plasma concentrations.
- A very long $t_{1/2}$ (> 30 h) was evidenced in a few patients, therefore, caution is needed with ropivacaine when used at high doses (*e.g.*, 300 or 375 mg), upon repeated infiltration administration.
- The plasma concentration ratio of umbilical venous/umbilical artery (UA/UV) or $UA_{unbound}/UV_{unbound}$ was about 0.8. Therefore, ropivacaine is distributed to the fetus.
- Bioavailability of the two strengths, 5 and 7.5 mg/ml is comparable.
- The plasma clearance of ropivacaine is reduced by 70% during co-administration of a selective and potent CYP1A2 inhibitor, fluvoxamine. This reduction could be of clinical importance during long-term administration. A selective and potent inhibitor of CYP3A4 (ketoconazole) slightly reduces (about 15% decrease) the clearance of ropivacaine, therefore, this reduction may not likely be of clinical relevance. However, ropivacaine was administered 1 hour after ketoconazole. Therefore, this study may not accurately represent the interaction upon concomitant administration in that the magnitude of effect may actually be higher upon concomitant administration. Also, the maximum recommended daily dose of ketoconazole (400 mg) was not used in this study.

APPENDIX I

Study 94R083: 72-h continuous epidural infusion with 20 and 30 mg/h using ropivacaine 2 and 3 mg/ml for postoperative pain relief following major orthopedic surgery - a pharmacokinetic and clinical evaluation.

Reference: Volume 10 - 12

Investigators: J.W. van Kleef, M.D., Ph.D.

Study Locatic

Department of Bioanalysis, Astra Pain Control AB, Sweden (Analytical)

Formulation:

Treatment	Strength & Dosage Form	Lot #
A	2 mg/ml, 50 ml-vial (infusion)	1202-4-1
B	3 mg/ml, 50 ml-vial (infusion)	1203-2-1
A & B	5 mg/ml, 20-ml ampoule (bolus)	471-36-1

Objective:

Primary: To obtain the plasma concentration-time profile of ropivacaine (both total and free concentrations) when infused epidurally for 72 h and to compare the pharmacokinetics variables obtained for two groups, using two different infusion rates.

Secondary:

- To determine the change in the plasma concentration of α_1 -acid glycoprotein (AAG) with time.
- To estimate the urinary excretion of unchanged ropivacaine.
- To assess the plasma levels and the urinary excretion of the major metabolites 3-OH-ropivacaine (3-OH-R), N-depropylated ropivacaine (PPX) and 2-OH-methyl ropivacaine.
- To exploratively estimate clinical efficacy and tolerability.

Study Design: Double blind, randomized with two parallel treatment groups conducted in 24 patients. An epidural bolus injection of 50 or 75 mg ropivacaine 5 mg/ml was given prior to surgery and the infusion pump was then immediately started with the patients randomized to epidural infusion rates of 20 or 30 mg/h ropivacaine for 72 h. If the postoperative degree of motor block exceeded one (according to the modified Bromage scale) or if the sensory block exceeded T4, the infusion rate could be reduced by 2 ml/h.

Assessment Methods:

Pharmacokinetics: Peripheral venous blood samples for assays of ropivacaine (total and free plasma concentrations), major metabolites (3-OH-R, PPX and 2-OH-methyl-ropivacaine) and AAG were taken during the infusion period and during 6 h after the end of infusion. Urine was collected at 12-h intervals to estimate the urinary excretion of unchanged ropivacaine and the major metabolites.

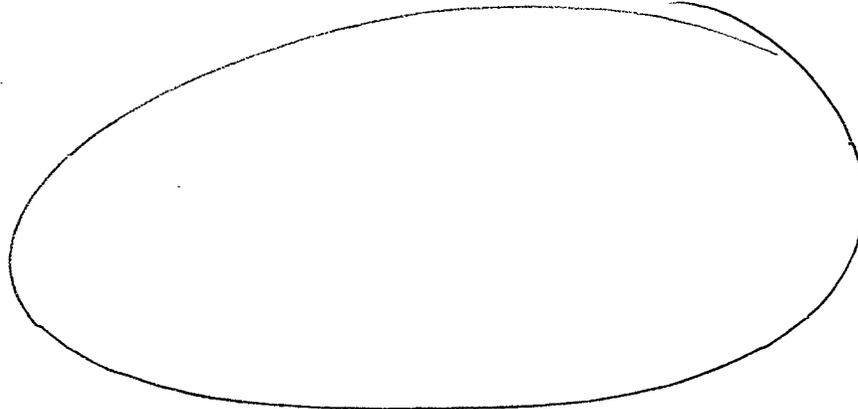
Efficacy assessments: Sensory (by temperature perception changes using an ice cube) and motor block (by modified Bromage scale), postoperative pain scores at rest (VAS at 8:00, 12:00 and 20:00 hours during the treatment period and at the end of the infusion) and amount of PCA morphine and number of PCA requests.

Safety assessments: Cardiovascular changes, body temperature, blood loss during and after surgery, clinical chemistry, and adverse events.

Statistical Methods: The clinical efficacy and safety variables in the study were evaluated by summary measures and graphical presentations. The pharmacokinetic variables were evaluated for a

dose effect using Wilcoxon (mid) rank sum test and nonparametric confidence intervals. The statistical significance level was set to 0.05.

Analytical Methodology:



Results and discussion:

Total and free ropivacaine plasma concentrations: The mean (SD) dose of ropivacaine administered during the 72-h treatment (include a bolus dose) for 20 and 30 mg/h group are 1493.92±9.9 mg (55.4±10.6 mg) and 2020.8±206.2 (54.2±9.7), respectively. The summary of PK parameters for total and unbound ropivacaine after continuous infusion of 20 and 30 mg/h is listed in in the Table below:

	Ropi 2 mg/ml	Ropi 3 mg/ml
AUC ₀₋₇₈ , total (mg•hr/L)	132.23	142.95
AUC _{0-∞} , total (mg•hr/L)	135.5	147.3
AUC ₀₋₇₈ , unbound (mg•hr/L)	4.69	5.08
AUC _{0-∞} , unbound (mg•hr/L)	4.9	5.34
f _u ¹	3.5%	3.5%
CL (L/h)	11.03	13.7
CL _u (L/h) ²	304.8	378.4
T _{1/2} (hr)	5.0±2.5	5.7±2.6

¹based on total plasma concentration at the end of infusion (i.e., at 72 h)

²AUC_{unbound, 0-∞} / AUC_{total, 0-∞} ³CL_u = dose / AUC_{unbound, 0-∞}

The total plasma concentration increased continuously with time, ranging from _____ and from _____ following a continuous infusion of 20 mg/h and 30 mg/h, respectively (Figure 1). However, the free concentration of ropivacaine seemed to be reaching steady state after 24 – 36 hours of continuous infusion with a mean C_{ss, u} of about 0.06 mg/L and 0.07 mg/L for ropivacaine 20 mg/h and 30 mg/h, respectively (Figure 1). Figure 2 show the mean free plasma (C_u) levels with the mean free fraction (f_u) versus time. The f_u decreased with time until around 36 hours, and then it became steady, which is consistent with the C_u profile. The AAG plasma concentration decreased slightly during the initial hours of infusion but increased thereafter through out treatment

period as shown in Figure 3. Figure 4 shows the mean f_u and mean AAG plasma levels as a function of time for both treatment groups.

Figure 1: Mean (SD) total and unbound plasma concentrations after continuous 72-h epidural infusion of ropivacaine 20 mg/h (n = 14) and 30 mg/h (n = 7) for post-operative pain relief after major knee and hip surgery.

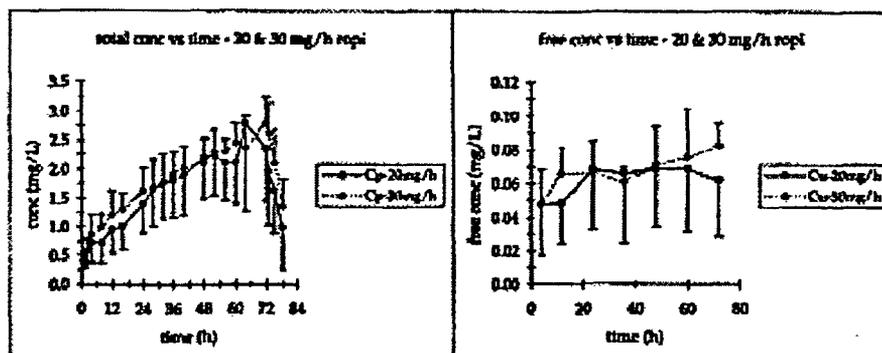


Figure 2: Mean (SD) free plasma levels (C_u), together with the mean free fraction versus time (f_u) following epidural infusion with ropivacaine 20 and 30 mg/h.

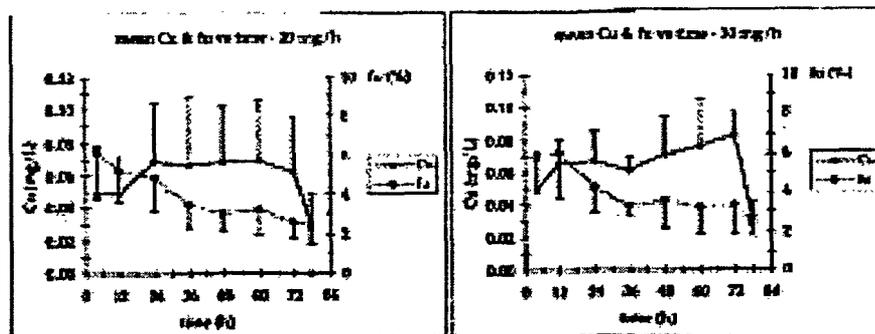


Figure 3: Mean (SD) plasma concentrations of α_1 -acid glycoprotein versus time in all patients.

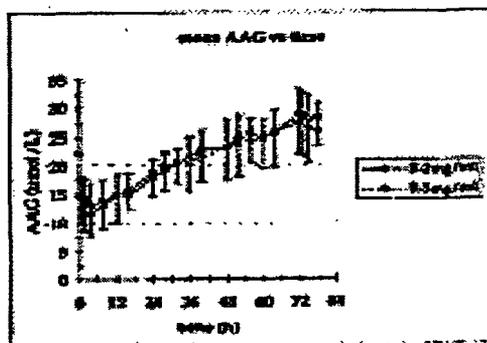
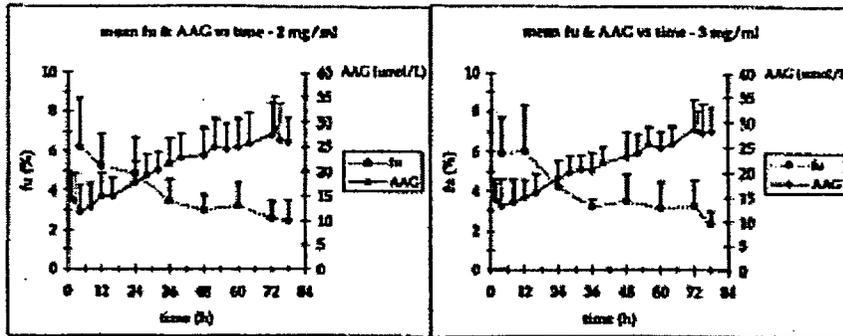


Figure 4: Mean (SD) unbound fraction (fu) and plasma levels of AAG after continuous 72-h epidural infusion of ropivacaine 20 mg/h and 30 mg/h for post operative pain relief after major knee and hip surgery.



Plasma metabolites and Urinary Excretion: The mean (\pm SD) total and free plasma concentrations of ropivacaine (Ropi) and unconjugated N-depropylated ropivacaine (PPX), and its ratio as well as estimated sum of total “activity” at the time of the end of infusion are shown in the Table below (right). It has been shown in rats that the maximum mean tolerated unbound plasma concentration of PPX was about 12 times higher than that of unbound ropivacaine. Therefore, the “activity” was defined by “ $Ropi_u + PPX_u / 12$ ”. No plasma concentrations of 3-OH-ropivacaine and 2-OH-methyl-ropivacaine were detected. The mean (\pm SD) urinary excretion of ropivacaine, 3-OH-R and PPX during the treatment with ropivacaine 2 and 3 mg/ml for 72 h and within 6 h of the end of infusion as % of the total administered ropivacaine dose are shown in the Table below (left). There was no recovery of the 2-OH-methyl-ropivacaine in the urine during this period.

	Plasma concentration (mg/L)				Urinary excretion		
	20 mg/h		30 mg/h		f_c^3 (%)	20mg/h	30mg/h
	Total	Free	Total	Free		1.8 \pm 2.0	1.5 \pm 0.6
PPX	1.0 \pm 0.4	0.44 \pm 0.19	1.2 \pm 0.4	0.52 \pm 0.16	f_m^4 , 3-OH-R(%)	19 \pm 6	19 \pm 4
Ropi	2.4 \pm 0.9	0.06 \pm 0.03	2.6 \pm 1.0	0.09 \pm 0.03	f_m^4 , PPX(%)	10 \pm 3	11 \pm 4
Ratio	0.54 \pm 0.3 ¹	0.1 \pm 0.05 ²	0.56 \pm 0.2 ¹	0.13 \pm 0.04 ²	% of dose ³	31 \pm 5	31 \pm 4

¹ratio = PPX/Ropi

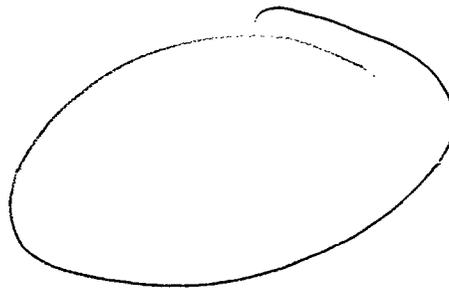
⁴fraction metabolized.

²activity

³fraction excreted unchanged.

⁵Cumulative urinary excretion as % of given dose.

The pain scores (VAS) at rest were assessed at scheduled times during the treatment period. The figure below shows the individual pain scores-time profile for ropivacaine 2 mg/ml (left) and 3 mg/ml (right) group.



Summary:

- The mean (SD) doses of ropivacaine administered during the 72-h treatment (include a bolus dose) for 20 and 30 mg/h group are 1493.92 ± 9.9 mg (55.4 ± 10.6 mg) and 2020.8 ± 206.2 (54.2 ± 9.7), respectively.
- The total plasma concentrations increased with time throughout the treatment period (in relation to the increase in AAG), however, the free concentrations leveled off at around 24-36 hr after the start of infusion with a mean $C_{ss,u}$ of about 0.06 mg/L and 0.07 mg/L for ropivacaine 20 and 30 mg/h, respectively. This $C_{ss,u}$ level is below the threshold for CNS toxicity.
- Large variability was seen in AUC in both treatment groups. The increase in mean AUC (and AUC_u) after the epidural infusion of 30 mg/h compared to 20 mg/h was only about 10%. The terminal half-life was estimated to be about 5 h, with CL of 11-14 L/h.
- The AAG plasma concentration decreased slightly during the first few hours of infusion but then increased throughout the treatment period. The f_u -time profile of AAG appears to be identical with C_u ropivacaine-time profile.
- The plasma concentration of PPX was on average about half of that of ropivacaine. The mean unbound fraction (f_u) of PPX was calculated to be 42% (44% based on average PPX_u). Therefore, about 39% (41.2 and 36.7% for 2 and 3 ml/h group) of the 'CNS activity' was due to PPX_u; e.g., activity due to PPX = $1.9 \mu\text{mol}\cdot\text{L}^{-1}/12 = 0.1583$; $C_{u,ropivacaine} = 0.226 \mu\text{mol}\cdot\text{L}^{-1}$; $0.1583 \times 100/(0.1583+0.226) = 41.2\%$. In addition, plasma concentrations of 3-OH-ropivacaine were minimal (*i.e.*, LOQ level).
- 3-OH-R and PPX are the major metabolites excreted in urine during 72-h epidural infusion; about 2% excreted as unchanged ropivacaine, and about 19% and 10% as 3-OH-R and PPX.
- It appears that there is no significant difference in pain scores (VAS) between the two doses.

Comment:

It would have been more accurate if comparison (s) between PPX and ropivacaine was made based on their AUCs rather than one-time point estimate of concentration. Also, urine collection should have been longer than 6 hours after the end of infusion (*i.e.*, 6 hrs represents only one half-life) to estimate f_e or f_m accurately; only 31% (mean) of total dose was recovered with present design.

Study 94R084: Continuous 72 hour epidural infusion of ropivacaine for pain management after orthopedic surgery: a clinical and pharmacokinetic evaluation.

Reference: Volume 19 - 20

Investigators: David Scott, MB, BS, FANZCA

Study Location: _____
Department of Bioanalysis, Astra Pain Control AB, Sweden (Analytical)

Formulation: Ropivacaine 2 mg/ml solution for injection in 50 ml vials (Lot # 1202-4-1).

Objective:

To obtain information on the efficacy, tolerability and pharmacokinetics of ropivacaine during 72 hour epidural infusion after orthopedic surgery.

Study Design:

A single center, open label, uncontrolled study conducted in eleven patients. Within one hour of the end of surgery an epidural infusion of ropivacaine 2 mg/ml was to be started at 6 ml/h. The infusion was then adjusted during the 72 hours infusion period according to pain scores rated by the patient on a Visual Analogue Scale (VAS). If a pain score was over 30 mm, the infusion rate was increased by 2 ml/h up to a maximum of 14 mg/ml. Each increase was preceded by a 6 ml top-up of ropivacaine 2 mg/ml. Bolus doses of 3-5 mg of Morphine intramuscularly were to be given at the patient's request as rescue medication.

Assessment Methods:

Pharmacokinetics: Peripheral venous blood samples were obtained for assays of ropivacaine (total and free plasma concentrations) and α_1 -acid glycoprotein (AAG) at regular intervals during and after the infusion. Urine was collected at 12-hour intervals to estimate the urinary excretion of unchanged ropivacaine and the major metabolites (3-OH-ropivacaine and pipercoloxylidide, PPX).

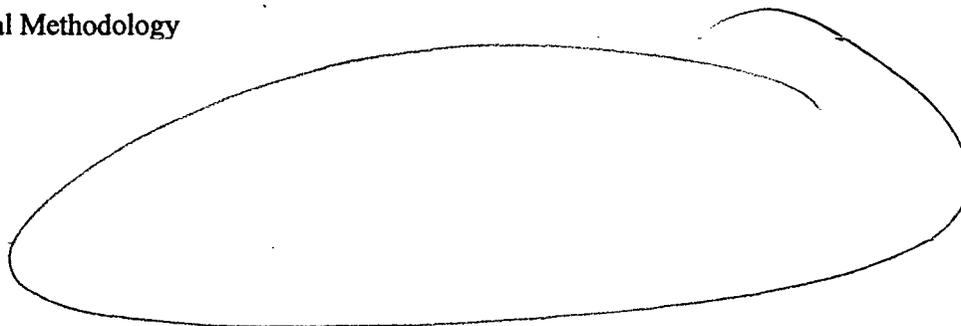
Efficacy assessments: Sensory (by pin-prick) and motor block (by modified Bromage scale) and Wound pain at rest was assessed using a Visual Analogue Scale (VAS)

Safety assessments: ECG, blood pressure and pulse rate, body temperature, laboratory assessments and adverse events.

Statistical Methods:

Simple descriptive statistics and graphs were used. The pharmacokinetics were summarized by calculated Wilcoxon 1-sample 95% confidence intervals and associated Hodges-Lehmann estimates.

Analytical Methodology

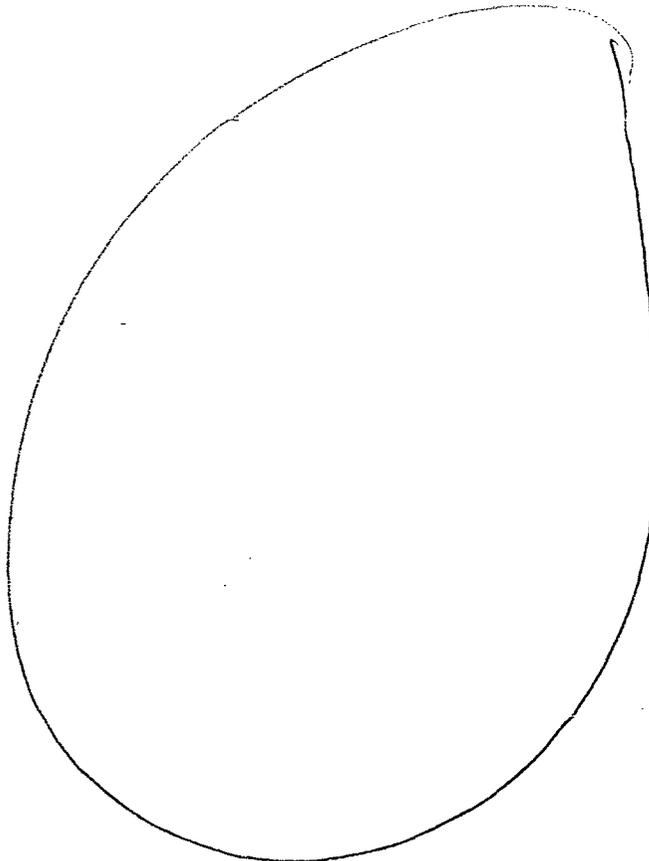




Results:

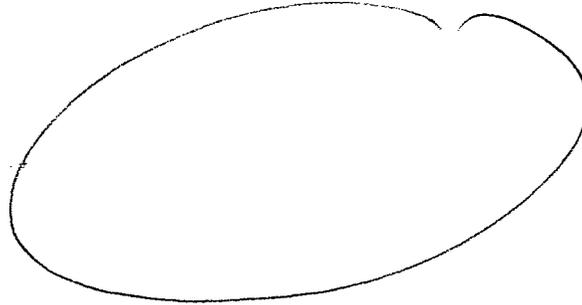
Total plasma concentrations: The total individual doses given during the treatment varied between 690 and 1559 mg. The total plasma concentration increased during the treatment period but the unbound concentrations leveled off more. The highest individual total plasma concentration (C_{high}) of ropivacaine was _____ who received a total dose of 1517 mg. The individual C_{high} values varied between _____. The terminal half-life was estimated to be 6.0 ± 3.2 h, calculated with linear regression based on between 71 to 82 h time-points. Figure 1 shows the individual total and free plasma concentration-time profiles of ropivacaine.

Figure 1

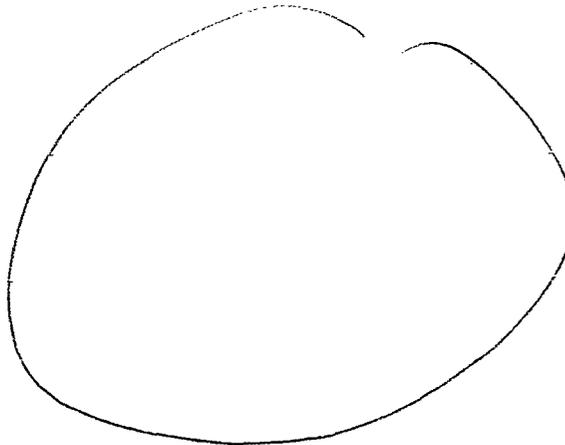


Free plasma concentrations: The highest individual free plasma concentration ($C_{\text{high, u}}$) of ropivacaine was _____ in a patient who received a highest total dose 1559 mg. The individual $C_{\text{high, u}}$ values for all the included patients were _____. The individual free fraction (f_u) varied between 1.2-14.1% during the course of the study. The sponsor stated that there was no correlation between f_u and the total plasma concentration of ropivacaine (Figure 2).

Figure 2: The individual free fraction (f_u) versus total plasma concentrations (left) and versus time (right) after individualized epidural infusion with ropivacaine 2 mg/ml for up to 72 h.



α_1 -acid glycoprotein (AAG): The plasma level of AAG in the samples taken before surgery were $20 \pm 10 \mu\text{mol/L}$ and increased to $33 \pm 10 \mu\text{mol/L}$ in the last sample taken 74-83 h after the start of the post-operative infusion. Individual plasma concentrations of AAG as a function of time (left) and individual f_u versus plasma concentrations of AAG (right) after the start of post-operative treatment are shown below; the dotted lines (right) show the range of AAG values in healthy subjects.



Urinary excretion: The urinary recovery of ropivacaine, 3-OH-R (conjugated and unconjugated) and PPX during the treatment and within 10 h after stop of infusion was in total 20-39% of the given dose; mean 1.6% excreted as unchanged ropivacaine and about 18% and 10% excreted as 3-OH-R and PPX, respectively.

Summary:

- The total individual doses given during the treatment varied between 690 and 1559 mg.
- Total plasma concentrations increased with time throughout the treatment period but the free concentrations leveled off more. The highest individual total plasma concentration (C_{high}) of ropivacaine was determined to be _____ while the individual free plasma concentrations ($C_{\text{high, u}}$) ranged from _____.
- The mean terminal half-life was estimated to be 6 h (*flip-flop* kinetics).
- The AAG plasma concentration increased during the course of the study, with a trend towards a decreasing free fraction of ropivacaine with time.
- The urinary recovery of ropivacaine, 3-OH-R (conjugated and unconjugated) and PPX during the treatment and within 10 h of the end of infusion was in total 20-39% of the given dose with mean 1.6% was excreted as unchanged ropivacaine and about 18% and 10% was excreted as 3-OH-R and PPX.
- Interpretation by the sponsor regarding f_u versus total plasma ropivacaine concentration as "no correlation" seems to be erroneous. It should be stated that f_u was higher at the earlier time but leveled out and maintained constant level at around 24 h (see Figure 1).

Study 94R080 (M8): An open study using 150 mg and 187.5 mg of ropivacaine 7.5 mg/ml in epidural anesthesia for Cesarean delivery: a clinical and pharmacokinetic evaluation.

Reference: Volume 17 - 18

Investigators: Lars Irestedt, MD, PhD

Study Location: _____
Department of Bioanalysis, Astra Pain Control AB, Sweden (Analytical)

Formulation: Ropivacaine 7.5 mg/ml solution for injection in 20 ml ampoules (Lot # 472-48-7)

Objective: To investigate the efficacy, tolerability and pharmacokinetics of the epidural administration of 150 mg, 187.5 mg and 225 mg ropivacaine 7.5 mg/ml used for Caesarean section.

Study Design: A single center, open, non-randomized, rising dose design clinical trial for which 3 consecutive dose groups were planned; eight women scheduled for elective Caesarean section each received 150 mg (20 ml) ropivacaine 7.5 mg/ml and another 8 women received 187.5 mg (25 ml). The third dose group (225 mg) was never entered into the trial due to the results from the first two groups (the decision was mainly based on excessive sensory blocks and more frequent events of hypotension in the 187.5 mg than in the 150 mg group). The patients received ropivacaine epidurally as a single dose injected in 5 minutes with a motorized syringe.

Assessment Methods:

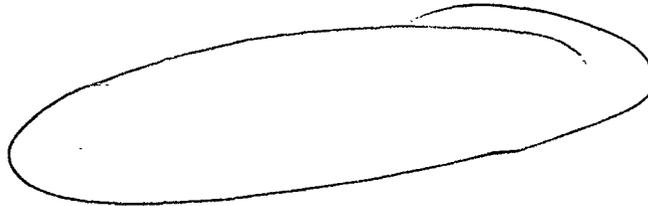
Pharmacokinetics: Peripheral maternal venous blood samples, and umbilical venous and arterial blood samples from the umbilical cord (at the time of delivery) were collected for ropivacaine (total and free) and α_1 -acid glycoprotein.

Efficacy assessments: Sensory and motor block, quality of anesthesia as judged by the anesthesiologist, and pain and discomfort scores using a verbal Numerical Rating Scale (NRS).

Safety assessments: Apgar score 1 and 5 minutes after birth, Neonatal Neurologic and Adaptive Capacity Score (NACS) 2 hours and 24 hours after birth, and Adverse events.

Statistical Methods: The efficacy, safety and pharmacokinetic parameters in the study were evaluated by summary measures and graphical presentations. Additionally, the pharmacokinetic variables were evaluated for dose proportionality using non-parametric confidence intervals.

Analytical Methodology



Results:

Total and free plasma ropivacaine concentrations: the results are summarized in Table 1 and Figures 1-3. The 90% confidence interval for the ratio (187.5 mg/150 mg) for AUC, C_{max} and $C_{max,u}$ are 1.14-2.17, 1.04-1.82 and 1.09-1.5, respectively. The free fraction C_{max} (f_u, C_{max}) was estimated to be

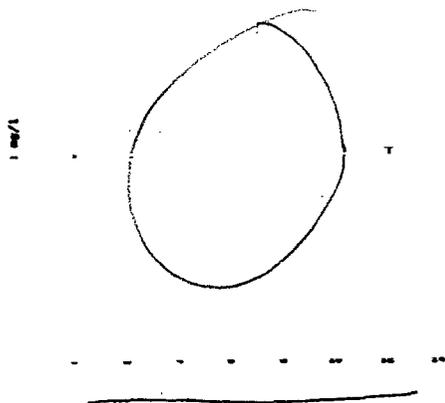
9.6±1.7% and 9.5±2.1% after 150 mg and 187.5 mg respectively. The f_u at delivery was almost the same as f_u, C_{max} 10.2±1.7% and 9.2±2.3% respectively.

Table 1: The mean (±SD) values for PK parameters following an epidural injection of 150 mg and 187.5 mg ropivacaine (Ropi)

	Ropi 150 mg	Ropi 187.5 mg
AUC _{0-∞} (mg•min/L)	432 ± 117	679 ± 258
C _{max} (mg/L)	1.13 ± 0.18	1.61 ± 0.57
C _{max, u} (mg/L)	0.11 ± 0.02	0.14 ± 0.04
T _{max} (min)	43 ± 14	34 ± 9
T _½ (hr)	5.7 ± 1.6	7.1 ± 3.0
CL (ml/min)	330 ± 105	291 ± 156
MV (mg/L)	1.01 ± 0.25	1.39 ± 0.38
MV _u (mg/L)	0.1 ± 0.018	0.12 ± 0.014
UV (mg/L)	0.33 ± 0.1	0.42 ± 0.11
UV _u (mg/L)	0.08 ± 0.02	0.1 ± 0.02
UA (mg/L)	0.27 ± 0.1	0.33 ± 0.11
UA _u (mg/L)	0.06 ± 0.01	0.07 ± 0.01

MV, UV and UA = ropivacaine concentrations at the time of delivery in the maternal vein, umbilical venous and umbilical artery, respectively.
u = unbound

Figure 1: The total plasma concentrations-time profile of ropivacaine following an epidural injection of 150 mg and 187.5 mg ropivacaine.



Umbilical venous and Umbilical arterial plasma concentrations of ropivacaine: The total plasma concentrations of ropivacaine in the UV samples were lower than the total concentrations of ropivacaine in the peripheral maternal vein (MV) at delivery with ratios of about 0.3 after both doses. Whereas, the ratio of UV_u/MV_u was about 0.8 irrespective of dose (Figure 2).

α_1 -acid glycoprotein (AAG): The plasma concentrations of AAG in peripheral maternal vein in the samples taken before drug administration and 12 h after the injection of ropivacaine were estimated to be equal with approximately 12 $\mu\text{mol/L}$. The mean AAG in the umbilical vein and umbilical artery were lower than in the maternal vein, with 5 and 4 $\mu\text{mol/L}$ respectively. However, $\%f_u$ for the UV and UA are higher than that of the MV as shown in Figure 5.

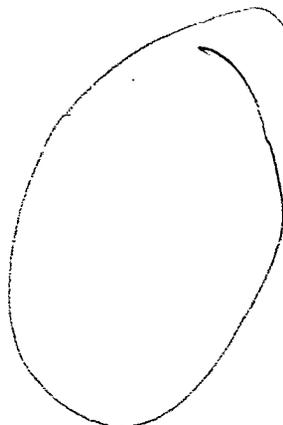


Figure 5: Individual free fraction (f_u) of ropivacaine in peripheral maternal vein (MV), in the umbilical vein (UV) and in the umbilical artery (UA) at the time of delivery is plotted against the AAG concentration after 150 mg and 187.5 mg ropivacaine 7.5 mg/ml administration for Cesarean section.

Summary:

- Unbound ropivacaine appears to increase dose-proportionally (*i.e.*, $C_{\text{max, u}}$, MV_u , UV_u and UA_u) between 150 and 187.5 mg doses.
- The estimated apparent CL ranged from _____ However, the AUCs used in the calculations of CL may not be accurate due to the large residual area (AUC extrap = 3 - 47%) which influences the estimate of clearance.
- The estimated terminal $t_{1/2}$ was 6-7 hours after the two doses. The sponsor indicated that this $t_{1/2}$ reflects a so called flip-flop situation, and is not the true elimination $t_{1/2}$.
- The free concentrations at the time of delivery were higher in the mothers than in the neonates with ratios between the umbilical vein and the peripheral maternal vein (UV_u / MV_u) of about _____ in both groups.
- The MV_u is below the threshold for CNS toxicity, 0.6 mg/L _____
- The plasma concentrations of both total and free ropivacaine in the blood leaving the fetus (UA) were lower than in the blood entering the fetus (UV), with ratios of about 0.8 for both UA/UV and UA_u / UV_u . This can be due to elimination and distribution from the fetus itself².

¹Edvardsson N, Sjövall J, Henriksson J. Acute tolerability of ropivacaine and bupivacaine after i.v. infusion to volunteers. Astra Report 802-550-LC-0100-01, 1994.

²Datta S, Bredberg E, Sandin S. A double blind comparative study between ropivacaine and bupivacaine in anaesthesia for Caesarean section. Astra Report 802-550-LC-0128-01, 1994.

Study 94R086: An open Study using 300 mg, 375 mg and 450 mg of ropivacaine for postoperative pain relief after hernia repair: a clinical and pharmacokinetic evaluation.

Reference: Volume 26 - 27

Investigators: Nils Pettersson, M.D.

Study Location: _____
Department of Bioanalysis, Astra Pain Control AB, Sweden (Analytical)

Formulation: Ropivacaine 7.5 mg/ml solution for injection in 20 ml ampoules (Lot # 472-49-7)

Objective: To investigate the efficacy, tolerability and pharmacokinetics of field block/infiltration with ropivacaine when used for postoperative pain relief after hernia repair, and the results will serve as the basis for the choice of ropivacaine dose used for hernia repair in comparative studies.

Study Design: A single center, open, non-randomized, rising dose design clinical trial for which 3 consecutive dose groups were planned; ten male patients scheduled for elective, primary, unilateral, inguinal hernia repair each received 300 mg ropivacaine 7.5 mg/ml. Another 10 patients received 375 mg. One patient who was to receive 375 mg accidentally was given 450 mg. The study was discontinued after two dose groups. The third dose group (450 mg) was never entered into the trial. The median time for infiltration of ropivacaine was 5 minutes (min/max 2-11 min).

Assessment Methods:

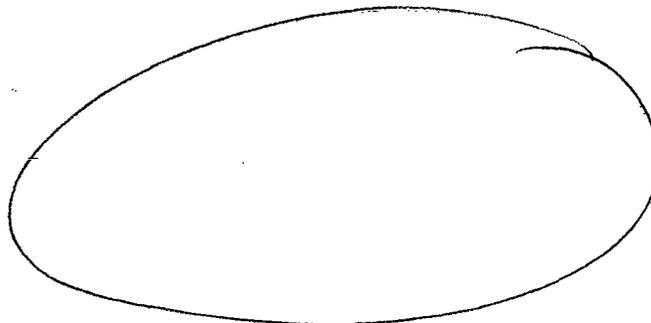
Pharmacokinetics: Peripheral venous blood samples were collected for ropivacaine (total and free) and α -1-acid glycoprotein at regular intervals during the 24 hours after administration of the study drug.

Efficacy assessments: Time to first administration and the total amount of analgesics consumed during 24 hours following the study drug using Citodon tablets, and Pain by the visual analogue scale (VAS).

Safety assessments: ECG, blood pressure and heart rate, body temperature, blood chemistry and hematology and adverse events.

Statistical Methods: The efficacy and safety variables were evaluated by summary measures and graphical presentations. The pharmacokinetic variables were evaluated for dose proportionality using non-parametric confidence intervals.

Analytical Methodology



_____ compounds.

Results: Figure 1 shows the mean plasma concentrations of ropivacaine after the infiltration of 300 mg and 375 mg ropivacaine 7.5 mg/ml at the end of surgery.

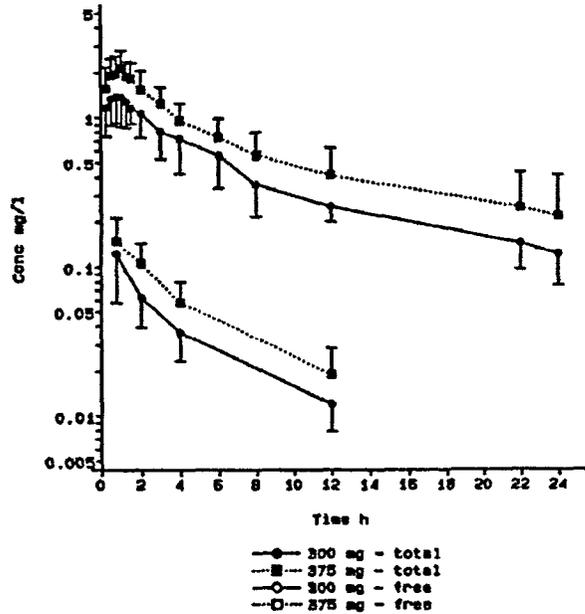


Figure 1: Mean (SD) plasma concentration-time profiles of ropivacaine following 300 and 375 mg dose.

Total and free plasma ropivacaine concentrations: The mean (\pm SD) values for PK parameters after infiltration of 300, 375 and 450 mg ropivacaine are summarized in the table below;

	Ropivacaine 300 mg	Ropivacaine 375 mg	Ropivacaine 450 mg ¹
AUC _{0-∞} (mg•min/L)	697 ± 138	1260 ± 582	1533
C _{max} (mg/L)	1.49 ± 0.43	2.23 ± 0.70	1.45
T _{max} (min)	46 ± 18	59 ± 26	14
C _{u, 45} (mg/L)	0.123 ± 0.065	0.15 ± 0.063	0.095
Mean f _u ²	4.1-7.6%	4.0-7.9%	6.6%
t _{1/2} (hr)	10.9 ± 3.7	14.9 ± 9.8	31.9

¹n = one subject

²C_{u, 45}/ C_{max} x 100

The pain (VAS, Figure 2) was plotted versus the estimated terminal $t_{1/2}$, showing increased analgesia (lower VAS score) in patients with longer $t_{1/2}$.

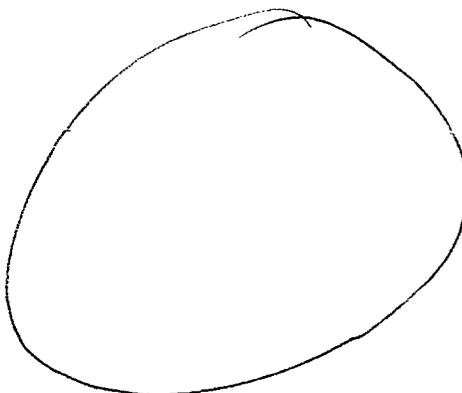


Figure 2: Individual pain at mobilization AUCM12 (VAS) plotted against the terminal $t_{1/2}$, (*flip-flop absorption dependent elimination*) after infiltration.

α_1 -acid glycoprotein (AAG): The mean plasma concentration of AAG in the sample taken just prior to the first injection of the study drug was estimated to be 16 $\mu\text{mol/L}$ _____) and in the 24-h sample to be 19 $\mu\text{mol/L}$ _____

Summary:

- $C_{\text{max}, u}$ in some patients after 300 and 375 mg for infiltration may approach the threshold for CNS toxicity (e.g., 0.234 and 0.227 mg/L).
- The analysis of dose-proportionality in the present study was inconclusive.
- The estimated terminal $t_{1/2}$ of 5-33 h is longer than that reported after intravenous administration, about 2 h^{1,2}, indicating absorption-dependent elimination.
- Caution is needed in repeated infiltration with ropivacaine when used at these high doses, because a very long $t_{1/2}$ was evidenced in a few patients.
- Analgesia represented as pain at mobilization seems to be inversely correlated with the terminal $t_{1/2}$; i.e. increased analgesia was seen in the patients where ropivacaine was slowly removed from the site of administration (long absorption $t_{1/2}$).
- The sponsor stated that the planned 3rd group never entered into the trial since there was no increase in clinical effect with the 375-mg dose and an increased variation in plasma concentrations with the increased dose.

¹Gustafsson LL, Magnusson A, Emanuelsson B-M, Sandin S. Pharmacokinetics of ropivacaine in volunteers after three intravenous doses. Astra Report 802-550-LK-0080-01, 1994.

²Lee A, Fagan D, Lamont M, Tucker GT, Halldin M, Scott DB. Disposition kinetics of ropivacaine in humans. Anesth Analg 1989;69:736-8.

Study 95R088: An open pharmacokinetic and tolerability study of ropivacaine 7.5 mg/ml, used for brachial plexus block in patients undergoing surgery of the upper limb.

Reference: Volume 21 - 22

Investigators: Johannes Buttner, MD

Study Location _____

_____); Department of Bioanalysis, Astra Pain Control AB,
Sweden (Analytical)

Formulation: Ropivacaine 7.5 mg/ml solution for injection in 50 ml vials (Lot # 472-50-7). The volumes administered using the axillary approach to achieve brachial plexus block were 30, 35 and 40 ml ropivacaine, 7.5 mg/ml, corresponding to 225, 262.5 and 300 mg respectively.

Objective: The primary objective was to investigate the general tolerability (expressed as observed adverse events) and pharmacokinetics of 225-300 mg ropivacaine 7.5 mg/ml used in axillary brachial plexus block. The secondary objectives were to investigate the quality of anesthesia (motor and sensory block) and to register the first request for postoperative analgesics.

Study Design: Open pilot study conducted in fourteen patients (2 females and 12 males; 21-66 years age) who were undergoing elective reconstructive or plastic surgery in the hand and forearm. The brachial plexus block was performed via the axillary approach. The dose was increased in 3 steps, two patients receiving 30-ml (225-mg) ropivacaine 7.5 mg/ml and another two receiving 35 ml (262.5 mg). Ten patients received the total dose of 40-ml (300-mg). If the axillary brachial plexus block treatment was inadequate for the intended surgical procedure, another anaesthetic regimen could be used (e.g. general anesthesia) at the discretion of the investigator. Intramuscular Dipidodor® (piritramide) 7.5 mg for the treatment of postoperative pain was to be administered at the request of the patient and at the discretion of the investigator according to normal routines.

Assessment Methods:

Pharmacokinetics: Total and unbound plasma concentrations of ropivacaine and α_1 -acid glycoprotein (AAG) were monitored for 24 hours after administration of the study drug.

Clinical assessments: The degrees of sensory and motor block were assessed in the n. axillaris, n. medianus, n. radialis, n. ulnaris and n. musculocutaneous at defined time points until the block had regressed. ECG, pulse oximetry, blood pressure and heart rate were recorded before surgery, during the operation and thereafter at defined intervals.

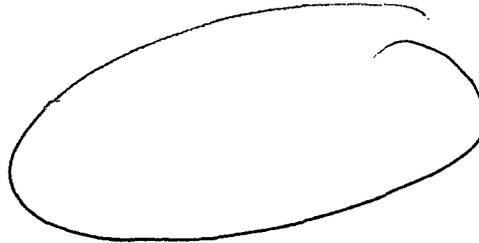
Statistics: The efficacy variables and most of the safety variables in the study were evaluated by summary measures and graphical presentation. ECG traces were evaluated by a cardiologist. No formal hypothesis tests were performed. There was no separate analysis for subgroups (except treatment groups).

Analytical Methodology:

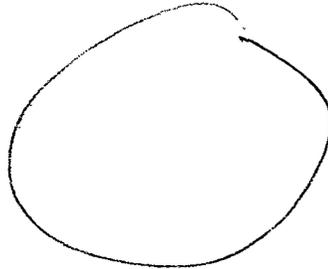
Results: The summary of PK parameter values of ropivacaine (total and free) following 3 doses is listed in the table below.

	Ropivacaine 30 ml (n=2)	Ropivacaine 35 ml (n=2)	Ropivacaine 40 ml (n=10)
AUC _{0-∞} (mg•h/L)	8.2 & 8.7	9.1 & 9.2	12.9±3.3
C _{max} (mg/L)	2.37 & 1.8	1.87 & 1.75	2.32±0.83
C _{u, 45} (mg/L)	0.154 & 0.088	0.168 & 0.099	0.114±0.056
T _{max} (min)	31 & 15	62 & 31	54±22
t _{1/2} (hr)	3.1 & 4.9	4.7 & 5.1	6.8±3.2

Figures shown below are the individual total and free plasma concentration-time curves after the administration of 225, 262.5 and 300 mg ropivacaine 7.5 mg/ml for brachial plexus block.



The mean f_u was estimated to be $4.8 \pm 1.6\%$, and the individual free fractions varied between 1.3% and 9.1%. No correlation was seen between f_u and the total plasma concentration (C_{tot}) of ropivacaine as shown in the Figure below.



α_1 -acid glycoprotein (AAG): The mean plasma concentration of AAG in the samples taken prior to the block and in the 24-h samples were estimated to be 18 $\mu\text{mol/L}$, ranging _____ respectively.

Summary statistics of mean onset and duration and their corresponding mean plasma total ropivacaine concentrations of sensory block after ropivacaine 300 mg are shown in the table below;

	Analgesia onset		Duration analgesia		Anesthesia onset		Duration anesthesia	
	Time (min)	Conc (mg/L)	Time (h)	Conc (mg/L)	Time (min)	Conc (mg/L)	Time (h)	Conc (mg/L)
Musculocutaneous	14.5	1.44	9.5	0.36	43.5	2.19	8.9	0.4
Radialis	15	1.47	12.3	0.248	44.5	2.2	5.9	0.62
Medianus	10	1.1	13.8	0.215	25	1.93	8.4	0.426
Ulnaris	6	0.7	13.6	0.22	24.5	1.92	6.7	0.53
Axillaris	25	1.93	2.2	1.37	-	-		

Summary statistics of mean onset and duration and their corresponding mean plasma total ropivacaine concentrations of motor block after ropivacaine 300 mg are shown in the table below;

	Onset partial (min)		Duration partial (h)		Onset complete (min)		Duration complete (h)	
	Time (min)	Conc (mg/L)	Time (h)	Conc (mg/L)	Time (min)	Conc (mg/L)	Time (h)	Conc (mg/L)
Musculocutaneous	14.3	1.44	9.0	0.38	32.0	2.1	4.8	0.8
Radialis	15.5	1.51	13.1	0.23	32.0	2.1	5.2	0.7
Medianus	13.5	1.38	12.5	0.242	32.5	2.12	6.7	0.53
Ulnaris	14.3	1.44	14.1	0.205	24.8	1.92	6.8	0.526
Axillaris	20.5	1.76	2.2	1.37	-	-	5.0	0.45

Summary:

- It is difficult to determine dose-proportionality due to only 2 subjects in two lower dose groups.
- f_u is calculated to be about 5-9%, based on the one-point estimate $C_{u,45}$ and C_{max} .
- Rather than stating that 'no correlation' was found regarding the relationship between f_u and C_{tot} , it should be interpreted as ' f_u was constant throughout the study time' (*i.e.*, linear relationship with about 5% of $C_{tot} = C_u$).
- The plasma levels of AAG did not change between the samples taken before the dose administration and the 24-h samples.
- Edvardsson *et al.*¹ reported that free arterial concentrations above 0.34 mg/L will result in CNS toxic effects. Some patients in the 300 mg group may approach the threshold for CNS toxicity (*e.g.*, $C_{u,45} = 0.264$ mg/L).
- Observing the onsets and duration of effects, the effect compartment(s) concentrations appear to be shifted to the right from the plasma concentrations, assuming it requires similar concentrations for the onset and the end of effect (*i.e.*, arises slowly & eliminates slowly from the effect compartment).

¹Edvardsson N, Sjövall J, Henriksson J. Acute tolerability of ropivacaine and bupivacaine after i.v. infusion to volunteers. Astra Report 802-550-LC-0100-01, 1994.

Study 96R099: Effect of fluvoxamine and ketoconazole on the pharmacokinetics of single dose intravenous ropivacaine. An open, randomized, 3-way crossover study in healthy volunteers.

Reference: Volume 13 - 14

Investigators: Lars L Gustafsson, M.D, Ph.D.

Study Location: _____

Department of Bioanalysis, Astra Pain Control AB, Sweden (PPX in plasma);

Formulation: (lot numbers are not provided)

Study drug	Strength & Dosage Form	Dose
A	2 mg/ml injection solution, 50 ml vial	40 mg
B	25 mg fluvoxamine (Fevarin®) tablet	100mg
C	100 mg ketoconazole (Fungoral ®) tablet	400 mg

Objective:

To investigate the effects of CYP1A2 (fluvoxamine) and CYP3A4 inhibition (ketoconazole) on the pharmacokinetics of ropivacaine.

Study Design:

Twelve healthy volunteers, males and females, were studied in a randomized, open, balanced crossover study design of three periods, each separated by a washout period of 7-15 days. Subjects received the following doses;

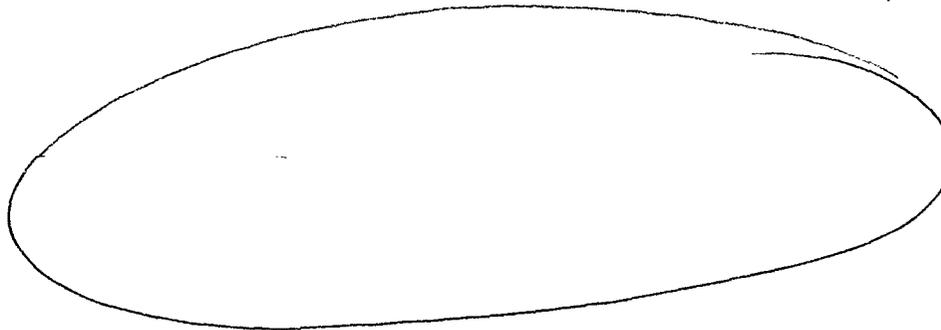
- ropivacaine hydrochloride 40 mg as a 20-min i.v. infusion
- ropivacaine i.v. infusion co-administered with oral (25 mg bid for 2 days) fluvoxamine.
- ropivacaine i.v. infusion co-administered with oral ketoconazole (100 mg bid for 2 days).

The oral drugs (inhibitors) were given as two daily doses (8AM & 8PM) for two days with the first day being the day before administration of ropivacaine, altogether 4 doses. On the second day of inhibitor administration, 1 h after the morning dose, the infusion of ropivacaine started.

Assessment Methods:

Venous plasma was collected and analyzed for total concentration of ropivacaine base, unbound concentration and N-depropylated ropivacaine (PPX). Urine was collected over 24 h and analyzed for ropivacaine, 3-OH-ropivacaine (conjugated and unconjugated) and PPX. In addition, all the subjects were screened for CYP1A2 activity by a caffeine test, to be related to the clearance of ropivacaine and urinary excretion of the metabolite 3-OH. Pulse rate and blood pressure were monitored during the study periods, and body temperature was recorded before and after the administration of ropivacaine.

Analytical Methodology:



Results:

The total plasma concentration-time profiles of ropivacaine and resulting PK parameters after ropivacaine alone and with ketoconazole or fluvoxamine are shown in Table 1 and Figures 1-2. The hepatic extraction ratio of ropivacaine was estimated to be 0.38 ± 0.12 ($E_H = CL_p / (C_p / C_b) \times 1 / \text{hepatic blood flow}$). The mean $t_{1/2}$ of 3-OH-ropivacaine was 4.4 ± 1.3 h, based on urinary excretion.

Table 1: Summary of PK parameters following ropivacaine (Ropi) iv and co-administration of ketoconazole (keto) or fluvoxamine (fluvo).

	Ropi	Ropi + keto	Ropi + fluvo
AUC _{0-∞} (mg•h/L)	1.8 ± 0.62	2.13 ± 0.67	5.51 ± 1.5
C _{max} ¹ (mg/L)	1.23 ± 0.21	1.32 ± 0.19	1.46 ± 0.24
V _{ss} (L)	40 ± 5	38 ± 4	33 ± 7
CL (L/h)	21.2 ± 6.6	18.1 ± 6.1	6.7 ± 1.6
t _{1/2} (hr)	1.9 ± 0.5	1.9 ± 0.5	3.6 ± 1.1
f _u (%)	5.8 ± 1.5	5.9 ± 2.0	5.5 ± 1.2
AAG (μmol/L)	15 ± 4	15 ± 4	16 ± 4
PPX (nmol/L) ²	62 (36, 79)	18 (0, 29)	332 (268, 469)
f e ³	1.01 ± 0.01	0.0	0.01 ± 0.01
f _{m, 3-OH} ⁴	0.39 ± 0.05	0.47 ± 0.07	0.13 ± 0.07
f _{m, PPX} ⁵	0.01 ± 0.02	0.0	0.17 ± 0.06
Total ⁶	0.41 ± 0.05	0.47 ± 0.07	0.31 ± 0.07

¹C_{max} = C_{stop}

²Median PPX (1st and 3rd quartiles) concentration in plasma at 8 h after the start of infusion.

^{3,4,5}The fraction of dose excreted as unchanged ropivacaine, 3-OH-ropivacaine and PPX in urine.

⁶The total fraction of dose excreted in urine

Figure 1: Total plasma concentrations of ropivacaine after 40 mg ropivacaine given as a 20-min iv infusion alone (left), during coadministration of ketoconazole (middle) and during coadministration of fluvoxamine (right) to 12 healthy subjects.

Fig. 1

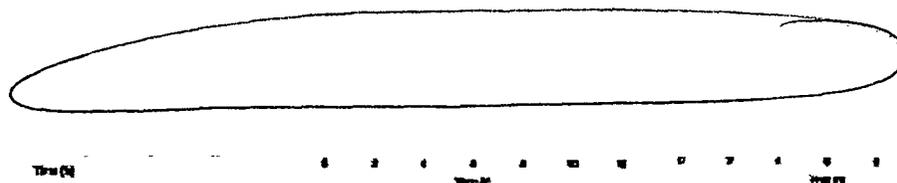


Figure 2: Total plasma concentrations of PPX at 8, 10 and 24 h after start of an intravenous infusion of 40 mg ropivacaine (left), during coadministration of ketoconazole (middle) and during coadministration of fluvoxamine (right) in 12 healthy subjects



Conclusions:

- Co-administration of fluvoxamine resulted in a 70% reduction in clearance of ropivacaine, the magnitude of reduction was similar in the fraction of the dose excreted as 3-OH- ropivacaine. This indicates that the observed reduction in CL arises mainly from a reduction of 3-OH formation, most likely through the inhibition of CYP1A2.
- When fluvoxamine was co-administered, there was an increase in PPX formation, indicating an increase in the amount of metabolite formed via CYP3A4. The K_m values *in vitro* for the formation of 3-OH-ropivacaine by CYP1A2 and PPX by CYP3A4 are 16 μM and 400 μM respectively⁶. When metabolism via CYP1A2 is inhibited, the concentration of ropivacaine increases and thus more PPX can be formed via CYP3A4 despite the higher K_m .
- The results of this study verify the previous results of *in vitro* studies, showing that CYP1A2 and CYP3A4 are important enzymes for the metabolism of ropivacaine. CYP1A2 is the quantitatively most important enzyme since the plasma clearance of ropivacaine is reduced by 70% during co-administration of a selective and potent CYP1A2 inhibitor (fluvoxamine). This reduction could be of clinical importance during long-term administration. A selective and potent inhibitor of CYP3A4 (ketoconazole) slightly reduces clearance (about 15% decrease), therefore, this reduction may not likely be of clinical relevance. However, ropivacaine was administered 1 hour after ketoconazole. Therefore, this study may not accurately represent the interaction upon concomitant administration in that the magnitude of effect may actually be higher upon concomitant administration. Also, the maximum recommended daily dose of ketoconazole (400 mg) was not used in this study.

6. Ekström G and Gunnarsson U-B. Ropivacaine, a new amide type local anaesthetic agent is metabolised by cytochromes P450 1A and 3A4 in human liver microsomes. Drug Metabol Disp 1996;24:955-961.

Bioavailability: Comparison of PK parameters after 150 mg ropivacaine for epidural anesthesia in cesarean section using 5 mg/ml or 7.5 mg/ml: Study I18 and I19 were submitted in NDA 20533-1S and M8 is referring to the study 94R080.

Plasma concentrations after 150 mg ropivacaine for epidural anesthesia in cesarean section were similar when solutions of 5 or 7.5 mg/ml were used. The resulting summary statistics of PK parameters (Table 1) and bioequivalence estimates based on Hodges-Lehmann medians with 90% confidence intervals (Table 2) from these studies are shown below;

Table 1: Summary statistics after epidural block with 150 mg ropivacaine PK studies in cesarean section patients.

	Formulation (mg/mL)	n	Mean	SD	Min	Max	Ref
Cmax (mg/L)	5	10	1.3	0.29			I18
	7.5	28	1.5	0.28			I19
	7.5	8	1.1	0.18			M8
AUC total (mg*h/L)	5	10	9.8	3.89			I18
	7.5	-	-	-			I19
	7.5	8	7.2	1.94			M8
Maternal vein unbound (mg/L)	5	26	0.099	0.026			I18
	7.5	27	0.089	0.040			I19
	7.5	8	0.100	0.018			M8
Umbilical vein unbound (mg/L)	5	26	0.072	0.016			I18
	7.5	28	0.060	0.015			I19
	7.5	7	0.080	0.018			M8

Table 2: Bioequivalence estimates for epidural block with 150 mg ropivacaine given as a 5 or 7.5 mg/ml solution in cesarean section patients based on Hodges-Lehmann medians with 90% confidence intervals for pairwise ratios.

	Formulation (mg/mL)	n	Ref	HL- estimate	Lower 90%-limit	Upper 90%-limit
Cmax (mg/L)	5 vs 7.5	10 vs 28	I18 vs I19	1.16	0.97	1.31
	5 vs 7.5	10 vs 8	I18 vs M8	0.89	0.71	1.04
AUC total (mg*h/L)	5 vs 7.5	10 vs 8	I18 vs M8	0.81	0.52	1.08

Summary: Comparative bioavailability appears to be shown between the 5 and 7.5 mg/ml strengths, used in epidural nerve block cesarean patients.

APPENDIX II

(Attachment from NDA 20533-1S reviewed
by Suresh Doddapaneni, Ph.D. 3/25/95)

DRUG FORMULATION DEVELOPMENT:

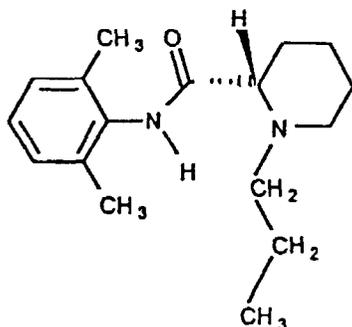
Chemistry And Nomenclature:

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-dimethylphenyl)-amide hydrochloride monohydrate.

Structural formula:



Molecular formula: C₁₇H₂₆N₂O HCl H₂O

Molecular weight: 328.89 (as hydrochloride monohydrate), 274.43 (as base)

Generic name: Ropivacaine hydrochloride monohydrate

Laboratory code name: LEA 103

Chemical And Physical Properties:

Ropivacaine is a white crystalline powder with a melting range of 269.5-270.6° C. The pKa 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, WC, q) 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:

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.

ANALYTICAL TECHNIQUES FOR BIOLOGICAL FLUIDS:

In all body fluids, concentrations are reported as ropivacaine base or bupivacaine base.

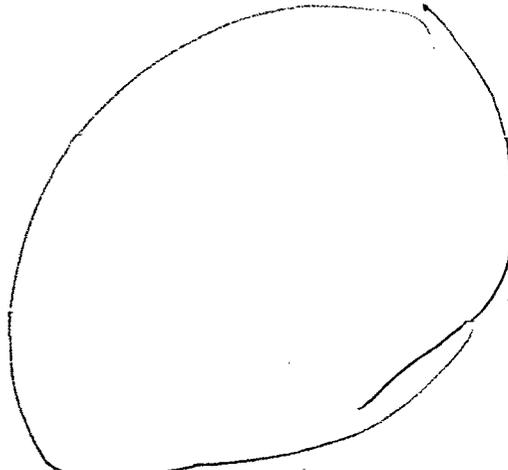
Ropivacaine (base) 1 μmol/liter = 0.274 mg/liter.

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.

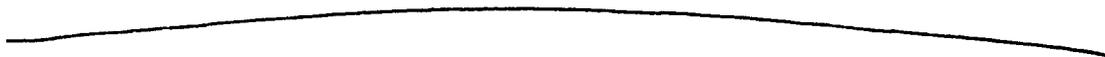
TOTAL CONCENTRATION OF ROPIVACAINE IN PLASMA AND URINE:

Ropivacaine Determined By Gas Chromatography;

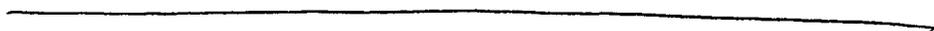
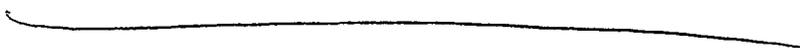
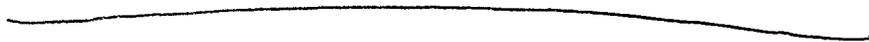


Ropivacaine And [²H₃]-Ropivacaine Determined By Gas Chromatography/Mass Spectrometry;

The total amount of ropivacaine and [²H₃]-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



Unbound Concentrations in Plasma;



α_1 -Acid Glycoprotein in Human Plasma:



1a



1p

Racemization of Ropivacaine in Urine Samples from Man;

Metabolites in Human Plasma and Urine

Validation;

All analytical test procedures were carefully validated before continuous use and then during use in clinical studies.

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].

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-533 SEI-002	Name: Naropin™(Ropivacaine HCL) injection
Sponsor: Astra Pharmaceuticals, L.P. 725 Chesterbrook Blvd Wayne, PA 19087-5677	
Submission Type: Supp NDA	Submission Date: September 24, 1998
Reviewer: Shinja R. Kim, Ph.D.	

sNDA Filing Memorandum

Synopsis

Ropivacaine has been approved for the production of local or regional anesthesia for surgery, for postoperative pain management and for obstetrical procedures. Astra pharmaceuticals has submitted sNDA 20-533, an efficacy supplement, in support of labeling revisions that provide for increasing utility of ropivacaine (and the additional information on metabolism); increasing the dosage for nerve block anesthesia using 7.5 mg/mL (from current 5 mg/mL) and for extending the duration of treatment for postoperative analgesia up to 72 hours (from up to 24 hours) using ropivacaine 2 mg/mL.

Eight clinical studies, involving 119 subjects and patients ranging from 19 to 80 years of age, were conducted to support the submitted supplement as follows:

1. 72 hour continuous infusion with 20 and 30 mg/h ropivacaine 2 and 3 mg/mL for postoperative pain relief following major orthopedic surgery
2. Effect of fluvoxamine and ketoconazole on the pharmacokinetics of single dose intravenous ropivacaine in healthy volunteers.
3. Pharmacokinetics, tolerability and initial clinical efficacy of ropivacaine gel in patients with active distal ulcerative colitis
4. An open study using 150 mg and 187.5 mg of ropivacaine 7.5 mg/mL in epidural anesthesia for caesarean delivery.
5. Continuous 72 Hour epidural infusion of ropivacaine for pain management after orthopedic surgery.
6. An open pharmacokinetic and tolerability study of ropivacaine 7.5 mg/mL, used for brachial plexus block in patients undergoing surgery of the upper limb.
7. A clinical study of ropivacaine 7.5 mg/mL and bupivacaine 5 mg/mL for brachial plexus block in patients undergoing surgery of the upper limb.
8. An open study using 300 mg, 375 mg and 450 mg of ropivacaine for postoperative pain relief after hernia repair.

In addition, *in vitro* metabolism information was provided.

Assay validation for the methods used to analyze the plasma samples have been submitted. The pharmacokinetic section of the package insert is organized in the ADME format, annotated and seems to contain the usual information characterizing the dosage form and the drug. The effects of gender, race, renal and hepatic insufficiency on the pharmacokinetics of the drug have not been provided. Also no information on pharmacokinetics in pediatric or elderly populations has been provided.

Comments to be sent to the Sponsor

1. Please summarize any studies available in the literature on PK information on geriatric population and update the information in the package insert according to 21 CFR 201.57 (f) (10) in the NDA.
2. Please submit in the NDA, summarization of study(s) from the literature (along with articles) regarding the information of the effects of gender, race, age (e.g., pediatric use), renal and hepatic insufficiency on the pharmacokinetics of the drug.
3. Please provide individual study summaries on a diskette in MICROSOFT WORD format.

Recommendation

A quick review of the Human Pharmacokinetics and Bioavailability section of sNDA 20-533 did not reveal any obvious deficiencies and the supplement has been adequately indexed. Therefore, from the standpoint of the Office of Clinical Pharmacology and Biopharmaceutics, sNDA 20-533 can be filed. The comments above should be forwarded to the firm.

/S/

Shinja R. Kim, Ph.D.

Division of Pharmaceutical Evaluation II

RD/FT_

151
11/13/98

Ramana Uppoor, Ph.D., Team Leader

cc:

sNDA (Original), HFD-170 (Divisional File, Medical Officer),

HFD-870 (ChenME, Uppoor, Kimsh), HFD-870 (Lesko), CDR (Barbara Murphy)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-533 SE~~1~~002

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Sponsor: Astra Pharmaceuticals, L.P. 725 Chesterbrook Blvd Wayne, PA 19087-5677

Submission Type: Supp NDA

Submission Date: September 24, 1998

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/S/

Shinja R. Kim, Ph.D.
Division of Pharmaceutical Evaluation II

/S/

3/98

Ramana Uppoor, Ph.D., Team Leader

RD/FT