

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
018692Orig1s000

Trade Name: MARCAINE® SPINAL

***Generic or
Proper Name:*** bupivacaine HCL in dextrose spinal injection

Sponsor: Sterling Drug Inc.

Approval Date: 05/04/1984

Indication: MARCAINE® Spinal is indicated for the production of subarachnoid block (spinal anesthesia). Standard textbooks should be consulted to determine the accepted procedures and techniques for the administration of spinal anesthesia.

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
NDA 018692/S-000**

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 018692/S-000

APPROVAL LETTER

NDA 18-692

Sterling Drug Inc.
90 Park Avenue
New York, NY 10016

MAY 04 1984

Attention: Edward J. Hirsch, Ph.D.

Gentlemen:

Please refer to your October 13, 1981 new drug application submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Marcaine Spinal (bupivacaine hydrochloride 0.75% with dextrose 8.25% injection).

We also acknowledge receipt of your additional communications dated February 7, March 1, March 31, and May 3, 1983 amending the application.

The application was filed May 3, 1983.

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. However, the drug is not to be distributed until final printed labeling has been reviewed and accepted by the Agency. The labeling is to be identical to the attached revised draft labeling.

In addition, we would appreciate your submitting, in duplicate, the advertising copy which you intend to use in your immediate or proposed promotional or advertising campaign. Please submit one copy to the Division of Drug Advertising with a copy of the package insert and the other to the Division of Surgical-Dental Drug Products.

The enclosures summarize the conditions relating to the approval of the application.

Please submit one market package of the drug when available.

Sincerely yours,

Robert J. Temple, M.D.
Acting Director
Office of Drug Research and Review
Center for Drugs and Biologics

cc: NYK-DC (HFR-2100)
NDA 18-692

HFN-160

HFN-100/Temp le

HFN-616

Doc. Rm. 160

R/D: JPHannan 4/19/84

R/D init by PHRussell 4/24/84, CPHoiberg 4/23/84, JKInscoc 4/23/84

HDickstein 4/23/84, GBoyer 4/23/84

FT td W0689Y 4/25/84

APPROVAL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 018692/S-000

OTHER ACTION LETTER(s)

NDA 18-692

Sterling Drug, Inc.
Attention: Edward J. Hirsch, Ph.D.
90 Park Avenue
New York, NY 10016

JUL 20 1982

Gentlemen:

Please refer to your New Drug Application dated October 13, 1981 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Marcaine Spinal (bupivacaine HCL 0.75% with dextrose 8.25% injection).

Please also refer to your amendments dated November 5 and 9, 1981, and February 19 and March 10 and 26, 1982.

APPEARS THIS
WAY ON
ORIGINAL

We have completed the review (~~except for our Biopharmaceutics review~~) of this application as submitted with draft labeling. However, before the application may be approved, it will be necessary to submit final printed labeling. The generic name of this formulation must appear at least once on each page of the package insert. The labeling should be identical in content to the draft labeling except for the following revisions:

Clinical Pharmacology: Change the second paragraph of that section so that it reads:



Contraindications: Change this section to read:

The following conditions preclude the use of spinal anesthesia:

1. Severe hemorrhage, severe hypotension or shock and arrhythmias, such as complete heart block, which severely restrict cardiac output.
2. Local infection at the site of proposed lumbar puncture.
3. Septicemia.

Warnings: Change this section to read:



Precautions: Change this section to read:

General

The safety and effectiveness of spinal anesthesia depend on proper dosage, correct technique, adequate precautions and readiness for emergencies. Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use (see WARNINGS and ADVERSE REACTIONS). (b) (4)

There should be careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness after local anesthetic injection. Restlessness, anxiety, (b) (4)

The following conditions may preclude the use of spinal anesthesia, depending upon the physician's evaluation of the situation and ability to deal with the complications or complaints that may occur:

1. Pre-existing diseases of the central nervous system, such as those attributable to pernicious anemia, polyomyelitis, syphilis, tumor ^{(b)(4)}
2. Hematological disorders predisposing to coagulopathies or anticoagulant therapy. Trauma to a blood vessel during the conduct of spinal anesthesia may, in some instances, result in uncontrollable central nervous system hemorrhage or soft tissue hemorrhage.
3. Chronic backache and preoperative headache.
4. Hypotension and hypertension.
5. Technical problems (persistent paresthesias, persistent bloody tap).
6. Arthritis or spinal deformity.
7. Extremes of age.
8. Psychosis or other causes of poor cooperation.

Under "Pregnancy" in the Precautions section of the Package Insert,

^{(b)(4)}

^{(b)(4)} for Patients

When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of spinal anesthesia.

Clinically Significant Drug Interactions

The administration of local anesthetic solutions containing epinephrine (or norepinephrine) to patients receiving monoamine oxidase inhibitors, ^{(b)(4)} ^{(b)(4)} may produce severe, prolonged, ^{(b)(4)} hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs (b) (4) and ergot-type (b) (4) drugs may cause severe, persistent, hypertension or cerebrovascular accidents.

(Under Pregnancy Category, (b) (4))

Labor and Delivery

(b) (4)

Pediatric Use

(b) (4)

Adverse Reactions: Change this section to read:

The most commonly encountered acute adverse experiences which demand immediate countermeasures following the administration of spinal anesthesia are hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia. (b) (4)

(b) (4)

(b) (4)

Respiratory System: Respiratory paralysis or underventilation may be noted as a result of upward extension of the level of spinal anesthesia and may lead to secondary hypoxic (b) (4). Preanesthetic medication, intraoperative analgesics and sedatives, as well as surgical manipulation, may contribute to underventilation. This will usually be noted within minutes of the injection of spinal anesthetic solution, but because of differing maximal onset times, differing intercurrent drug usage and differing surgical manipulation, it may occur at any time during surgery or the immediate recovery period.

Cardiovascular System: Hypotension due to loss of sympathetic tone is a commonly encountered extension of the clinical pharmacology of spinal anesthesia. This is more commonly observed in patients with shrunken blood volume, shrunken interstitial fluid volume, cephalad spread of the local anesthetic and/or mechanical obstruction of venous return. Nausea and vomiting are frequently associated with hypotensive episodes following the administration of spinal anesthesia. High doses, or inadvertent intravascular injection, may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, bradycardia, heart block, ventricular arrhythmias and possibly cardiac arrest.

Central Nervous System: Respiratory paralysis or underventilation secondary to cephalad spread of the level of spinal anesthesia (see Respiratory System discussion above) and hypotension for the same reason (see Cardiovascular System ^{(b)(4)}) are the two most commonly encountered central nervous system related adverse observations which demand immediate countermeasures.

High doses, or inadvertent intravascular injection, may lead to high plasma levels and related central nervous system toxicity characterized by excitement and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest.

(b)(4)

Allergic: Allergic type reactions are rare and may occur as a result of sensitivity to ^{(b)(4)}. These reactions are characterized by signs of urticaria, pruritis, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and, possibly, anaphylactoid like symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitively established.

Overdosage: Add a section titled OVERDOSAGE, as follows:

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use or to underventilation (and perhaps apnea) secondary to upward extension of spinal anesthesia. Hypotension is commonly encountered during the conduct of spinal anesthesia, due to relaxation of sympathetic tone and, sometimes, contributory mechanical obstruction of venous return.

Management of Local Anesthetic Emergencies: The first consideration (b) (4) best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after injection. At the first sign of change, oxygen should be administered.



Hypotension, due to sympathetic relaxation, may be managed by giving intravenous fluids (such as isotonic saline or lactated ringer's solution), (b) (4)

(b) (4), and, if indicated, by giving plasma expanders or whole blood.

If not treated immediately, (b) (4)

[Redacted text block]

Endotracheal intubation (b) (4)

[Redacted text block]

Dosage and Administration:

In addition, we note that changes in autoclaving directions, regarding how often this product may be autoclaved, and changes regarding discoloration or particulate matter as related to clinical usage were agreed to during a May 5, 1982 telephone conversation between Dr. Karen Putterman of your firm and Dr. David L. Scally of the Division of Surgical-Dental Drug Products. Please note that the text below has been slightly altered since that conversation to conform to 21 CFR 201.57 (j):

(b) (4)
 The sentence regarding autoclaving directions should be changed to read: "(b) (4) may be autoclaved once at 15-pound pressure at 121 degrees C (250 degrees F) for 15 minutes." The sentence which follows (b) (4) will be deleted.

DOSAGE AND ADMINISTRATION:

End the DOSAGE AND ADMINISTRATION section with the following statement: "MARCANE^R Spinal should be inspected visually for discoloration and particulate matter prior to administration; solutions which are discolored or which contain particulate matter should not be administered."

HOW SUPPLIED:

The second paragraph of this section (b) (4) will be changed to read: "(b) (4) may be autoclaved once at 15-pound pressure at 121 degrees C (250 degrees F) for 15 minutes. Do not administer solutions which are discolored or which contain particulate matter."

In addition, we recommend that you develop and implement the use of a chromatographic assay which more effectively differentiates the active drug substance and internal standard from major impurities and degradation products.

If additional information relating to the safety and effectiveness of the drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Please submit twelve copies of the printed labels and other labeling.

If necessary, we will forward comments from our ongoing biopharmaceutics review as soon as it is available.

Sincerely yours,

Robert Temple, M.D.
Acting Director
Office of New Drug Evaluation
National Center for Drugs and
Biologics

BUF-DO(HFR-2200)

BUF-DO(HFR-2200)

APPROVABLE

CC: ~~HFD-160~~ NDA 18-692 Mr. Koch HFD-160

Dr. Jean HFD-160 Dr. Scally HFD-160, RD JMSinger 4/23/82 HFD-616

Doc Rm 160, HFD-100

RD init by GBoyer 4/23/82, JKInscoc 4/23/82, CRodriguez 4/26/82,

CRSinopoli 4/23/82, JPMann 4/26/82

Revised by JMSinger 5/7/82

FT by bd 4/27/82(W1072P) revised and retyped bd 5/7/82

Revised by DLScally 6/28/82

init by JPMann 6/29/82

FT AK 6/30/82

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 018692/S-000

LABELING

MARCAINE Spinal—brand of bupivacaine HCl, 0.75% with dextrose, 8.25% injection

type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitely established.

Other: Nausea and vomiting may occur during spinal anesthesia.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use or to underventilation (and perhaps apnea) secondary to upward extension of spinal anesthesia. Hypotension is commonly encountered during the conduct of spinal anesthesia due to relaxation of sympathetic tone, and sometimes, contributory mechanical obstruction of venous return.

Management of Local Anesthetic Emergencies: The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be administered.

The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to a high or total spinal, consists of **immediate** attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask. This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control the convulsions. A 50 mg to 100 mg bolus IV injection of succinylcholine will paralyze the patient without depressing the central nervous or cardiovascular systems and facilitate ventilation. A bolus IV dose of 5 mg to 10 mg of diazepam or 50 mg to 100 mg of thiopental will permit ventilation and counteract central nervous system stimulation, but these drugs also depress central nervous system, respiratory and cardiac function, add to postictal depression and may result in apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and, when appropriate, a vasopressor dictated by the clinical situation (such as epinephrine or epinephrine to enhance myocardial contractile force).

Hypotension due to sympathetic relaxation may be managed by giving intravenous fluids (such as isotonic saline or lactated Ringer's solution), in an attempt to relieve mechanical obstruction of venous return, or by using vasopressors (such as epinephrine which increases the force of myocardial contractions) and, if indicated, by giving plasma expanders or whole blood.

Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated after initial administration of oxygen by mask if difficulty is encountered in the maintenance of a patent airway, or if prolonged ventilatory support (assisted or controlled) is indicated.

Recent clinical data from patients experiencing local anesthetic-induced convulsions demonstrated rapid development of hypoxia, hypercarbia, and acidosis with bupivacaine within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis plus myocardial depression from the direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur. Underventilation or apnea due to a high or total spinal may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted and maintained for a prolonged period if necessary. Recovery has been reported after prolonged resuscitative efforts.

The supine position is dangerous in pregnant women at term because of aortocaval compression by the gravid uterus. Therefore during treatment of systemic toxicity, maternal hypotension, or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished.

The mean seizure dosage of bupivacaine in rhesus monkeys was found to be 4.4 mg/kg with mean arterial plasma concentration of 4.5 mcg/mL. The intravenous and subcutaneous LD₅₀ in mice is 6 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg respectively.

DOSAGE AND ADMINISTRATION

The dose of any local anesthetic administered varies with the 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. The smallest dose and concentration required to produce the desired result should be administered. Dosages of MARCAINE Spinal should be reduced for elderly and debilitated patients and patients with cardiac and/or liver disease.

For specific techniques and procedures, refer to standard textbooks.

The extent and degree of spinal anesthesia depend upon several factors including dosage, specific gravity of the anesthetic solution, volume of solution used, force of injection, level of puncture, and position of the patient during and immediately after injection.

Seven and one-half mg (7.5 mg or 1.0 mL) MARCAINE Spinal has generally proven satisfactory for spinal anesthesia for lower extremity and perineal procedures including TURP and vaginal hysterectomy. Twelve mg (12.0 mg or 1.6 mL) has been used for lower abdominal procedures such as abdominal hysterectomy, tubal ligation, and appendectomy. These doses are recommended as a guide for use in the average adult and may be reduced for the elderly or debilitated patients. Because experience with MARCAINE Spinal is limited in patients below the age of 18 years, dosage recommendations in this age group cannot be made.

Obstetrical Use: Doses as low as 6 mg bupivacaine hydrochloride have been used for vaginal delivery under spinal anesthesia. The dose range of 7.5 mg to 10.5 mg (1 mL to 1.4 mL) bupivacaine hydrochloride has been used for Cesarean section under spinal anesthesia.

In recommended doses, MARCAINE Spinal produces complete motor and sensory block.

Unused portions of solutions should be discarded following initial use.

MARCAINE Spinal should be inspected visually for discoloration and particulate matter prior to administration; solutions which are discolored or which contain particulate matter should not be administered.

HOW SUPPLIED

Single-dose ampuls of 2 mL (15 mg bupivacaine hydrochloride with 165 mg dextrose), in Uni-Nest™ Unit Dose Pak of 10 (NDC 0024-1229-10)

Store at controlled room temperature, between 15 °C and 30 °C (59 °F and 86 °F).

MARCAINE Spinal solution may be autoclaved once at 15 pound pressure, 121 °C (250 °F) for 15 minutes. Do not administer any solution which is discolored or contains particulate matter.

Winthrop-Breon

Winthrop-Breon Laboratories
Division of Sterling Drug Inc.
New York, NY 10016

Issued June 1984

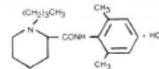
MARCAINE® Spinal

Brand of bupivacaine HCl, USP, 0.75% with dextrose, USP,
8.25% injection

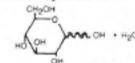
STERILE HYPERBARIC SOLUTION FOR SPINAL ANESTHESIA

DESCRIPTION

Bupivacaine hydrochloride is 2-Piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, a white crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone. It has the following structural formula:



Dextrose is D-glucopyranose monohydrate and has the following structural formula:



MARCAINE Spinal is available in sterile hyperbaric solution for subarachnoid injection (spinal block).

Bupivacaine hydrochloride is related chemically and pharmacologically to the aminoacyl local anesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage.

Each 1 mL of MARCAINE Spinal contains 7.5 mg bupivacaine hydrochloride and 82.5 mg dextrose. The pH of this solution is adjusted to between 4.0 and 6.5 with sodium hydroxide or hydrochloric acid.

The specific gravity of MARCAINE Spinal is between 1.030 and 1.035 at 25°C and 1.03 at 37°C. MARCAINE Spinal does not contain any preservatives.

CLINICAL PHARMACOLOGY

Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems (CNS). At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Recent clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after unintended direct intravascular injection of bupivacaine. Therefore, when epidural anesthesia with bupivacaine is considered, incremental dosing is necessary.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors and shivering, progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited stage.

Pharmacokinetics: The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution. A dilute concentration of epinephrine (1:200,000 or 5 mcg/mL) usually reduces the rate of absorption and peak plasma concentration of MARCAINE, permitting the use of moderately larger total doses and sometimes prolonging the duration of action.

The onset of action with MARCAINE is rapid and anesthesia is long lasting. The duration of anesthesia is significantly longer with MARCAINE than with any other commonly used local anesthetic. It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced.

The onset of sensory blockade following spinal block with MARCAINE Spinal is very rapid (within one minute); maximum motor blockade and maximum dermatome level are achieved within 15 minutes in most cases. Duration of sensory blockade (time to return of complete sensation in the operative site or regression of two dermatomes) following a 12 mg dose averages 2 hours with or without 0.2 mg epinephrine. The time to return of complete motor ability with 12 mg MARCAINE Spinal averages 3½ hours without the addition of epinephrine and 4½ hours if 0.2 mg epinephrine is added. When compared to equal milligram doses of hyperbaric tetracaine, the duration of sensory blockade was the same but the time to complete motor recovery was significantly longer for tetracaine. Addition of 0.2 mg epinephrine significantly prolongs the motor blockade and time to first postoperative narcotic with MARCAINE Spinal.

Local anesthetics appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. MARCAINE with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, nonionized drugs readily enter the fetal blood from the maternal circulation.

Depending upon the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

Pharmacokinetic studies on the plasma profiles of MARCAINE after direct intravenous injection suggest a three-compartment open model. The first compartment is represented by the rapid intravascular distribution of the drug. The second compartment represents the equilibration of the drug throughout the highly perfused organs such as the brain, myocardium, lungs, kidneys, and liver. The third compartment represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized.

Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic or renal disease, addition of epinephrine, factors affecting urinary pH, renal blood flow, the route of drug administration, and the age of the patient. The half-life of MARCAINE in adults is 2.7 hours and in neonates 8.1 hours.

Amide-type local anesthetics such as MARCAINE are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecolylxylidine is the major metabolite of MARCAINE.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine.

When administered in recommended doses and concentrations, MARCAINE does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

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INDICATIONS AND USAGE

MARCAINE Spinal is indicated for the production of subarachnoid block (spinal anesthesia). Standard textbooks should be consulted to determine the accepted procedures and techniques for the administration of spinal anesthesia.

CONTRAINDICATIONS

MARCAINE Spinal is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type.

The following conditions preclude the use of spinal anesthesia:

1. Severe hemorrhage, severe hypotension or shock and arrhythmias, such as complete heart block, which severely restrict cardiac output.
2. Local infection at the site of proposed lumbar puncture.
3. Septicemia.

WARNINGS

LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS and PRECAUTIONS.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST, AND, POSSIBLY, DEATH.

Spinal anesthetics should not be injected during uterine contractions, because spinal fluid current may carry the drug further cephalad than desired.

A free flow of cerebrospinal fluid during the performance of spinal anesthesia is indicative of entry into the subarachnoid space. However, aspiration should be performed before the anesthetic solution is injected to confirm entry into the subarachnoid space and to avoid intravascular injection.

MARCAINE solutions containing epinephrine or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because a severe persistent hypertension may occur. Likewise, solutions of MARCAINE containing a vasoconstrictor, such as epinephrine, should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result.

Until further experience is gained in patients younger than 18 years, administration of MARCAINE in this age group is not recommended.

Mixing of the prior or intercurrent use of any other local anesthetic with MARCAINE cannot be recommended because of insufficient data on the clinical use of such mixtures.

PRECAUTIONS

General: The safety and effectiveness of spinal anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See WARNINGS and ADVERSE REACTIONS.) The patient should have IV fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anesthetic that results in effective anesthesia should be used. Aspiration for blood should be performed before injection and injection should be made slowly. Tolerance varies with the status of the patient. Elderly patients and acutely ill patients may require reduced doses. Reduced doses may also be indicated in patients with increased intra-abdominal pressure (including obstetrical patients), if otherwise suitable for spinal anesthesia.

There should be careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness after local anesthetic injection. Restlessness, anxiety, incoherent speech, light-headedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Spinal anesthetics should be used with caution in patients with severe disturbances of cardiac rhythm, shock, or heart block.

Sympathetic blockade occurring during spinal anesthesia may result in peripheral vasodilation and hypotension, the extent depending of the number of dermatomes blocked. Blood pressure should, therefore, be carefully monitored especially in the early phases of anesthesia. Hypotension may be controlled by vasoconstrictors in dosages depending on the severity of hypotension and response of treatment. The level of anesthesia should be carefully monitored because it is not always controllable in spinal techniques.

Because amide-type local anesthetics such as MARCAINE are metabolized by the liver, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs. However, dosage recommendations for spinal anesthesia are much lower than dosage recommendations for other major blocks and most experience regarding hepatic and cardiovascular disease dose-related toxicity is derived from these other major blocks.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of potent inhalation agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Because it is not known whether amide-type local anesthetics may trigger this reaction and because the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures, and dantrolene. (Consult dantrolene sodium intravenous package insert before using.)

The following conditions may preclude the use of spinal anesthesia, depending upon the physician's evaluation of the situation and ability to deal with the complications or complaints which may occur:

- Preexisting diseases of the central nervous system, such as those attributable to pernicious anemia, poliomyelitis, syphilis, or tumor.
- Hematological disorders predisposing to coagulopathies or patients on anticoagulant therapy. Trauma to a blood vessel during the conduct of spinal anesthesia may, in some instances, result in uncontrollable central nervous system hemorrhage or soft tissue hemorrhage.
- Chronic backache and preoperative headache.
- Hypotension and hypertension.
- Technical problems (persistent paresthesias, persistent bloody tap).
- Arthritis or spinal deformity.
- Extremes of age.
- Psychosis or other causes of poor cooperation by the patient.

Information for Patients: When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of spinal anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the MARCAINE Spinal package insert.

Clinically Significant Drug Interactions: The administration of local anesthetic solutions containing epinephrine or 1-orepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals of most local anesthetics including bupivacaine to evaluate the carcinogenic potential have not been conducted. Mutagenic potential or the effect on fertility have not been determined. There is no evidence from human data that MARCAINE Spinal may be carcinogenic or mutagenic or that it impairs fertility.

Pregnancy Category C: Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine hydrochloride was administered to these species in doses comparable to 230 and 130 times respectively the maximum recommended human spinal dose. There are no adequate and well-controlled studies in pregnant women of the effect of bupivacaine on the developing fetus. Bupivacaine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. This does not exclude the use of MARCAINE Spinal at term for obstetrical anesthesia. (See **Labor and Delivery**.)

Labor and Delivery: Spinal anesthesia has a recognized use during labor and delivery. Bupivacaine hydrochloride, when administered properly, via the epidural route in doses 10 to 12 times the amount used in spinal anesthesia has been used for obstetrical analgesia and anesthesia without evidence of adverse effects on the fetus.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously and electronic fetal monitoring is highly advisable.

It is extremely important to avoid aortocaval compression by the gravid uterus during administrations of regional block to parturients. To do this, the patient must be maintained in the left lateral decubitus position or a blanket roll or sandbag may be placed beneath the right hip and the gravid uterus displaced to the left.

Spinal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Spinal anesthesia has also been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. This has not been reported with bupivacaine.

There have been reports of cardiac arrest during use of MARCAINE 0.75% solution for epidural anesthesia in obstetrical patients. The package insert for MARCAINE hydrochloride for epidural, nerve block, etc, has a more complete discussion of preparation for, and management of, this problem. These cases are compatible with systemic toxicity following unintended intravascular injection of the much larger doses recommended for epidural anesthesia and have not occurred within the dose range of bupivacaine hydrochloride 0.75% recommended for spinal anesthesia in obstetrics. The 0.75% concentration of MARCAINE is therefore not recommended for obstetrical epidural anesthesia. MARCAINE Spinal (bupivacaine HCl 0.75% with dextrose 8.25%) is recommended for spinal anesthesia in obstetrics.

Nursing Mothers: It is not known whether local anesthetic drugs are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when local anesthetics are administered to a nursing woman.

Pediatric Use: Until further experience is gained in patients younger than 18 years, administration of MARCAINE Spinal in this age group is not recommended.

ADVERSE REACTIONS

Reactions to bupivacaine are characteristic of those associated with other amide-type local anesthetics.

The most commonly encountered acute adverse experiences which demand immediate countermeasures following the administration of spinal anesthesia are hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia. These may lead to cardiac arrest if untreated. In addition, dose-related convulsions and cardiovascular collapse may result from diminished tolerance, rapid absorption from the injection site, or from unintentional intravascular injection of a local anesthetic solution. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance.

Respiratory System: Respiratory paralysis or underventilation may be noted as a result of upward extension of the level of spinal anesthesia and may lead to secondary hypoxic cardiac arrest if untreated. Preanesthetic medication, intraoperative analgesics and sedatives, as well as surgical manipulation, may contribute to underventilation. This will usually be noted within minutes of the injection of spinal anesthetic solution, but because of differing maximal onset times, differing intercurrent drug usage and differing surgical manipulation, it may occur at any time during surgery or the immediate recovery period.

Cardiovascular System: Hypotension due to loss of sympathetic tone is a commonly encountered extension of the clinical pharmacology of spinal anesthesia. This is more commonly observed in patients with shrunken blood volume, shrunken interstitial fluid volume, cephalad spread of the local anesthetic, and/or mechanical obstruction of venous return. Nausea and vomiting are frequently associated with hypotensive episodes following the administration of spinal anesthesia. High doses, or inadvertent intravascular injection, may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, bradycardia, heart block, ventricular arrhythmias, and, possibly, cardiac arrest. (See **WARNINGS, PRECAUTIONS, and OVERDOSAGE** sections.)

Central Nervous System: Respiratory paralysis or underventilation secondary to cephalad spread of the level of spinal anesthesia (see **Respiratory System**) and hypotension for the same reason (see **Cardiovascular System**) are the two most commonly encountered central nervous system-related adverse observations which demand immediate countermeasures.

High doses or inadvertent intravascular injection may lead to high plasma levels and related central nervous system toxicity characterized by excitement and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest.

Neurologic: The incidences of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration, and the physical status of the patient. Many of these effects may be related to local anesthetic techniques, with or without a contribution from the drug.

Neurologic effects following spinal anesthesia may include loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness and paralysis of the lower extremities, and loss of sphincter control all of which may have slow, incomplete, or no recovery; hypotension; high or total spinal block; urinary retention; headache; backache; septic meningitis; meningitis; arachnoiditis; slowing of labor; increased incidence of forceps delivery; shivering; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid; and fecal and urinary incontinence.

Allergic: Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and, possibly, anaphylactoid-like symptomatology (including severe hypotension). Cross sensitivity among members of the amide-

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 018692/S-000

MEDICAL REVIEW(S)

NDA 18-692

Date Completed: 15 June 1983

REVIEW AND EVALUATION OF CLINICAL DATA AND LABELING (Final Printed Labeling for NDA Approval)

Sponsor: BREON Division of Sterling Drug Inc.
N.Y.C.

Name of Product: Marcaine Spinal (bupivacaine HCl 0.75% with dextrose 8.25%)

Category and Use: Amide type local anesthetic; this NDA is for subarachnoid injection (spinal anesthesia)

Date of Submissions: May 3, 1983 (final printed labeling)
March 31, 1983 (supplemental reprints)

Additional Relevant Reviews: My Original NDA Review dated 19 FEB'82
My review dated 25 March 1983
Memorandum of 29 March 1983 Meeting

CLINICAL SUMMARY:

3 May 1983 Submission: The final printed package insert submitted on 3 May 1983 is clinically acceptable. This package insert reflects agreements on labeling made by the clinical staff of BREON and the clinical staff of HFN-160 at the meeting of 29 March 1983.

The sponsor's summary and analysis of Dr. Moore's study is also submitted for the record. The difference between BREON's and Dr. Moore's analysis of duration is explained sufficiently in the Memorandum of the 29 March 1983 Meeting.

31 March 1983 Submission: Another copy of the writing in support of obstetrical use of bupivacaine for spinal anesthesia is submitted, this time with copies of the references cited. This draft was prepared by BREON in conjunction with Gerard Ostheimer, M.D. of Brigham and Women's Hospital and has already been summarized in my review dated 25 March 1983. For conclusions and recommendations based upon this draft, see 25 March 1983 review; essentially, the clinical staff of HFN-160 accepts their point of view (Drs. Mann, Russell & Scally) and recommends use of this product in obstetrics (for the initial package insert).

Some of the references will be briefly cited; these will make more sense if followed with a copy of my 25 March 1983 review and/or the above cited draft by BREON and Dr. Ostheimer:

G.A. McGuinness, et. al., Univ. of Iowa, Anesthesiology 49: 270-273, 1978
The authors note previous studies at smaller doses revealed no neurobehavioral changes in infants of mothers who received bupivacaine epidural anesthesia. They used a large mean dose of 168 mg bupivacaine in ten cases of epidural anesthesia for delivery by Cesarean section. A comparative group of ten cases involved mothers who received tetracaine spinal anesthesia for Cesarean section (10 + 2 mg). Infants in the two groups were indistinguishable after delivery in terms of their motor organization, responsiveness to external stimuli, and habituation to repetitive stimuli. Detectable neurobehavioral

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effects were absent at 4 hour and 24 hour (after delivery) testing; the examiner was unaware of the anesthetic management of the mother.

R. Hodgkinson, et. al., Albert Einstein (Bronx) and U. of Texas (San Antonio), Am. J. Obst. Gynec. 132(6): 670-674, Nov. 1978. Fifty mothers received spinal anesthesia with 6-8 mg tetracaine spinal for Cesarean section. The results were compared to fifty mothers who received ketamine for induction of general anesthesia and fifty mothers who received Propofol for general anesthesia. Neonatal neurobehavioral testing was performed at 8 hours of age and 24 hours later by an evaluator who did not know which form of anesthesia the mother received. Spinal anesthesia was associated with the greatest percentage of high scores at both the test periods for overall assessment, pinprick response, tone, rooting, sucking, Moro response, placing, alertness and total decrement or habituation scores.

S. Datta, G.W. Ostheimer, et. al., Brigham & Women's, Anesthesiology 53: S303, Sept. Supplement 1980.

Fifty healthy parturients undergoing elective Cesarean section received 55-65 mg of lidocaine by subarachnoid block. The interval between drug usage and delivery was 13 minutes and the interval between incision and delivery was 126 seconds. Apgar scores and acid base determinations were as expected in normal obstetrical practice. The important thing to note is that, at delivery, maternal ^{ve} venous blood and umbilical vein and artery blood was collected for lidocaine determination; the mean values were in the clinically insignificant range:

Mean Values (ug/ml)	
Maternal vein	0.63
Umbilical vein	0.17
Umbilical artery	0.11
Fetal/maternal ratio (UV/MV) = 0.4	

J. Meyer and H. Nolte, Inst. Anesth. Minden, West Germany, Regional-Anaesthesie 1: 38-40, 1978.

An isobaric spinal anesthetic was administered to 11 patients with 15 mg bupivacaine. The initial CSF concentration was 284 ug/ml and after 240 minutes it was only 7 ug/ml. "At the administered amount of 15 mg bupivacaine, it could not be detected in the blood plasma."

T.K.Abboud, et. al., U. of Southern Calif., Anesthesiology 55: A315, Sept. Supplement 1981.

The results of epidural anesthesia with three different local anesthetics were compared in 87 patients: bupivacaine 0.5% (n = 28), chloroprocaine (2-3%?) (n = 28 and lidocaine 1.5% (n = 31).

The indication was labor and delivery. Neonatal examinations were performed at 2 & 24 hours of life using the Early Neonatal Neurobehavioral Scale (ENNS). Results were also compared to evaluation of 10 infants whose mothers had not received medications or anesthesia for labor and delivery. The important thing to note is that ENNS, cord acid base status & Apgar scores showed no differences between the three groups. Also, none of the 3 groups scored lower than the control group for any of the ENNS tests.

An expanded version of this was also published in Anes. & Analg. (61:638-644, 1982).

S. Datta, et. al., Brigham & Women's, Anesthesiology 52: 48-51, 1980.

Epidural anesthesia was performed for Cesarean section with bupivacaine 0.75% (n = 15), chloroprocaine 3% (n = 15) & etidocaine 1% (n = 10). The important thing to note at this time is that fetal outcome, as determined by Apgar scores, acid-base status and neurobehavioral testing (2 & 4 hours of age, performed by a person who was not involved in anesthetic management) were equally good in all groups. Eighty to 90 percent of the neonates in each group had high scores in all of the neurobehavioral test variables and none were markedly depressed.

J. Scanlon, et. al., Brigham and Women's, Anesthesiology 45: 400-405, 1976.

This was the first neurobehavioral study involving bupivacaine. Twenty newborns were evaluated at 2 to 4 hours of life after their mother had received bupivacaine epidural for labor and vaginal delivery. No neurobehavioral modifications were noted as a group; these infants did not have the decrease in muscle tone and strength that had been observed in an earlier study involving lidocaine and mepivacaine.

CONCLUSION AND RECOMMENDATION:

The final printed package insert submitted on 3 May 1983 is clinically acceptable and in accordance with that agreed to and accepted by the clinical staff of HFN-160 and the clinical staff of BREON at the Meeting of 29 March 1983.

This is all explained on page one of this review. The rest of this review is for the record only and to assist in possible future retrieval.

This application can now be approved clinically under 505 (b) (1) and 505 (b) (6) of the Federal Food, Drug, and Cosmetic Act.

David L. Scally

David Lawrence Scally, M.D.
Medical Officer---HFN-160 *DLR 6/15/83*

NDA 18-692
HFN-160

HFN-220

F/D DLScally 6/15/83

JGM 6/16/83

NDA 18-692

Date Completed: 25 March 1983

REVIEW AND EVALUATION OF CLINICAL DATA AND LABELING

Sponsor: STERLING DRUGS (BREON)
NYC

Name of Product: Marcaine Spinal (bupivacaine HCl 0.75% with dextrose 8.25% injection), subject of approvable letter dated 20 July 1982

Date of Submissions: 1 March 1983 (replaces second part of 7 Feb. 1983 submission)
7 Feb. 1983 (replaces 23 Sept. 1982 submission)
23 Sept. 1982

CLINICAL SUMMARY:

A labeling conference on this pending NDA is long overdue, and it is now scheduled for Tuesday 29 March 1983 at 10:30 hours. This review is intended as preparation for that meeting and to make recommendations concerning usage of Marcaine Spinal in obstetrical anesthesia.

OBSTETRICAL ANESTHESIA/ANALGESIA:

The sponsor feels that the portion of the letter dated 20 July 1982 which requests that the package contain the following (PRECAUTIONS section) excerpt be changed:

[REDACTED] (b) (4)

The revision would add instructions for use of MARCAINE Spinal in obstetrics. The support for use of MARCAINE Spinal in Obstetrics is written by Breon Labs. in consultation with Gerard W. Ostheimer, M.D., Director of Obstetric Anesthesia, Brigham & Women's Hospital, Boston, Massachusetts.

The main argument centers around the fact that there are now at least five publications which demonstrate that epidural bupivacaine is not associated with known neurobehavioral alteration in the newborn (five references cited). The recommended dose of bupivacaine for spinal anesthesia is 1/10 that required for epidural anesthesia. The fetal/maternal ratio at delivery for epidural bupivacaine is about 0.3, depending on the clinical conditions of course, and this is considered clinically acceptable for a local anesthetic. Two studies have shown no neurobehavioral changes in the newborn when spinal anesthesia with tetracaine was used for cesarean delivery (two references cited). Clinical data employing lidocaine 55-65 mg for subarachnoid block before cesarean delivery (S.Data, et. al., from Dr. Ostheimer's group, reference cited) reveals relatively low maternal vein concentration at delivery (mean 0.63 ug/ml) relatively low umbilical vein (mean 0.17 ug/ml) & umbilical artery (mean 0.11 ug/ml) concentrations and an acceptable fetal/maternal ratio (0.4). A reference is also cited in which it was not possible to detect bupivacaine at any concentration in venous plasma (20 samples in 5 patients) following the injection of 15 mg isobaric bupivacaine with 15 ug epinephrine added (to provide anesthesia for lower body surgery). "SINCE ABOUT 1/10 THE AMOUNT OF BUPIVACAINE IS USED FOR SPINAL ANESTHESIA AS IS USED FOR EPIDURAL ANESTHESIA, IT COULD BE EXPECTED THAT ONLY 1/10 THE DRUG COULD REACH THE FETUS. SINCE THERE WERE NO NEUROBEHAVIORAL EFFECTS WITH EPIDURAL DOSES, THERE WOULD CERTAINLY BE NO NEUROBEHAVIORAL EFFECTS WITH SPINAL DOSES."

For those unfamiliar with neurobehavioral research, let it be noted that neurobehavioral studies are imperfectly controlled or uncontrolled. The withholding of known safe and effective analgesics/anesthetics from a comparable group of patients in labor poses ethical problems that have not been effectively solved. I am familiar with the neurobehavioral studies supporting no effect for bupivacaine and it is my opinion that they meet the current and prevailing standard, imperfect though it be.

A negative study is cited by BREON, much to their and Dr. Ostheimer's credit (D.B. Rosenblatt, et. al., St. Mary's Hospital, London, etc., The Influence of Maternal Analgesia on Neonatal Behavior: II. Epidural Bupivacaine. British Jl. Obst. & Gynaec. 88: 407-413, April 1981). They point out a number of faults with that study: 1. Specific information about the obstetric variables encountered is totally lacking, 2. The approach to perinatal pharmacokinetics is naive, 3. There is no reported evaluation of acid-base status of mother and newborn at the time of delivery; this seems especially crucial in view of the statement "infants with greater exposure to bupivacaine in utero were more likely to be cyanotic and unresponsive to their surroundings"; cyanosis directly attributable to bupivacaine has never been noted (at Brigham and Women's Hospital), 4. To relate drug exposure at birth to behavior on day 42 without considering environmental factors is to ignore a very important variable, 5. Increased muscle tone with increased exposure to bupivacaine contradicts all previous experience;

when local anesthetics effect neonatal muscle tone they generally are associated with decreased muscle tone, and finally 6. No attempt to avoid hypotension is described; intravenous glucose (5%) was started but not for rehydration (this could also cause neonatal hypoglycemia).

I have examined that publication and have the impression that BREON & Dr. Ostheimer were being most kind in their critique of the publication. It is an attempt to correlate neurobehavioral testing during the first 42 days of life with total maternal dose of epidural bupivacaine, umbilical cord blood concentration and "drug exposure" (some figure, units not given, derived from umbilical cord concentration multiplied by the time from first administration of bupivacaine until delivery). Maternal selection is not described. The number of patients who participated is not stated. Duration of labor is not taken into consideration or otherwise noted. Maternal complications are not noted. There are no understandable tables of "drug exposure" (mean, range and, as noted above, units). As already cited above, patients were not hydrated and information on blood pressure is not provided. The claim is made that infants with greater exposure to bupivacaine in utero were more likely to be cyanotic and unresponsive to their surroundings. Visual skills and alertness decreased with increased cord blood concentration, particularly on the first day of life but throughout 6 weeks. Adverse effects of bupivacaine on infant motor organization, "his ability to control his own state of consciousness" and response to stress were also observed. Muscle tone alone appeared to improve with increase in the value of the drug variables. I recommend that this paper, containing no meaningful tables correlating neurobehavioral alterations with bupivacaine administration to the mother before delivery, be ignored.

REVIEWER'S IMPRESSION:

It is the opinion of this reviewer that the sponsor and consultant have provided sound and logical for use of Marcaine (bupivacaine HCl) Spinal support in obstetrical anesthetic practice. The initial package insert should contain prescribing information for use of Marcaine Spinal in obstetrics.

REVIEW OF THE PACKAGE INSERT:

This need not be a definitive review of the draft package insert (contained in the submission dated 7 Feb.83). All that need be done now is make notes for discussion with the sponsor at the upcoming meeting, now scheduled for Tuesday 29 March 1983 at 10:30 hours.

page 4---middle of page, under Pharmacokinetics: Consider changing the reference to epinephrine prolonging the duration of action so that it reads "-----sometimes prolonging the duration of action." There seems little doubt that epinephrine prolongs the action of bupivacaine for spinal anesthesia, but this is a general discussion of many uses and dosages of bupivacaine and epinephrine cannot account for the unusually prolonged duration of some peripheral nerve blocks.

page 5--top, under discussion of onset and duration: Change: "-----following a 12 mg dose averages 2 hours with or without 0.2 mg epinephrine."

To: [REDACTED] (b) (4) [REDACTED] (b) (4) [REDACTED] (b) (4)

Reference: D.C.Moore, Anes. & Analg. 59: 743-750, 1980, especially Table I, top of page 746. This is available on page 280, etc., of NDA Vol. 1.1.

page 15---bottom, under Clinically Significant Drug Interactions: Change the first sentence ("The administration of-----or hypertension.") so that it reads: "The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension."

Add also a separate paragraph which reads: "Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine."

The earlier draft was a mistake of my own doing, and now that I have a second chance to correct it (see Memorandum from Acting Director, HFD-100, dated 23 JUN '82, and my reply Memorandum, dated 25 June 1982) I might as well try.

Note, also, that some of this information is repeated (see page 11 of the draft package insert). Is this really necessary? (Ask sponsor at meeting).

page 19----middle of page (ADVERSE REACTIONS): End the paragraph ("The most commonly-----") with: "Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production or competition of other drugs for protein binding sites, may diminish individual tolerance."

Source: Approvable letter dated 20 July 1982 and page 12 of the printed Class Labeling Guideline for Local Anesthetics (subject of Federal Register Notice 47FR: 41636 Sept. 21, 1982).

[REDACTED] (b) (4)
page 26----Change (mean seizure threshold) of bupivacaine in the rhesus monkeys) to read: "----- (mean)-----arterial plasma concentration of 4.5 ug/ml."

Reference: E.S.Munson, et. al., Etidocaine, Bupivacaine, and Lidocaine Seizure Thresholds in Monkeys, Anesthesiology 42: 471-478, 1975, especially Table I on page 472.

CONCLUSIONS AND RECOMMENDATIONS:

Logical support has been provided for use of Marcaine Spinal in obstetrical anesthesia. The initial package insert should now contain prescribing information for such usage.

The review of the package insert, contained in the 7 Feb. 1983 submission, is for discussion with the sponsor at the upcoming meeting, now scheduled for Tuesday 29 March 1983 at 10:30 hours. Final recommendations will, hopefully, be made after that meeting.

David L. Scally

David L. Scally, M.D.
Medical Officer----HFN-160

AK 3/28/83

JM
3/28/83

NDA 18-692

HFN-160

HFN-220

R/D DLScally 3/25/83

R/D Init. by PHRussell 3/28/83, JPMann 3/28/83

Doc. Room 160

MAR 30 1983

Review and Evaluation of Clinical Data (Original NDA)

Sponsor: Sterling Drug Inc.
90 Park Ave., N.Y.C. 10016
(212-972-4141)

Name of Product: Marcaine Spinal (bupivacaine hydrochloride 0.75% with dextrose 8.25% injection)

Date of Submission Under Review: 13 October 1981 (First and original application).

Category and Use: This application is for use as a spinal anesthetic (also known as subarachnoid or intrathecal injection) at dosages approximately 1/10 those already approved for local infiltration, peripheral nerve block and epidural block.

(Breon-Div. of Sterling)

Related Applications: Marcaine is approved for local infiltration, peripheral nerve block and epidural block. The patent has expired and generic applications, with literature support, have been approved for [redacted] (b)(4). Both [redacted] (b)(4) for bupivacaine for spinal anesthesia [redacted] (b)(4)

Reviews by Colleagues:

1. First, see the Pharmacology and Toxicology Review of D.H.Jean, Ph. D., dated 18 Dec. 1981. Dr. Jean has the impression that the preclinical data supports approvability of this application and recommends approval from a pharmacology standpoint. I agree.

2. Second, see the Chemistry and Manufacturing Control Review of Mr. Stanley Koch, dated 12 November 1981. Multiple manufacturing control deficiencies, cited by Mr. Koch, make this application non-approvable from a manufacturing controls standpoint. I am concerned with only one of these points; Mr. Koch has called it to my attention, and again noted in his text, that the lower limit of the pH will be [redacted] (b)(4) or [redacted] (b)(4) (see pages 6, 7 and 10 of the review and page 2 of a resulting 18 December 1981 letter to the sponsor). I know of no harm that could result from this low pH, particularly at the low volume employed. Still, we are now inquiring into the safety of unintended injection of larger volumes of local anesthetics into the subarachnoid space during the intended administration of epidural anesthesia; one of the factors in this inquiry, though not at present of established harm to patients, has to do with effect of marketed solutions of low pH on the patient outcome (localized prolonged neurological sequelae). In the meanwhile, it would be prudent not to introduce additional products of low PH, intended for spinal anesthesia or for which unintended spinal anesthesia is possible, onto the market without additional justification. I thus support this particular deficiency called to my attention by the Chemistry Reviewer.

INDEX:

Daniel C. Moore, M.D. (Most important U.S. Study)----pages 2-5.
Brett B. Gutsche, M.D.---page 6-7. Wm. F. Kennedy, M.D.---page 8.
Eugene Pflug, M.D.---page 8. A.P.Winnie, M.D.---page 9. R.L.Watson---page 9.
Literature Support---pages 10-17 (additional information is available on pages 146 through 287 of Volume 1.1 of this application).
Conclusions (including review of the potential package insert)---pages 18 to 24.
Recommendations-----page 24.

Daniel C. Moore, M.D.
Department of Anesthesiology
Virginia Mason Clinic and Mason Hospital
Seattle, Washington.

2

APPEARS
THIS WAY
ON ORIGINAL

is
Summary derived from a very
informative pre-publication
draft of Dr. Moore, revised
in May of 1980.

This was a randomized double-blind comparison of bupivacaine and tetracaine in 435 patients. Of these, 235 had operations on the lower extremity or perineum (Group I) and 200 patients had intra-abdominal gynecological surgery (Group II).

Either 500 mg or oral (b)(4) or 30-60 mg of flurazepam was administered for sleep the night before surgery. Preanesthetic medication consisted of meperidine 150 mg or morphine 15 mg, plus atropine 0.4 mg, administered intramuscularly one hour prior to anesthesia.

Each drug was dispensed in 2 ml ampules containing 0.75% drug (tetracaine or bupivacaine) in 8.25% dextrose. Patients in Group I received 1 ml of solution (7.5 mg of tetracaine or bupivacaine) and those in Group II received 1.6 ml (12 mg). These dosages were in keeping with Dr. Moore's previous experience and previous total dosage of tetracaine, having made the judgement (from previous clinical investigators and animal research) that the potency of bupivacaine and tetracaine are similar for spinal anesthesia. In Group I (b)(4) and the first 100 patients in Group II, the local anesthetic solution did not contain epinephrine. In the remaining 100 patients in Group II, 0.2 mg of epinephrine (standard for Dr. Moore, an authority on use of local anesthetics in clinical practice) was added to the local anesthetic solution.

Data was gathered in the operating room by the investigator & in the recovery room by trained registered nurses, with the investigator subject to call. Postoperative rounds were made by the investigator. Onset of analgesia was judged to start when the patient could not distinguish cold when the skin was touched by an alcohol sponge (every five seconds testing was conducted, using a stopwatch); the area tested was below the iliac crest in the distribution of the lateral femoral cutaneous nerve. Maximum sensory analgesia and the dermatome level of same was evaluated by progressively pinching the lower extremities, abdomen and thorax with Allis forceps at 30 second intervals timed by the clock in the operating room, until an unchanged sensory level occurred. Sensory analgesia was considered maximum when the patient did not respond to closure of the forceps to its first ratchet.

If the scheduled surgery caused pain, anesthesia was considered unsatisfactory and patients with unsatisfactory anesthesia were not included in the analysis of the variables studied; manipulation of abdominal viscera and the diaphragm was expected to cause pain, because spinal anesthesia does not ordinarily block the phrenic or vagus nerves and associated pain fibers, so discomfort or pain associated with traction on or packing off of viscera did not result in the anesthesia being considered unsatisfactory. Surgical procedures lasting longer than the duration of action of the local anesthetic resulted in the anesthesia being coded as satisfactory and the duration of effectiveness recorded.

The degree of motor blockade, in the lower extremities, was graded from zero (free movement of legs and feet) through 3 (unable to flex knees or to move legs); see footnote in Table I of Dr. Moore's pre-publication draft, page 37 of NDA 18-692, Volume 1.1 for additional details.

of recovery

Postoperative evaluation consisted of response to Allis forceps, as indicated, in Group I. In Group II, the duration of sensory anesthesia was based on its regression of two dermatomes (previous standard of the author). Motor function was considered normal when the patient could run the heel of one foot accurately up the skin covering the anterior surface of the tibia of the other leg from ankle to knee without the heel wavering, with both legs.

Finally, the time when narcotic for pain was administered was recorded.

3

In addition, cerebrospinal fluid was drawn from 100 of these patients to conduct a special in vitro study of presence or absence of precipitate under aerobic and anaerobic conditions.

RESULTS:

GROUP I--Unsatisfactory analgesia resulted in one female with bupivacaine (0.8%) and in 9 males and 10 females with tetracaine (17%); these patients were eliminated from analysis of variables, as planned, leaving 120 bupivacaine patients and 95 tetracaine patients for analysis. Maximal analgesia was to the seventh thoracic dermatome (+2) and time to occurrence was 9 minutes (+4) for both bupivacaine and tetracaine. The duration of satisfactory analgesia prior to supplementation was 100 minutes \pm 30 for bupivacaine and 80 \pm 24 for tetracaine. The degree of motor block, on the previously cited 0 to 3 scale, was 2.4 \pm 0.7 for bupivacaine and 2.7 \pm 0.5 for tetracaine. The duration of motor blockade was 162 \pm 49 minutes for bupivacaine and 188 \pm 56 minutes for tetracaine. Sixty two percent of the bupivacaine patients (74/120) and 76% of the tetracaine patients in Group I required a narcotic and/or tranquilizer for pain in the first 24 hours postoperatively.

The bupivacaine patient with unsatisfactory anesthesia was undergoing lower extremity surgery. Five tetracaine patients undergoing lower extremity surgery, 2 undergoing transurethral resection of the prostate, 9 undergoing vaginal hysterectomy and 3 undergoing other (rectal, penile, testicular, etc.) surgery account for the 19 cases of unsatisfactory anesthesia in Group I.

Remember that this is a pure study of onset and duration of bupivacaine and tetracaine, in that epinephrine was not added in Group I clinical investigation.

GROUP II--Unsatisfactory anesthesia occurred in 13 patients who did not receive epinephrine, 5 for bupivacaine and 8 for tetracaine, and 13 patients who received epinephrine, 7 for bupivacaine and 6 for tetracaine. As stated, these patients were excluded from analysis of variables.

Without epinephrine, essentially the same maximum level of analgesia was achieved with both drugs (to about the fourth thoracic dermatome in both cases; the degree of motor block in the cases analyzed was judged complete in all cases for both drugs (scale rating of "3"). The duration of satisfactory analgesia prior to supplementation was, for all practical purposes, identical for both drugs (92 \pm 16 minutes for bupivacaine and 88 \pm 14 minutes for tetracaine). Tetracaine was slightly faster in achieving maximum thoracic dermatome level of analgesia (8 \pm 2 minutes versus 10 \pm 4 minutes for bupivacaine). The time for maximum degree of motor blockade (in this case from a rating of "zero" to a rating of "3") was also faster for tetracaine than for bupivacaine (8 \pm 4 minutes versus 13 \pm 8 minutes). The duration of motor blockade was longer for tetracaine than for bupivacaine (234 \pm 51 minutes versus 202 \pm 49 minutes). Remember, again, that patients with unsatisfactory anesthesia were excluded from analysis. Analysis of 45 bupivacaine cases and 42 tetracaine cases.

With epinephrine 0.2 mg, essentially the same maximum level of analgesia was achieved for both drugs (fourth thoracic dermatome \pm 2 for bupivacaine and third thoracic dermatome \pm 2 for tetracaine). Maximum sensory level was achieved in about the same amount of time for both drugs (9 \pm 3 minutes for bupivacaine and 11 \pm 7 for tetracaine). The duration of satisfactory analgesia prior to supplementation was 136 \pm 30 minutes for bupivacaine and 113 \pm 37 minutes for tetracaine. The degree of motor block, in all cases for analysis, was maximum ("3" on the rating scale). Analysis of 43 bupivacaine cases and 44 tetracaine cases. The onset (not maximum onset) was slightly faster

for bupivacaine (about 40 seconds mean versus 47 seconds mean, allowing 11-21 seconds variability). The duration of motor blockade in the lower extremities for bupivacaine was 279 ± 60 minutes; 371 ± 67 minutes for tetracaine. The time of first narcotic administration for bupivacaine was 196 ± 41 minutes; 229 ± 68 minutes for tetracaine.

The duration of motor blockade was prolonged by a mean of 38% by the addition of 0.2 mg epinephrine to the bupivacaine solution (a mean of 279 minutes versus a mean of 202 minutes). The duration of satisfactory analgesia prior to supplementation was prolonged by a mean of 48% by the addition of 0.2 mg of epinephrine to the bupivacaine solution (a mean of 92 minutes versus a mean of 136 minutes). The time of first narcotic administration was similarly prolonged by a mean of 21% (162 minutes versus 196 minutes). Maximum degree of motor blockade was slightly slower when bupivacaine was administered without epinephrine (13 minutes versus 10 minutes mean). All of this is in keeping with the previously well known fact that the administration of epinephrine to final spinal anesthetic solutions (usually about 0.2 mg total) will add about half as much time again to the effective duration of action of the spinal anesthesia; the figure of 48% for duration of satisfactory analgesia, during surgery, is right onto half as much time again duration. See Table 6, page 42 of Volume 1.1, NDA 18-692. Results for tetracaine were, briefly, similar (see Table 5, same reference).

No differences in the incidence of complications between the two drug treatment groups were noted. Nausea and vomiting without hypotension were noted in 10% of the patients (45) during surgery; operative hypotension was noted in 16% of the patients (71) during surgery (not unexpected because of the relaxation of sympathetic tone which occurs from spinal anesthesia----this is easily managed by people trained in the practice of anesthesia by screening of patients who might be harmed by such practice and use of large volume parenteral therapy and, sometimes, vasopressors to manage the condition when it occurs); one case of cephalad spread of local anesthetic drug was noted (0.23%). In this latter case, a thirty degree Trendelenberg position was requested by the surgeon about 75 minutes after the injection of 12 mg of tetracaine; within five minutes, the level of analgesia had moved from the fourth thoracic to the second cervical dermatome, requiring general anesthesia, endotracheal intubation and assisted respiration for 45 minutes. The only postoperative complication was that 6 (six) of the 435 patients developed postoperative headache (1.4%).

The pH of human cerebrospinal fluid drawn from 100 patients under anaerobic conditions ranged from 7.30 to 7.45 (mean 7.36). When 1.5, 3, or 4.5 ml of 0.75% bupivacaine was placed immediately into vacume test tubes along with 6, 4.5 and 3 ml of human cerebrospinal fluid, respectively, no precipitate occurred during an eight week observation period (anaerobic conditions). Also, 2 mg of bupivacaine in 2 ml of human cerebrospinal fluid, placed immediately into a 2 ml vacume test tube, did not flake or precipitate during observation for one year. Under aerobic conditions, bupivacaine precipitated when the pH of human cerebrospinal fluid reached or exceeded 7.54.

Dr. Moore concludes that bupivacaine 0.75% in 8.25% dextrose with or without 0.2 mg epinephrine (0.2 ml of 1:1000) is safe and reliable for the production of ~~loea~~ spinal anesthesia. Whether it is a more satisfactory drug than tetracaine for spinal block is debatable. Epinephrine 0.2 mg significantly prolongs the duration of effectiveness of bupivacaine (and tetracaine, as is already well known). The high incidence of unsatisfactory anesthesia from the test tetracaine solution in the low dose study cannot be fully explained; his staff is accustomed to a different tetracaine preparation (crystalline, lyophilized) and differing results are

not uncommon when preparations are changed (experience of this reviewer with use of local anesthetics, especially tetracaine for spinal anesthesia); it may also be that milligram for milligram the sensory effect of bupivacaine may be greater than that of tetracaine and that the difference comes more into play in surgical procedures requiring lower dosages.

Tetracaine is, at least in the United States, the standard product for the production of spinal anesthesia. This study demonstrates that bupivacaine is at least as reliable as tetracaine.

Clinically speaking, there is little to choose from regarding onset time, maximum block, dermatome level, etc. between 12 mg of tetracaine and 12 mg of bupivacaine. Effective sensory anesthesia times are similar for the two drugs (12 mg) and epinephrine prolongs the duration of effective anesthesia in both cases. The times of motor blockade are similar, except that epinephrine appears to prolong the motor blockade of tetracaine longer than that of bupivacaine. Let's just say that bupivacaine 12 mg hyperbaric spinal anesthesia provides about 1½ hours of effective surgical anesthesia and that use of 0.2 mg epinephrine will prolong the effective surgical anesthesia time by about half again. Marketing experience will undoubtedly provide greater dose-time correlations of use to individual clinicians.

Detailed management of spinal hypotension is not provided, however this lack of information is no great loss to the practicing anesthesiologist because they routinely manage this common complication with large volume parenterals and/or vasopressors.

Clinical investigation of Brett B. Gutsche, M.D., Professor of Anesthesia and Obstetrics & Gynecology, Univ. of Pennsylvania, Philadelphia. (6)

STUDY I--This was an open "pilot study" in 19 obstetrical patients. The solution was 0.75% bupivacaine in 8.25% dextrose. Doses ranged from 6 mg for vaginal delivery (4 cases) to 7.5-12 mg for cesarean section and tubal ligation (15 patients). The superficial summary notes that there were no unexpected complications and that the investigator concludes that the quality of spinal anesthesia with bupivacaine is adequate for vaginal deliveries as well as for cesarean sections and tubal ligations.

STUDY II----Encouraged by the above, a double-blind randomized parallel comparison of equal mg dosages of hyperbaric tetracaine (0.75% in 8.25% dextrose) and hyperbaric bupivacaine was undertaken. Fifty female patients undergoing cesarean section entered the study and 26 received hyperbaric bupivacaine while 24 received hyperbaric tetracaine. The dosage was 7.5-12 mg of either tetracaine or bupivacaine. In 12 of the bupivacaine patients and 17 of the tetracaine patients 0.2 mg of epinephrine was added. An additional 17 patients undergoing bilateral post-partal tubal ligation received either hyperbaric bupivacaine (9 patients) or hyperbaric tetracaine (8 patients). The dosage was again 7.5-12 mg.

Complications were only as expected from the clinical pharmacology of spinal anesthesia and the resulting sympathetic denervation of a transient nature (keep in mind that inferior vena caval compression contributes in late pregnancy). Fifteen bupivacaine patients experienced hypotension (8 with a systolic blood pressure greater than 90 and 7 below 90) as did eighteen tetracaine patients (12 greater than 90 and 6 below). All were controlled readily with vasopressors (not otherwise detailed in the summary). The tubal ligation patients experienced no complications.

In the cesarean section group, onset of the block occurred in about one minute (bupivacaine). Maximum anesthesia was noted (bupivacaine) in about 10 minutes with the addition of epinephrine to the solution and in about 14 minutes without the addition of epinephrine. "Onset times were similar for tetracaine solutions". Regression of anesthesia started at about the same time whether or not epinephrine was employed (85 versus 82 minutes, in favor of epinephrine). Regression was complete at 269 minutes average when epinephrine containing solutions were employed and at 219 minutes average without epinephrine. Tetracaine regression started in a mean of 127 minutes when epinephrine was added and in a mean of 92 minutes without epinephrine. Regression in the tetracaine cases was complete in 377 minutes with epinephrine and in 260 minutes without epinephrine. The summary fails to indicate criteria for onset of regression and completion of regression. The anesthesiologist rated the blocks excellent or satisfactory in all bupivacaine cases and in 22 of the 26 tetracaine cases (4 unsatisfactory). There were no other significant differences between tetracaine and bupivacaine. Supplementation of anesthesia was required in three tetracaine cases and three bupivacaine cases. Criteria for excellent, satisfactory and unsatisfactory clinical ratings are not provided in the summary.

In the 17 tubal ligation cases, one tetracaine patient had an inadequate block. Onset averaged 1-2 minutes for both drugs and time to maximum anesthesia averaged 13 minutes for bupivacaine and 10 minutes for tetracaine. Regression began on the average of 86 minutes and was complete by 410 minutes for bupivacaine; these times were 68 and 216 minutes for tetracaine. These cases were all apparently without epinephrine, but this is not specifically stated in the summary.

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REVIEWER'S COMMENTS:

This summary is extremely superficial. It is not clear what effect the dosage range had on onset and duration; correlation of results by dosage is not provided. There are no tables or graphs accompanying this summary. The management of spinal hypotension is not detailed, however this lack of information is no great loss to the practicing anesthesiologist because they routinely manage such cases with large volume parenterals and/or vasopressors. Criteria for onset, duration, onset of regression and completion of regression are not provided. More important, this study summary cannot be used to establish obstetrical safety because fetal outcome is not discussed at all. Under these circumstances, this double-blind randomized parallel comparison of tetracaine and bupivacaine for spinal anesthesia is no more useful than the usual uncontrolled study in which patients serve as their own control; the drug certainly works, when compared to the patient serving as her own control, and it is certainly safe and free of complications not in keeping with the clinical pharmacology of spinal anesthesia; onset and duration data, for the potential package insert, cannot be obtained from this study summary.

A one page draft, with multiple tables (8 slides), appears in the literature support section (pages 270-279 of Volume 1.1). Once again, there is no information of fetal outcome.

William F. Kennedy, jr, D.
Univ. of Washington
Seattle

8

This was an open study. Forty eight patients were given an average of 10 mg (range 7.5-12.5 mg) 0.75% bupivacaine in hyperbaric solution, made with the addition of 8.25% dextrose (specific gravity 1.030-1.035). Three additional patients received a similar 0.5% bupivacaine hyperbaric solution.

Ninety six percent of the 0.75% patients had anesthesia which was defined as "excellent", meaning that it was completely satisfactory both objectively and subjectively for the procedure. (46/48). The two remaining patients required some sort of supplementation, intravenously in one case (drugs not stated) and requiring a second anesthetic technique to complete the procedure in the second case. The three 0.5% bupivacaine cases were rated either excellent (2) or satisfactory (1), satisfactory meaning that some intravenous supplementation was required. No adverse reactions were reported.

A. Eugene Pflug, M.D.
Univ. of Washington and U.S.V.A.H.
Seattle

Ninety nine patients for elective surgery were randomly assigned so that 49 patients received spinal anesthesia with bupivacaine 7.5 mg/ml in 5% glucose and 50 patients received tetracaine 7.5 mg/ml in 5% glucose. Doses were individualized according to age, weight, height, anticipated surgery, etc., standardized into groupings. The study was double-blinded so that the clinician knew the dosage of drug, the concentrations being the same, but did not know the identity of the test drug in each case. Injection was in the lateral recumbent position. Mephentermine 30 mg was injected as a prophylactic vasopressor through a skin wheal raised prior to the insertion of the spinal needle. Parenteral diazepam was utilized liberally before and during anesthesia on an individualized basis. Management was otherwise standard (intravenous fluids, etc.) and need not be detailed here.

No significant difference was found between the mean values for time of onset, time of maximum anesthesia, dermatome level of anesthesia or duration of spinal anesthesia produced by equal amounts of bupivacaine and tetracaine. Both bupivacaine and tetracaine provided satisfactory spinal anesthesia for all of the surgical procedures studied. The only difference noted in comparing the 2 drugs was in the incidence of motor function blockade; complete leg paralysis was noted in 100% of the tetracaine patients who received the 10 mg dose (12) versus 42% for bupivacaine (5/12). Onset of anesthesia averaged 3-3.3 minutes, maximum anesthesia took 12.7-13.7 minutes, with a dermatome level to T8. Duration of anesthesia was in the 120-200 minute range and was generally longer for the higher doses than it was for the lower doses (about 121-142 minutes versus 189-198 minutes, in favor of longer duration for the higher doses). One patient developed a headache after tetracaine which resolved with conservative treatment (not otherwise described). Three patients, all in the bupivacaine group, developed a drop in systolic blood pressure of 20% or more below the pre-operative level; these patients responded to routine management with large volume parenteral therapy (increasing intravenous fluids) and intravenous ephedrine.

This summary is derived from the sponsor's summary on pages 50-51 of Volume 1.1 and from a publication by the investigators (.A.E.Pflug, et. al., Anes. & Analg. 55:489-492, 1976) contained on pages 227-229 of Volume 1.1. The authors conclude that the results obtained with bupivacaine and tetracaine spinal anesthesia were clinically the same, except for an occasional decreased motor blockade with bupivacaine, when equal hyperbaric doses are used for similar procedures. (Not much information on the type of surgery is provided.)

Alon Palm Winnie, M.D.
Abraham Lincoln University
Chicago

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This was an open study in 25 patients. Hyperbaric bupivacaine was employed (specific gravity 1.030 to 1.035 with 8.25% dextrose) for patients undergoing above the knee amputation under spinal anesthesia. Five patients received 10 mg bupivacaine as 0.25% solution, ten patients received 10-15 mg of 0.5% solution and ten patients received 10-15 mg as 0.75% solution. Anesthesia was judged satisfactory or excellent in all cases (not defined in the summary). No adverse experiences were observed. There appeared to be no significant differences between groups with regard to results, but it was judged to small a study for definitive conclusions in this regard.

Robert L. Watson, M.D.
Walter Reed Army Medical Center
Washington, D.C.

This was a study in 19 patients undergoing urological or lower extremity surgery under spinal anesthesia. Bupivacaine 0.5% was employed in doses ranging from 4 to 15 mg, open label style. The solutions were made hyperbaric by the addition of 0.9 to 1.4 ml of 10% dextrose. Onset of anesthesia was noted between 1-5 minutes after injection, but motor blockade took an average of 15 minutes. Complete motor blockade occurred in 54% of the patients who received 7.5 mg or less bupivacaine and in 83% of those who received 10 mg or more bupivacaine. Duration of sensory anesthesia ranged between one and four hours, with a trend towards increased duration at higher doses. There were nine cases of hypotension (not otherwise defined in the sponsor's summary) managed with ephedrine.

Note: Dr. Watson is now Chief of Anesthesia at Walter Reed. This study was performed about 10 years ago, during a previous tour of duty at Walter Reed in a more junior position.

Peer C. Lund, M.D.
Conemaugh Valley Memorial Hospital
Johnstown, Pa.

The sponsor cites this study for completeness. An open study of 100 patients is supposed to have been initiated in October of 1971 and completed in 1973. Case reports and study summary were repeatedly requested, according to the sponsor, and never received from the investigator.

LITERATURE SUPPORT:

(10)

Nineteen articles from the medical literature are submitted, some in translation form when indicated. Dr. Pflug's article has already been cited. The clinical investigation of Dr. Moore, already summarized, is also the subject of a publication (Anes. & Analg. 59: 743-750, 1980). The other articles will now be summarized, sometimes briefly, as indicated:

L. Ekblom and B. Widman, Acta Anaes. Scand. Supplement 23:419-425, 1966. This was a very early study, under double-blind conditions, in 40 patients who received either 2 ml of 1% tetracaine or 2 ml of 0.75% LAC-43 (bupivacaine), presumably before the drug had a name. Injection was in the 3-4 lumbar interspace, in the sitting position. The solution is described as hypertonic (specific gravity 1.035-1.040) with the pH adjusted to 4.5; this would also be hyperbaric, since cerebrospinal fluid has a specific gravity of 1.0045. The formulation is not clear from the publication.

No difference in onset time, spread or duration of anesthesia could be detected. Duration was 274 ± 12 minutes for LAC-43 and 306 ± 16 minutes for tetracaine (from first onset to total regression). The intensity of motor blockade with tetracaine was complete in all cases, but in the case of LAC-43 four out of twenty patients had incomplete motor blockade. The degree of sensory blockade was also inferior in the LAC-43 group as compared to the tetracaine group. These differences may be accidental because they are based on 2 unsatisfactory evaluations and 2 no anesthesia evaluations for LAC-43 that could have been accounted for by technical problems (experienced clinicians generally have more effective blocks than inexperienced clinicians, provided that they stick to products and techniques that have worked for them in the past, but a block which does not produce the desired effect is always a possibility for any clinician, no matter how competent). Sensory anesthesia was still judged "perfect" in 16 LAC-43 cases and 18 tetracaine cases.

M. Antal, et. al., ACTA Chirurgica Academiae Scientiarum Hungaricae, Tomus 17 (4), 305-310, 1976. The reference is in English, despite the title of the publication. This article deals with the experience of the authors with use of spinal bupivacaine anesthesia in Traumatological Surgery. Two hundred and forty patients, mostly between the ages of 21 to 80 years, one third over 60 years of age, received bupivacaine 0.5% for spinal anesthesia. Epinephrine 1:200,000 was used in only 36 of these cases. Doses ranged from 12.5 mg to 25 mg total or 2.5 to 5 ml (average dose 0.25 mg/kg). This suggests that glucose may not have been added, but this subject is not discussed so we don't know much about the formulation. The 2-3 or 3-4 lumbar interspace was generally utilized.

Surgery was generally for trauma (pelvis, knee, other bones, soft parts, etc.), for the most part performed late in the day. Patients judged not suitable for spinal anesthesia for standard textbook reasons, including those in shock, were excluded. There were 129 acute cases and 111 non-acute cases. Patients all received standard pre-anesthetic medication, such as diazepam, meperidine, promethazine, atropine, etc. Surgery generally took less than 1 hour (114 cases) or between 1 & 2 hours (106 cases). There were only 3 cases which took over 3 hours. There were 107 patients judged to be in good general condition, 75 fair and 58 poor.

Analgesia began 3 to 5 minutes after administration and reached a peak in 10 to 15 minutes; at that time the level extended to the height of the seventh to

tenth thoracic segment. Anesthesia was generally of long enough duration for the surgery; it was judged good in 206 cases, satisfactory in 22 cases and unsatisfactory in 12 cases, generally to be so because of problems of technique. judged

The duration of postoperative analgesia was evaluated in 50 patients. This duration generally ranged from 5 hours to about 10 hours (2 cases less than 5 hours and 4 cases more than 10 hours). What was being measured is not exactly clear, but it had something to do with the length of the painless post-operative period in 50 patients who gave reliable answers; this reviewer's guess is that they were measuring something similar to (D.C. Moore's Study) time to need for postoperative analgesics.

Intraoperative complications (19.7% of all patients) were as expected for spinal anesthesia (hypotension 28, bradycardia 8, tachycardia 3, nausea and vomiting 6, others 3). Postoperative disturbances of gastrointestinal nature and bladder motility are described as slight and transitory. Postoperative headache, ranging from mild to severe, were frequently noted; the exact incidence is unclear, but extra surveillance of 20 selected cooperative patients revealed a 15% incidence of mild headache and a 5% incidence (one case) of severe headache. This problem generally responded to bed rest (recumbent) and extra fluid intake.

No meningo myelopathy or neuroparalysis was observed.

The authors conclude that, with proper patient selection, spinal bupivacaine anesthesia is a reliable and promising method. It also helps stretch limited resources when a great number of trauma patients have to be cared for simultaneously.

G.G. Szappanyos (Anes., Univ. Hosp. of Geneva, Switzerland), Der Anaesthetist, 18 Band 10, Heft, Oktober S. 330-333, 1969 (18:330-333, 1969 ?).

This is a report of an early open study in 100 surgical patients of all adult ages, undergoing a representative variety of surgical procedures, for which anesthesia was provided with 5 to 14 mg of 1% bupivacaine (spinal anesthesia with conventional precautions and perioperative drugs). The solution consisted of 10 mg bupivacaine per ml, with 7 mg NaCl and 0.5 mg sodium pyrosulfate, pH 3.4. Some were hyperbaric (addition of 10% dextrose), some were hypobaric (8 ml of distilled water) and some were isobaric (3.5-4 ml cerebrospinal fluid); epinephrine 0.2-0.4 mg was sometimes added as 0.1% solution.

Onset averaged 30-90 seconds. All 100 anesthetics were judged good to excellent in terms of relaxation of abdominal musculature; operations could be performed without additional anesthesia. In the case of 5-8 mg, the feet and knees could be moved slightly. In the case of between 8-14 mg, a complete motor block of the lower extremities was obtained. Without epinephrine, the duration of analgesia was between 50-128 minutes, depending on the dose (approximate duration). With epinephrine, the analgesia varied from 95-195 minutes (approximate), depending on the dose. This covered the surgical time (20-185 minutes) so that no additional analgesics or anesthetics were needed during surgery. Operative complications were well in keeping with the known clinical pharmacology of spinal anesthesia. Headache, nausea, dizziness, backache, paresthesia and local reactions were not noted during the time period of 1-48 hours postoperatively. The author concludes that LAC-43 (bupivacaine) is potent, safe, very dependable and free of side effects when used for spinal anesthesia. Excellent analgesia is noted afterwards for a long time, as is excellent relaxation during surgery. Unexpected complications were not noted. Postanesthetic neurological complications were not observed. The product mixes well with dextrose, adrenalin, spinal fluid and distilled water.

P. Pietrobono and U. Maggi (Univ. of Pavia) (Italia?), Acta Anaesth. 22:461-476, 1971. The authors report on 300 cases of spinal anesthesia carried out with 1% hyperbaric bupivacaine for general surgery and urological procedures; dosages of bupivacaine are not obvious from the translation provided (the original document is not available to test my ability or lack of ability to translate from Italian?). The authors report favorably on this use. Complications were only as expected from the clinical pharmacology of spinal anesthesia, including a 1.3% incidence of headache. Their method of managing hypotension was not in keeping with current U.S. practices (100 mg hydrocortisone intravenously and either 15 mg methoxamine or 15 mg mephentermine intravenously), but it seemed to work for them. Much of this article is a general review of spinal anesthesia, citing, for instance, Dr. Daniel Moore's well known writings on technique and related matters.

F. Ramaioli and I. Pagani (also of Università degli Studi di Pavia, Anesthesia Dept.) Minerva Anesthesiologica 38: 1-12, Jan. 1972. The authors report on 321 cases of spinal anesthesia. Each 2 ml consisted of 20 mg Marcaine (1%) and 240 mg of glucose (12%) in water, specific gravity 1.035-1.040 or certainly hyperbaric. Surgery was generally orthopedic-traumatological. Patients ranged from 20-96 years of age, both sexes; 29 of these were over 80 years of age. Dosages ranged from 10-40 mg, with and without adrenalin. Results were generally favorable and the authors conclude that this type of spinal anesthesia is suitable for orthopedic-traumatological surgery. Complications were discussed in great detail, but they were basically those already known for spinal anesthesia; by implication, there were no prolonged sequelae (not specifically stated but obvious from the rest of the text of this translation). I note, again, use of hydrocortisone to manage hypotension, not standard in this country but it seemed to work for these authors.

El-Sherbiny, et. al. (Cairo Univ.), from presentation at the fifth World Congress of Anaesthes., Kyoto, Japan, Sept. 1972. Hyperbaric bupivacaine 0.5% was employed in 120 patients undergoing general surgery, gynecological surgery and orthopedic surgery at Cairo University. The dose was 2 ml or 10 mg of bupivacaine, administered between the third and fourth lumbar interspace. Maximal spread took about 3 minutes (pin prick test) and the time from onset to regression of surgical analgesia (complete sensation--pin prick presumably) was found to take 180 ± 15 minutes. Motor and sensory block was complete except in one case which was attributed to technical error (general anesthesia was carried out in this case). Side effects were as expected; hypotension was treated conventionally with ephedrine 15 mg i.m. as indicated. Patients were kept in bed for 24 hours after anesthesia to avoid headache; thus only two patients developed headache. No prolonged sequelae are cited, but one page is apparently missing (as suggested by a lack of Table 2, referred to in the text).

This brief abstract suggests that anesthesia practice in Egypt is very similar to that in the U.S. and that results from use of bupivacaine hyperbaric spinal are clinically acceptable. Although a page is apparently missing, complications cited are in keeping with the clinical pharmacology of spinal anesthesia.

Marjukka Puronto (Orthopadsches Krankenhaus der Invalidenstiftung, Helsinki), Anaesthetist (Springer-Verlag) 24: 408-411, 1975. Both the original article and an English translation are offered.

One hundred and seventy (170) patients of both sexes underwent orthopedic operations under hemi-spinal anesthesia (the injection was made on the side with the surgical site down and the non-surgical site up during the period of anesthetic onset to offer some sparing of autonomic effects, at least in theory, to poor risk patients). Patients were generally ASA Category III risk because of obesity (57), respiratory insufficiency (51), arterial hypertension (51), cardiac disease (81), post myocardial infarction (5) post pulmonary infarction (4) or metabolic disorders (11). Average patient age was 63 years. Ninety two patients underwent the insertion of a hip prosthesis and 78 patients underwent other operations on one lower extremity. The dose was 1 ml (or 0.7 to 1.5 ml, depending on the length of the back) of 1% hyperbaric bupivacaine (b) (4). About 1 mg of phenylephrine was added to prolong the block when the surgery was anticipated to exceed 3 hours. After 5-10 minutes the patient is placed supine, the level of anesthesia judged to have been set by then.

Blood pressure fell less than 20% in 11 cases, less than 10% in 58 cases and remained unchanged in 23 cases (hip prosthesis). Hypotension was not noted during the implantation of the acetabulum or femur cement. Results were similar for other types of surgery (less than 10% fall in 15, less than 20% fall in 20 and no change in 43). "No shock symptoms occurred".

The duration of anesthesia was determined on the basis of the first pain sensation in the patient, about 3 hours without phenylephrine and about 4 hours with phenylephrine.

Other adverse observations were about as expected (vomiting--30 or 17.8%, headache--5 or 3%, slight disorientation--3 or 1.8%---but remember that central nervous system premedicants were also employed, & dizziness--1 or 0.6%). No neurological damages were observed in the postoperative phase and none were reported later.

The authors lend their support to unilateral spinal anesthesia with 1% hyperbaric bupivacaine, particularly for hip surgery, judging it to be reliable, fast-acting, with minimal side effects and of sufficiently long duration (remember that the dose of about 10 mg is spread over a smaller effective area than if used for conventional spinal anesthesia).

A.K.ROY, et. al. (British Medical College and Civil Hospital, Ahmedabad), Ind. J. Anaesth., pages 60-67, February 1975.

This was a double-blind comparison of bupivacaine 1% (35 patients), mepivacaine 4% (37 patients) and lidocaine (as lignocaine) 5% (28 patients), all prepared in hyperbaric solution by Squibb-Sarabhai Chemicals, Baroda, to provide spinal anesthesia for general surgery in patients between the ages of 15-76 years (1972). Two ml of the coded drug was injected. The glucose concentration ranged from 7-9.5% and the specific gravity ranged from 1.031-1.037.

APPEARS THIS
WAY ON
ORIGINAL

Analgesia was complete in all cases, as was motor blockade in all but one mepivacaine case (judged, probably correctly, to be due to technical problems).

The average onset time was virtually identical for all three drugs (3 minutes or so). The duration of sensory analgesia was 276 minutes mean for bupivacaine, motor 201 minutes. This was longer than for mepivacaine (sensory 187 minutes and motor 145 minutes), and also longer than for lignocaine (lidocaine) (152 minutes sensory and 104 minutes motor).

A fall in blood pressure of 25% or more was noted in 28.5% of the bupivacaine cases, 16.2% of the case of mepivacaine and 10.5% in the case of lignocaine. All of the patients who had hypotension responded very well to supportive measures and vasopressors. Other complications, attributable to spinal anesthesia, were as expected from the clinical pharmacology of spinal anesthesia, including 5 cases of postoperative headache (one following bupivacaine, 2 following each of the other drugs).

The authors note (comparable onset and) more prolonged duration of action, both sensory and motor, following use of bupivacaine 1% hyperbaric solution, as compared to similar mepivacaine 4% and lignocaine 5% solutions. They recommend such use of this product and also speculate on use in rural areas where ideal conditions of operation do not always exist.

O.M.Pentti, et. al. (Anes., Middle Finland Central Hospital, Jyväskylä, Finland), Ann.Chir.Gynaecol.67: 185-189, 1978.

As if more support were needed, this is a report of 400 consecutive cases of bupivacaine spinal anesthesia (hyperbaric 1% solution, specific gravity 1.040 at 20 degrees C and pH 5). Patients ranged in age from 19-91 years; 43% were ASA Risk III or greater risk. The quality of anesthesia was judged good or perfect in 94% of the cases; analgesia always outlasted the surgery, which in turn lasted up to 3 hours. No serious complications were observed. Hypotension was frequently noted and easily managed by correction of hypovolemia, other conventional measures and use of vasopressors (b)(4) or (b)(4) is mentioned, unfamiliar by this name to this reviewer). Headache occurred in less than 6% of the patients & was never of prolonged duration.

spinal anesthesia attributable

It is specifically mentioned that no neurological symptoms (other than transient headaches) occurred while the patients were in the hospital or on followup for 3-5 years through the Middle Finland registry.

L.S.Nuutinen & T. Kangas (Anes., Univ. Central Hosp., Oulu, Finland), Annales Chirurgiae et Gynaecologiae 69: 164-166, 1980.

This is a report of 240 consecutive patients given spinal anesthesia with isobaric 0.5% bupivacaine. The study supports safety and efficacy for this solution, very different from the one in question in this New Drug Application. No serious complications were observed and no neurological complications were noted postoperatively during the time that patients remained on the ward, however, no long term neurological followup was done in these patients.

W.A.Chambers, D.B.Scott, et. al. (Dr. Scott is a well known local anesthetic clinical investigator of the Royal Infirmary, Edinburgh, Scotland), Abstract from the Sixth Annual ASRA Meeting, Atlanta, Ga., USA, 12-15 March 1981 (this meeting abbreviation is unfamiliar to this reviewer and the full meaning of the abbreviation is not spelt out).

This was a double-blind comparison of 2 ml, 3 ml and 4 ml of bupivacaine 0.5% hyperbaric solution (8% dextrose), 1.3 and 2 ml of a similar 0.75% solution, 10 patients per group. In addition, 7 patients received 3 ml of 0.75% hyperbaric solution. Volume of injection ^{of 0.5% solution} had a much greater effect

on duration of block than on height of block. On the average, block was to T4-5, with duration increasing as related directly to volume. Height of block did increase with volume of 0.75% solution (being T2 with 3 ml, T5 with 2 ml and T7 with 1.3 ml---average) as did duration. They did not like the level of the 3 ml 0.75% block and thus abandoned it after seven such blocks. They conclude, at the end of this very brief summary, that the use of a 0.75% solution, compared to a 0.5% solution, offers no apparent advantages. The durations are not cited, perhaps due to space limitations.

W.A. Chambers, D.B. Scott & H.H. Edstrom, Br. J. Anaes. 53: 279-282, 1981. Thirty female patients participated in a comparison of 0.5% bupivacaine with no glucose or 5% glucose or 8% glucose for gynecological procedures of a major nature. The hyperbaric solutions (5 & 8% glucose) produced greater cephalad spread and were suitable for lower abdominal surgery. The plain solution seldom affected the thoracic nerves and supplemental anesthesia was required in six of these eight patients in the isobaric group (no glucose), in contrast to one supplementation for among the hyperbaric patients. Diastolic blood pressure fell lower with 8% dextrose, but did not correlate with height of block statistically; systolic blood pressure changes were similar for all groups. Heart rate changes ranged from -20% to +22%, similar for all groups; mean heart rate was unchanged in all three groups in that the range evened it out. Two patients complained of nausea during periods of hypotension, rapidly responding to 15 mg dphedrine intravenously. Six patients developed post-spinal headache and the investigators considered this an unusually large number in view of the small sized needle used (25 gauge). No other complications are cited. Duration ranged from 140-160 minutes, unaffected by the baricity. 3 ml

P.J. Nightingale and T. Marstrand, (Anes. & Intensive Care, Sundby Hosp., Copenhagen, Denmark), Br. J. Anaes. 53: 369-370, 1981. The authors report on 410 patients over the age of 60 years who underwent orthopedic surgery under spinal anesthesia consisting of 0.5% bupivacaine, 3-4 ml, isobaric. The technique resembles a unilateral or "one legged" spinal in that the patients were kept in the lateral position until pain left the fracture site, after which the patients were placed supine. In 14 patients (3.4%), general anesthesia was needed because analgesia was absent or patchy. In the remaining 96.6%, anesthesia was sufficient for the procedure, sometimes needing 250 minutes (procedures were short, generally lasting 30-40 minutes, but preparatory positioning and reduction of the fracture sometimes took quite a while). Duration was a mean of 239 minutes (range 118-350). Arterial hypotension was noted in 37.7% of the patients, responding to a mean of 25 mg intravenous ephedrine (range 12.5 to 112.5 mg total); surprisingly, use of large volume parenteral therapy of hypotension is not mentioned. "Headache and nausea were rare but always resolved within 24 h." No long term complications are noted, but the subject is not mentioned.

A.E. Cameron, et. al. (Anes., Southland Hosp., Essex SSO ORY ?), Anaesthesia 36: 318-345, 1981.

The authors found the results of isobaric spinal anesthesia with 0.5% bupivacaine, 63 cases over a wide dosage range of 1 to 4 ml, to be poorly predictable and they objected to the high level achieved in some patients (the text, however, does not describe unacceptably high levels although the authors apparently did not like a level of analgesia that rose from T9 to T6 over about one hour in one 89 year old man who received 4 ml at a rate of 0.1 ml/second). Still, anesthesia for surgery was judged excellent in 57 patients (90%). One patient (a 78 year old female) arrested briefly (10-15 seconds) 3½ hours after the start of anesthesia; she was already on the postoperative observation ward

and motor power was beginning to return. There is no additional clinical description as to etiology or surgical procedure; the patient apparently recovered at any rate and it would be wrong to fault the drug, primarily, based upon this superficial narrative (and the time interval suggests other problems and/or aftercare).

H. Nolte, et. al. (Institut für Anaesthesiologie, Klinikum Minden, Bismarckstr 6-Bereich 1, Wahlen Sie bitte bei tel. Rückfragen die Rufnummer ?), Anaesthesist 26: 33-37, 1977 (Springer-Verlag).

This study testifies to the safety of 0.5% isobaric bupivacaine spinal anesthesia. The authors cite experience in 5001 cases; there were no cases of neurological disturbance noted during or after operation. Two to 4 ml were injected, with and without epinephrine 1:200,000.

Increased volume affected the mean thoracic segment achieved; the mean was T-10 for 2 ml, T-8 for 3 ml, T-7 for 4 ml and T-6 for greater than 4 ml, however there was a large deviation, usually no lower than T-11 at the lower dosage and up accordingly afterwards to about T-5 for greater than 4 ml. Anesthesia was judged "suffizient" or adequately effective in 95.2% of the cases, "unvollständig nach Grand une/oder Ausbreitung" or requiring supplementation with opiates or other analgesics in 4.2% of the cases and "insuffizient" or responded negatively in 0.6% of the cases. Most of the data analysis is on a sub group of 1019 patients of patients between less than 30 years of age through intermediates into a group described as above 70 years of age; surgery included utero-abdominal (35% of subseries), extremity (about 60%) and obstetrical delivery (about 6%). Apparently female patients predominated, but this is not perfectly clear.

Side effects were tabulated for 1022 cases: hypotension 13.7%, bradycardia 8.8%, arrhythmias 8.1%, tachycardia 0.9%, severe tachycardia 0.2% and other 1.7%. There were no deaths attributable to anesthesia. All of this appears typical for anesthesia and surgery in general and spinal anesthesia in particular.

Cerebrospinal fluid experiments, generally pooled from 10 patients, showed no changes in pH or precipitation under air exclusion conditions (as with blood gas analysis). For details of the in vitro experiment, consult the English translation and especially the part starting on page 239 of Volume 1.1.

This publication does much to support safety of bupivacaine for spinal anesthesia, admittedly a different formulation and a somewhat different technique, but it is a bit hard to follow because it deviates from the customary pattern of Methodology followed by Results. somewhat

An address of Dr. Nolte, "Current and Future Status of Spinal Anesthesia for Surgery", before the fourth annual meeting of the Society of Regional Anesthesia, Lake Buena Vista, Florida, was published in Regional Anesthesia 4: 10-13, 1979. This is available, starting on page 250 of Volume 1.1, for those who require additional information on isobaric bupivacaine and related topics. By then, Dr. Nolte was up to 6,228 cases, with severe complications in only four patients (0.06%); three patients developed high spinal anesthesia and required artificial ventilation; one patient incurred "massive hypotension" and respiratory insufficiency "due to inadequate observation and slow recognition of the complication", but even this patient incurred no irreversible damage thanks to immediate treatment once the condition was recognized; two patients suffered a severe fall in systolic blood pressure, followed by asystole and both were successfully resuscitated and had no permanent damage.

Four patients died on the operating table, all judged not related to anesthesia; one patient died after a tourniquet was placed on the leg with death due to pulmonary embolism while three died as the result of a massive fat embolism at the time of implantation of cement during artificial hip replacement. The simplicity of managing complications due to spinal anesthesia is noted (positioning, replacing volume deficit, use of atropine, etc.).

CONCLUSIONS:

1. Clinical investigation in the U.S. support safety and efficacy of bupivacaine for spinal anesthesia, thanks primarily to the summary provided of the work of Daniel C. Moore, M.D.. There are two satisfactory summaries of that work, one from the sponsor and one from a publication. Complications were as expected from experience with other drugs for spinal anesthesia, especially tetracaine (the standard for comparison in the United States). Onset was rapid, usually in one minute, reaching maximum blockade within 15 minutes in most cases (12 mg dose). The dose of 12 mg MARCAINE Spinal produced about 1½ hours of satisfactory sensory analgesia prior to the need for supplementation. The addition of 0.2 mg epinephrine will prolong effective sensory analgesia by about half as much time again. The duration of MARCAINE Spinal motor blockade is about 4 hours if no epinephrine is added and about 4.5 hours if epinephrine 0.2 mg is added. This compares favorably with the 12 mg dose of tetracaine except that motor blockade is more prolonged with tetracaine. At the lower dose of 7.5 mg, bupivacaine appears more effective than tetracaine.

In addition, solutions of bupivacaine are probably more chemically stable than tetracaine. Tetracaine is an ester and the n-butyl paraminobenzoic acid portion of that ester can precipitate out of solution in crystalline form while the solution is still within U.S.P. specification (experience learned from a regulatory matter in the early 1970's).

2. The other summaries provided for U.S. clinical investigations are unusually superficial. This is especially regrettable in the case of the controlled clinical investigation of Brett B. Gutsche, M.D. into obstetrical use of this product. On the basis of the summary provided, this product cannot be recommended for obstetrical use because there is no information on the effects of MARCAINE Spinal on neonatal outcome.

general surgical

This should not hold up approval; Dr. Moore's summary and literature support from Europe are more than sufficient to recommend approval. The risk to the neonate would appear to be minimal, based upon use of much larger doses of bupivacaine by the epidural route, including neurobehavioral studies. If clinicians were to ignore the WARNING against use in obstetrics (based upon insufficient data), the possibility of harm would be remote indeed.

3. Literature support from Sweden, Hungaria, Switzerland, Italia, Egypt, Finland, India, Scotland, Denmark, England, Germany and the United States (Dr. Moore, cited above) support safety and effectiveness of bupivacaine for spinal anesthesia (I hope that I have not left out any countries and have not misunderstood any address as to country of origin). This should be obvious from my summary of the literature. Keep in mind, however, that different formulations were frequently employed, particularly in the case of isobaric spinals (the subject of this NDA is a hyperbaric solution or a solution of greater specific gravity than cerebrospinal fluid).

4. REVIEW OF THE PACKAGE INSERT:

Description: I make no recommendations for this section.

Clinical Pharmacology: Change the second paragraph of that section so that it reads:



(b) (4)

20



(In addition, the generic name of this formulation must appear at least once on each page of the package insert).

Indications and Usage: I recommend no changes for this section.

Contraindications: Change this section to read:

The following conditions preclude the use of spinal anesthesia:

- 1. Severe hemorrhage, severe hypotension or shock and arrhythmias, such as complete heart block, which severely restrict cardiac output.
- 2. Local infection at the site of proposed lumbar puncture.
- 3. Septicemia.



(b) (4)

Warnings: Change this section to read:



(b) (4)

Precautions: Change this section to read:

General

The safety and effectiveness of spinal anesthesia depends on proper dosage, correct technique, adequate precautions and readiness for emergencies. Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use (see WARNINGS and ADVERSE REACTIONS).

(b) (4)



(SAME PARAGRAPH)

21

Reduced doses may also be indicated in patients with increased intraabdominal pressure, (b) (4)

(b) (4)

The following conditions may preclude the use of spinal anesthesia, depending upon the physician's evaluation of the situation and ability to deal with the complications or complaints which may occur:

1. Pre-existing diseases of the central nervous system, such as those attributable to pernicious anemia, poliomyelitis, syphilis, tumor, etc.
2. Hematological disorders predisposing to coagulopathies or patients on anticoagulant therapy. Trauma to a blood vessel during the conduct of spinal anesthesia may, in some instances, result in uncontrollable central nervous system hemorrhage or soft tissue hemorrhage.
3. Chronic backache and preoperative headache.
4. Hypotension and hypertension.
5. Technical problems (persistent paresthesias, persistent bloody tap).
6. Arthritis or spinal deformity.
7. Extremes of age.
8. (b) (4)

(b) (4) for Patients

. When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of spinal anesthesia.

Clinically Significant Drug Interactions

The administration of local anesthetic solutions containing epinephrine (or norepinephrine) to patients receiving monamine oxidase inhibitors, tricyclic antidepressants (b) (4) may produce severe, prolonged, hypotension or hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs (b) (4) may cause severe, persistent, hypertension or cerebrovascular accidents.

(Under Pregnancy Category, (b) (4)

Labor and Delivery

(b) (4)

(Nursing Mothers-----Keep this portion as written).

Pediatric Use

(b) (4)

Adverse Reactions: Change this section to read:

(b) (4)

(b) (4)

(b) (4)

Allergic: Allergic type reactions are rare and may occur as a result of sensitivity to the local anesthetic (b) (4). These reactions are characterized by signs of urticaria, pruritis, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and, possibly, anaphylactoid like symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitively established.

Overdosage: Add a section titled OVERDOSAGE, as follows:

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use or to underventilation (and perhaps apnea) secondary to upward extension of spinal anesthesia. Hypotension is commonly encountered during the conduct of spinal anesthesia, due to relaxation of sympathetic tone and, sometimes, contributory mechanical obstruction of venous return.

Management of Local Anesthetic Emergencies: The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after (b) (4). At the first sign of change, oxygen should be administered.

(b) (4)

(b) (4)

Hypotension, due to sympathetic relaxation, may be managed (b) (4)

If not treated immediately, both convulsions (b) (4)

Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated, after initial administration of oxygen by mask, if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

Dosage and Administration:

(b) (4)

How Supplied: I make no recommendations for change in this section of the package insert for MARCAINE Spinal.

RECOMMENDATIONS:

1. This application is approvable clinically with the package insert changes cited in the relatively large final section of CONCLUSIONS.
2. Although I agree with the Pharmacology Reviewer that this application is approvable from a pharmacology (and toxicology) standpoint, one point requires resolution. The potential package insert, as contained in the original submission dated 13 October 1981, lists MARCAINE Spinal as (b) (4). The soon to be printed Class Labeling for Local Anesthetics, prepared with the help of another member of the Pharmacology-Toxicology Staff, lists bupivacaine hydrochloride as "Pregnancy Category C."

This should be called to the attention of the Pharmacology-Toxicology Staff for definitive resolution.

David Lawrence Scally, M.D. *David L. Scally*
 Medical Officer---HFD-160

JPM 2/22/82 *2/19/82*

NDA 18-692
HFD-160
 HFD-180
 R/D DLScally 2/19/82
 R/D Init. by CRodriguez 2/19/82, JPMann 2/22/82
 Doc. Room 160

FEB 22 1982

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 018692/S-000

CHEMISTRY REVIEW(S)

MEMO RECORD

AVOID ERRORS
PUT IT IN WRITING

May 12, 1983

FROM: *Jan Koch* HFN-160

OFFICE

TO: File NDA 18-692

DIVISION

SUBJECT: *Marcaine Spinal FPL in 5/3-83 Amendment*

SUMMARY

Final printed package insert in subject 5/3/83 Amendment compared with draft insert dated 2/3/83 in the 2/7/83 RS, immediate container and carton labels with draft in the 2/19/82 Amendment, and, taking into consideration revision recommendations in Chemist Reviews, labeling is considered acceptable from standpoint of chemistry.

Jan Koch 5/12/83

MAY 14 1983

NDA 18-692
HFN 160
R/D Koch
DOC Room

CP/K
5/13/83

SIGNATURE

DOCUMENT NUMBER

NDA 18-692

Division of Surgical-Dental Drug Products
Chemist's Review #3

NDA 18-692

Date Completed: April 6, 1983

Sterling Drug, Inc.
90 Park Avenue
New York, NY 10016
AF 5-017

Proprietary Name: Marcaine Spinal
Non-proprietary: bupivacaine HCl 0.75% and dextrose 8.25% Injection
Dosage Form: sterile solution for subarachnoid anesthesia
Pharmacological Category: spinal anesthesia

Initial Submission Date: October 13, 1981
Submission subject of this review: February 7, 1983 RS

Remarks:

Chemist's Review #1 dated 11/12/81 addressed selected package insert deficiencies concerned with solution discoloration and particulate matter in the HOW SUPPLIED section, and the non-proprietary representation by the trademark Marcaine. These concerns were conveyed to the firm in the 12/18/81 Information Request letter. The 2/19/82 Amendment draft insert served to raise another point or two: Chemist's Review #2 (4/15/82) requested firm to (b)(4) consolidate references to solution autoclaving to the DOSAGE AND ADMINISTRATION section, and to add to this same section the 201.57(j) statement on parenteral particulate matter and discoloration. The Approvable letter which issued 7/20/82 made reference to these issues.

Review of this 2/7/83 RS insert revision raises the following cause for concern:

1. DESCRIPTION section - The solution pH range, which had been tightened earlier in the review of this NDA to 4-6.5, is once again designated in this section as (b)(4). This is in error. (b)(4)
(b)(4) our 7/20/82 Approvable letter called for the retention of the sentence (b)(4) "may be autoclaved once at 15-pound pressure at 121°C (250°F) for 15 minutes."
2. DOSAGE AND ADMINISTRATION section - Statement in our 7/20/82 Approvable letter on solution inspection for particulate matter and discoloration has been revised in latest draft; recommend statement be left as it was in our letter, but will accept current edition.
3. HOW SUPPLIED section - Statement on administration of discolored solutions in our 7/20/82 letter has been deleted, and should be retained.

There is no reference in the insert now to the (b)(4) solution discoloration during autoclaving.

NDA 18-692
page 2

Conclusion:

The Applicant should be promptly advised that the following revisions are needed in the February 7, 1983 draft package insert:

1.

[REDACTED] (b) (4)

2.

[REDACTED] (b) (4)

Otherwise, the Application remains in "Approvable" form from the standpoint of manufacturing and controls as stated in Chemist's Review #2 dated 4/15/82.

Stan Koch, Chemist

NDA 18-692

~~HFN-160~~, HFN-220

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R/D SKoch HFN-160 4/6/83

R/D Init Cholberg 4/6/83

ft mv 4/7/83 w1794P

APR 08 1983

Division of Surgical-Dental Drug Products
Chemist's Review No. 2

Date completed: April 15, 1982

NDA 18-692

Applicant: Sterling Drug, Inc.
90 Park Avenue, New York, NY 10016

AF 5-017

Proprietary name Marcaine Spinal

Non-proprietary name bupivacaine hydrochloride 0.75% with dextrose 8.25%

Dosage Form - sterile solution for subarachnoid anesthesia

Pharmacologic Category - spinal anesthetic

Initial submission date: October 13, 1981

Amendment dates: February 19, 1982, November 9, 1981, March 10 & 26, 1982,
and April 15, 1982

Received by Reviewing Chemist 2/22/82, 11/12/81, 3/10/82, 3/26/82, 4/15/82
respectively.

Received by BD: 2/22/82, 11/12/81, 3/10/82, 3/26/82, 4/15/82 respectively.

Supporting DMF 141 - Sterling Drug, Inc., Rensselaer, NY

Remarks:

The first chemist's review under this NDA was completed 11/12/81 and the deficiencies therein conveyed to the firm by telephone on 12/15/81, and by an Information Request letter, issued 12/18/81.

The 2/19/82 amendment raised several additional, or previously cited, problem areas. The Applicant was contacted by telephone on 2/24/82 and 2/26/82 (see MEMO) and informed by the following inadequacies and/or inquiries which remained at that time:

1. The finished drug active component assay chromatogram fails to demonstrate method capability to differentiate bupivacaine from its (b) (4).
(b) (4) I requested evidence of this capability. This request was item #4g in our 12/18/81 Info Request letter.
2. Considering the (b) (4), we made inquiry regarding the suitability and prospect of using the (b) (4).
3. Assurance is needed that the TLC procedure listed as a stability test to monitor dextrose purity and potency throughout the shelf-life of this drug is in fact stability-indicating and capable of determining dextrose content. This request was item #5b in our 12-18-81 Info Request letter.
4. After discussion with Don Meyers KC-DO (8-758-5524) concerning the finished drug active component GLC assay system suitability tests, the following revision and additions were requested by the aforementioned chemist in the system suitability test submitted in the 2-19-82 Amendment:

a.

b. include a specification for

c. include a specification for

The 3/10/82 amendment serves to (1) assure us that the [redacted] (b) (4), and will be used in this capacity via supplemental application if found to be suitable, (2) state that the TLC procedure under item 8p [redacted] (b) (4)

[redacted] and (3) complement the finished drug GLC system [redacted] (b) (4)

[redacted]. As system suitability tests now seen as complete, methods validation request and samples sent to HFD-106 on 3/10/82 for shipment to KC-D0. On 3/26/82 the firm informed us via Amendment that, using the finished drug GLC assay procedure,

[redacted] (b) (4) is nearly identical to that of bupivacaine. Sterling will monitor the [redacted] (b) (4)

[redacted] in the drug substance - see discussion under Laboratory Controls, this review.

The firm further agrees to include an [redacted] (b) (4). A revised listing of finished drug controls will accompany the submission of revised labeling (see 3/29/82 MEMO of telephone conversation).

This reviewer is not pleased with the [redacted] (b) (4). While these areas in need of strengthening are important, they may not be considered critical, and may be addressed in a manner which does not further delay action on this NDA. It is [redacted] (b) (4)

NDA 18-692
page 3

Conclusions:

This NDA is in "Approvable" form from the standpoint of manufacturing and controls with the understanding that (1) the labeling comments found in "Draft of Chemist's Part, Letter to Applicant" attached to this review will accompany the MO labeling revisions in an "Approvable" letter requesting revised draft labeling, and that (2) the "Approvable" or Approval letter contain a recommendation that the Applicant

(b) (4)
(b) (4)

Stanley Koch, Chemist

NDA 18-692

HFD-160

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R/D SKoch HFD-160 4/15/82

R/D Init CSinopoli 4/16/82

final typed mw 4/20/82

WANG 1042P

APR 23 1982

Only those sections of this NDA found lacking in the previous Chemist's Review #1 dated 11/12/81, or in which material changes have been made since the original submission, will be addressed in this review.

Synthesis:

Applicant says (b) (4) synthesis data in NDA 16-964 submission dated 8/28/70 remain current. Pages in this amendment which duplicate those in the Marcaine HCl (bupivacaine HCl injection) NDA refer to synthesis components, to a description of the process including reactant weights, reaction conditions, solvents, intermediates and purification steps, and to structural formula schematics. The process begins with (b) (4)

(b) (4)

(b) (4)

4 Page(s) has been Withheld in Full as b4 (CCI/TS)
immediately following this page

Request for Methods Validation of finished drug assay by GLC, and ID by TLC sent to HFO-610 on 3/9/82, ultimately to KC-DO. Analytical worksheets and results dated 3/25/82 received by this reviewer 4/13/82; TLC found active components present, and assay in duplicate (b) (4) (b) (4) bupivacaine HCl, for an average value of (b) (4)

Labeling

The recommendations we made regarding label concentration expression were accepted; label draft have been revised accordingly. The TM Marcaine (b) (4)

The statement in the HOW SUPPLIED section of the package insert regarding the use of autoclaved solutions (b) (4)

A thorough discussion of the subject of autoclaving instructions for these solutions with Drs. Mann and Scally resulted in the decision to put information of this nature (statement on autoclaving privileges, considerations concerning solution discoloration resulting from autoclave temperatures) in the (b) (4) section. As it is now, the insert contains words about autoclaving and (b) (4) discoloration (b) (4) in (b) (4) HOW SUPPLIED sections.

Other comments relating to the general requirements on content and format of human prescription drug labeling as found in 21CFR 201.57:

1. The DOSAGE AND ADMINISTRATION section should contain the statement on parenteral drug product particulate matter and discoloration as specified in 201.57(j).
2. The quantitative ingredient information (b) (4)

Establishment Inspections

Response from HFD-322 dated 11/17/81 indicates the Sterling Drug facilities at Rensselaer, NY and McPherson, Kansas are operating within the scope of CGMP regulations and requirements. The memorandum from HFD-322 dated 11/13/81 provides this assurance insofar as (b) (4) is concerned.

Draft of Chemist's Part, Letter to Applicant

The following comments apply to recommended revisions in the package insert:

1. It may be advisable to [REDACTED] (b)(4) the information concerning the [REDACTED] of Marcaine Spinal solutions, and the use of discolored solutions [REDACTED] (b)(4), to the DOSAGE AND ADMINISTRATION section. Statements on this subject in the 10/81 and 1/82 draft insert revisions are found in [REDACTED] (b)(4) [REDACTED] [REDACTED]
2. The DOSAGE AND ADMINISTRATION section should contain the statement on parenteral drug product particulate matter and discoloration as set forth in 201.57(j).

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 018692/S-000

PHARMACOLOGY REVIEW(S)

Review and Evaluation of Pharmacology and Toxicology Data

Resubmission of February 7, 1983

APPLICANT: Sterling Drug Inc., New York, NY 10016

DRUG: Marcain Spinal (bupivacaine HCl 0.75% with dextrose 8.25% Injection).

CATEGORY: Local Anesthetic.

TYPE OF SUBMISSION/DATE:

Resubmission of February 7, 1983.

EVALUATION:

The Resubmission is satisfactory from standpoint of pharmacology except under "Pregnancy Category C".

In order to achieve the uniformity in all package inserts, computation of human dosage has been based on a 50-kg subject. Thus the first sentence should (b)(4) read: Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine hydrochloride was administered (b)(4)

[Redacted]

(The computation was based on the (b)(4)

[Redacted]

ACTION INDICATED:

Communicate the deficiencies to Applicant.

Pharmacology portion of letter to Applicant:

In order to achieve uniformity in all package inserts, computation of human dosage has been based on a 50 kg subject. Thus under "Pregnancy Category C", the first sentence should (b)(4) read as follows:

Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine hydrochloride was administered

(b)(4)
[Redacted]

MAY 19 1983

NDA 18-692
Page 2

DISTRIBUTION:

Regular.

Dou Huey Jean, Ph.D.
Pharmacologist

cc: NDA 18-692
HFN 160
HFN 220
Doc Room 160
R/D D.H. Jean, 5/17/83
R/D Initialed by J.K. Inscce, 5/18/83
FT-jb, W1853P, D0056P

Applicant: Sterling Drug Inc.
New York, NY 10016

Date of Review: March 5, 1982

Date of Submission: October 13, 1981

Addendum to Review and Evaluation of Pharmacology and
Toxicology Data of December 18, 1981

MCJ
3-4-82

Drug: Marcaine Spinal (bupivacaine HCl 0.75% with dextrose 8.25% Injection).

Category: Amide type local anesthetic

Proposed clinical indication: a sterile hyperbaric solution for spinal anesthesia.

Comment and evaluation:

Two reports of Segment II reproduction studies were included in this application. They are subcutaneous administration of Win 11,318 to pregnant (b)(4) white rabbits, dated October 29, 1969 and subcutaneous administration of Win 11, 318 to pregnant (b)(4) rats, dated November 10, 1969. No teratogenic potential was evident, yet embryocidal effect was seen in rabbits at 25 mg/kg. In rat Segment III reproduction study which was not included in this application, increased maternal deaths and decreased pup survival rate were observed at 45 mg/kg, indicating adverse effects on late fetal development and/or lactating behavior. Although the apparent adverse effects may be secondary to the pharmacological effects of the drug on the dams, bupivacaine HCl should be classified as Pregnancy category C. It should be noted that the formulation (hyperbaric solution), the route of administration, and hence the dosage of this application are different from those used in the reproduction studies.

Conclusion and
Recommendation:

"Pregnancy" under Precaution in the Package Insert should be (b)(4) Pregnancy category C to indicate the embryocidal effect observed in rabbits and decreased pup survival rate and increased maternal deaths in rats.

Pharmacology portion of letter to Applicant:

Under "Pregnancy" in the Precaution section of the Package Insert, Pregnancy category [REDACTED] ^{(b) (4)} C to indicate the embryocidal effect observed in rabbits, decreased pup survival rate and increased maternal deaths in rats during organogenesis period and perinatal and postnatal period, respectively.

*Don Huey Jean
pharmacologist*

NDA 18-692
HFD-160, HFD-180
R/D DHJean HFD-160 3/5/82
R/D Init JKInscoc 3/4/82
doc room 160

MAR 09 1982

NDA 18-692

Review # 1

Applicant: Sterling Drug Inc.
New York, NY 10016

Date of Review: Dec. 18, 1981

Date of Submission: October 13, 1981

Review and Evaluation of Pharmacology and Toxicology Data

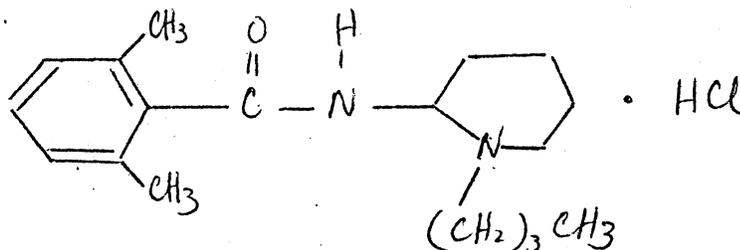
Original Submission of Oct 13, 1981

Original Summary

Drug: Marcain Spinal (bupivacaine HCl 0.75% with dextrose 8.25% injection).

Bupivacaine HCl

1-butyl-2,6-pipecoloxylidide hydrochloride



Formulation :

bupivacaine hydrochloride (anhydrous basis)	7.5 mg
dextrose, anhydrous	82.5 mg
water for injection qs ad	1.0 ml

pH is adjusted between 3.5 and 6.5 with NaOH or HCl. The specific gravity ranges between 1.030 and 1.035 (25°C/25°C).

Category: amide type local anesthetic

Proposed clinical indication: a sterile hyperbaric solution for spinal anesthesia.

Related IND's/NDA's/MF's: related to lidocaine hydrochloride.

IND 4,254: bupivacaine hydrochloride or Marcaine Injection, submitted on September 22, 1967

IND 6,043: Marcaine (bupivacaine hydrochloride) Spinal Injection, submitted on August 14, 1969.

NDA 16-964: Marcaine (bupivacaine hydrochloride) Injection, submitted on August 28, 1970.

11/18/81
12-18-81

DMF 2869 for McPherson, Kansas, revised September 30, 1981.

Preclinical studies and testing laboratories:

No new preclinical studies were submitted in this NDA. Preclinical studies that demonstrated the safety and efficacy for the proposed indication were submitted in the aforementioned related IND's and NDA's.

Container: see review by Chemist.

Package inserts: satisfactory from pharmacology standpoint.

Summary and evaluation:

Bupivacaine hydrochloride is 1-butyl-2,6-pipecoloxylidide hydrochloride, an amide type local anesthetic chemically related to lidocaine. Bupivacaine stabilizes the neuronal membrane and prevents initiation and transmission of nerve impulses, thereby effecting local anesthetic action. The onset of anesthesia following spinal anesthesia is very rapid (within 1 min) and maximal block is achieved within 15 min. Duration is 2 to 3 hours. Following injection of bupivacaine for caudal, epidural or peripheral nerve block in man, peak levels of bupivacaine in the blood are reached in 30 to 45 min, followed by a decline to insignificant levels during the next 3 to 6 hours. It is detoxified via conjugation with glucuronic acid in the liver. When administered in recommended doses and concentrations, bupivacaine does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

The application is for Sterile Hyperbaric Solution for Spinal Anesthesia which contains, in addition to 0.75% bupivacaine hydrochloride, 8.25% dextrose. The efficacy and safety for the proposed indication have been demonstrated in preclinical studies submitted previously in IND 4,254, IND 6,043 and NDA 16-964.

Segment II of reproduction studies were completed in rabbit and rat in 1969 following subcutaneous administration. No teratogenic potential was observed up to the highest dosages tested, i.e., 25 mg/kg in rabbit and 45 mg/kg in rat.

Carcinogenicity study has not been carried out and is not considered a requirement for the approvability of this drug which has been marketed since 1972.

Package inserts are satisfactory from pharmacology standpoint.

In summary, the application is recommended for approvable from pharmacology standpoint.

Conclusion and recommendation:

The efficacy and relative safety of the application have been demonstrated in preclinical studies. The application is recommended for approvable from pharmacology standpoint.

Pharmacology portion of letter to Applicant:

None.

*Douglas Jean
pharmacologist*

NDA 18-692
HFD-160, HFD-180
R/D DHJean HFD-160 12/18/81
R/D Init JKInscoc 12/18/81
doc room160

DEC 24 1981

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 018692/S-000

OTHER REVIEW(S)

NDA 18-692

Date Completed: 10 April 1984

REVIEW AND EVALUATION OF LABELING

Sponsor: Sterling Drugs
NYC

Name of Product: Marcaine Spinal

SUMMARY:

The 9 March 1984 Memorandum from The Acting Deputy Director, HFN-160, asks that some information about obstetrical complications of epidural use of bupivacaine be incorporated into the package insert and Summary Basis of Approval for Marcaine Spinal. On or about 16 March 1984 I read virtually the entire contents of that Memorandum over the telephone to E. J. Hiross, Drug Regulatory Affairs, Sterling Drugs, in order to facilitate this matter. On or about 2 April 1984, I received a draft copy from Sterling Drugs, courtesy of O. Wendell Welch, Regulatory Affairs. To that draft, I have appended my own version of needed changes. The rest of the pages of my review consists of that draft. The NDA can be approved when this draft is converted to final printed labeling.

David L. Scally David L. Scally, M.D.

for Dickstein 4/10/84

OK 4/25/84

Attachment: Draft revised package insert.

cc: NDA 18-692

HFN-160

FT: DLScally 4/10/84

Init by PHRussell 4/25/84, HLDickstein 4/10/84

Doc. Rm.

6 Page(s) of Draft Labeling has been
Withheld in Full as b4 (CCI/TS)
immediately following this page

MAY 02 1984

5/20/82

Bupivacaine HCL 0.75%
with dextrose 8.25% injection
(Marcoine Spinal)
NDA 18-692
Reviewer: Henry Malinowski

Sterling Drug Inc.
90 Park Avenue
New York, NY
Submission Dated:
November 5, 1981

REVIEW OF REQUEST FOR WAIVER OF IN VIVO BIOAVAILABILITY

Background

Marcoine Spinal is a hyperbaric formulation of bupivacaine HCL intended for subarachnoid anesthesia. Bupivacaine HCL has been in use for epidural, peripheral, nerve, caudal, infiltration and sympathetic blocks since 1973. This NDA is for a new intended use, subarachnoid anesthesia.

The firm, in this submission, is requesting a waiver of the in vivo bioavailability requirement.

Comment

1. In vivo bioavailability testing is not required for injectable local anesthetic solutions.

Recommendation:

The Division of Biopharmaceutics has received a request for a waiver of an in vivo bioavailability study (Submission dated 11/5/81 Volume 1 of 1). We agree that this drug product does not require in vivo bioavailability testing and therefore grant the waiver. This recommendation should be forwarded to the firm.

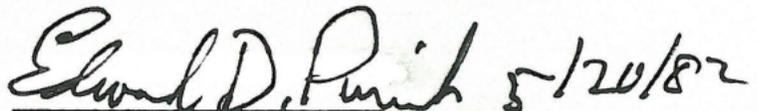


Bernard E. Cabana
Director, Division of Biopharmaceutics

Prepared by: Malinowski/jlp/4/13/82 (0604e)
/slt/4/20/82 (0604e)

cc: NDA ORIG., HFD-160, HFD-525 (Malinowski), HFD-525 (Skelly), Review, Drug, and Chron File.

RD initialed by Ed Purich, Ph.D.
FT initialed by Ed Purich, Ph.D.



MAY 21 1982

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 018692/S-000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

NOTICE OF APPROVAL NEW DRUG APPLICATION OR SUPPLEMENT		NDA NUMBER NDA 18-692
		DATE APPROVAL LETTER ISSUED
TO: HFN-616 HFV-20 Press Relations Staff (HFV-40) XXXXXXXXXXXXXXXXXXXXXXXX	FROM: <input checked="" type="checkbox"/> Bureau of Drugs <input type="checkbox"/> Bureau of Veterinary Medicine	
ATTENTION Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.		
TYPE OF APPLICATION <input checked="" type="checkbox"/> ORIGINAL NDA <input type="checkbox"/> SUPPLEMENT TO NDA <input type="checkbox"/> ABBREVIATED ORIGINAL NDA <input type="checkbox"/> SUPPLEMENT TO ANDA		CATEGORY <input checked="" type="checkbox"/> HUMAN <input type="checkbox"/> VETERINARY
TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG Marcaine Spinal		
DOSAGE FORM injectable		HOW DISPENSED <input checked="" type="checkbox"/> RX <input type="checkbox"/> OTC
ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.) bupivacaine hydrochloride 0.75%		
NAME OF APPLICANT (Include City and State) Sterling Drug Inc. 90 Park Avenue New York, NY 10016		
PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY local anesthetic		
COMPLETE FOR VETERINARY ONLY		
ANIMAL SPECIES FOR WHICH APPROVED		
COMPLETE FOR SUPPLEMENT ONLY		
CHANGE APPROVED TO PROVIDE FOR <div style="display: flex; justify-content: space-between;"> <div style="color: red; font-size: 1.2em;">(HFV-168)</div> <div style="color: red; font-size: 1.2em; transform: rotate(-15deg);">JUN 28 1984</div> </div>		
NAME James P. Hannan James P. Hannan, R.Ph.		FORM PREPARED BY DATE 3 May 1984
NAME Charles P. Hoiberg, Ph.D.		FORM APPROVED BY DATE May 3, 1984

NDA 10-092

Sterling Drug, Inc.
90 Park Avenue
New York, NY 10016

Attention: Edward J. Kross, Ph.D.

Gentlemen:

Please refer to your approved new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for bupivacaine Spinal (bupivacaine hydrochloride 0.75% with dextrose 8.25% injection).

We acknowledge receipt of your final printed labeling (FPL) dated June 13, 1984.

We have reviewed this final printed labeling and have found it acceptable. You are now permitted to distribute this drug.

Sincerely yours,

Patricia H. Russell, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc: NYK-DO (IFR-2100)

NDA 10-092

HFN-160

~~HFN-83~~

Doc. Room 160

R/D: JPHannan 6/22/84

R/D init by PGWalters for PHRussell 6/25/84, CPHoiberg 6/25/84,

JKInscoc 6/25/84, GBoyer 6/25/84

FT td W0390Y 6/26/84

CORRESPONDENCE

JUN 27 1984

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
National Center for Drugs and Biologics

Date : March 9, 1984

From : Acting Deputy Director (Medical)
Office of Drug Research and Review/HFN-101

Subject: Marcaine Spinal (bupivacaine HCl 0.75%), NDA 12-692

To : Acting Director
Division of Surgical/Dental Drug Products/HFN-160

The FPL for this drug was submitted before the agency and three manufacturers took actions because of maternal deaths from the 0.75% concentrations of bupivacaine. The Dear Doctor letter (August, undated) warned specifically against use of this concentration in obstetrical anesthesia, and did not limit the warning to any particular route.

Dr. Scally has explained to me that the dose delivered in spinal anesthesia is much lower than from epidural, paracervical block or intravenous regional anesthesia. He believes it very unlikely that the maternal deaths associated with 0.75% bupivacaine from these routes would occur with this concentration in spinal anesthesia. His logic seems sound, but nonetheless the labeling and the SBA for spinal bupivacaine 0.75% should not ignore the problems which have occurred with this concentration. Both the [REDACTED] (b) (4)

[REDACTED] We now have new information which should be discussed--the maternal deaths and the animal studies.

Please revise both the SBA and the FPL accordingly. I do not have copies of the revised labelings for bupivacaine 0.75% for already marketed products for the older routes. (When the package comes back here, please attach copies of these revised labelings.) Perhaps they can provide some appropriate language and be supplemented with discussion of why the spinal route is okay for this concentration in obstetrical anesthesia.

I recognize that we prefer not to ask a sponsor to revise FPL. If this product had already been marketed at the time of the Dear Doctor letter, its

Labeling would have required revision along with labeling of the other products.

Paula Botstein, M.D.

cc:

NDA 18-692

✓ HFN-160/CSO

HFN-160/Dr. Scally

HFN-100/Dr. Temple

Protstein/nkg/3/9/84/2542a

Date of Meeting: 29 March 1983

MEMORANDUM OF MEETING

Name of Product: MARCAINE (bupivacaine hydrochloride 0.75% with dextrose 8.25%) Spinal

Between: Lester Reich, M.D. and Karen Putterman, M.D. of the Medical Staff Breon & John G. D'Angelo, R. Ph., Compliance Supervisor, Drug Regulatory Affairs, Sterling Drugs

and:

James P. Mann, M.D., Patricia H. Russell, M.D. & David L. Scally, M.D. of HFN-160

Discussion centered around the submissions which I summarized and made recommendations on in my review dated 25 March 1983:

1. The support for use of Marcaine Spinal in Obstetrics, as written by Breon Laboratories in consultation with Gerard W. Ostheiner, M.D., Brigham and Women's Hospital, is judged clinically acceptable by this Division (Drs. Mann, Russell & Scally). In this regard, Dr. Mann recommended that I do a brief summary of some of the references cited in this document. Dr. Reich agreed to make copies available to facilitate such a review.

2. My review of the package insert (page 3 of review dated 25 March 1983) was next discussed. Drs. Reich and Putterman accepted all of my recommendations for change except one. It seems that their analysis of data as to duration of the 12 mg dose of bupivacaine spinal with and without epinephrine was performed differently than in the publication of Dr. Moore. Their criteria for duration was time to return of complete sensation in the operative site or regression of two dermatomes; Dr. Moore's criteria was duration of satisfactory analgesia prior to supplementation. They prefer to include their own analysis of data in the package insert: duration of sensory block averaged (b)(4) when epinephrine was employed and (b)(4) when epinephrine was not employed. The following change is to appear in the package insert: (b)(4)

This change was accepted by the clinical staff of HFN-160.

The meeting was concluded in the usual manner and the staff of Sterling and Breon was thanked for offering to provide the references cited above.

David L. Scally David Lawrence Scally, M.D. Medical Officer---HFN-160 01/20/15/83

NDA 18-692

HFN-160

R/D DLScally 3/29/83

R/D Init. by PHRussell 6/15/83

Doc. Room 160

JUN 20 1983

NDA 18-692

MAR 17 1983

Sterling Drug Inc
Attn: Edward J. Hiross, Ph.D
90 Park Avenue
New York, NY 10016

Gentlemen:

We acknowledge receipt of your resubmitted application for the following:

Name of Drug: Mercaine ^R Spinal (bupivacaine HCl 0.75% w/Dextrose 8.25%
Inj.)

NDA Number: 18-692

Date of resubmitted application February 7, 1983

Date of Receipt: February 15, 1983

All communications concerning this NDA should be addressed as follows:

National Center for Drugs and Biologics HFN 160
Attention: DOCUMENT CONTROL ROOM #18B-03
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

APPEARS THIS WAY ON
ORIGINAL

James P. Mann, MD
Director
Division of Surgical-Dental
Drug Products
Office of New Drug Evaluation
National Center for Drugs and Biologics

NDA 18-692

HFN-160

R/D: JLake 2/24/83

R/D init. by: CLedet 2/24/83, JPMann 2/24/83

Doc Room

FT Margarita 3/15/83 W0113M W2

RESUBMITTED APPLICATION ACKNOWLEDGEMENT

JUN 25 1982

David Lawrence Scally, M.D., Medical Officer-HFD-160

Pending NDA 18-692, MARCAINE Spinal, received 20 October 1981.
Memorandum regarding same from the Acting Director for New Drug
Evaluation, dated 23 June 1982.

Chalon Rodriguez, M.D., Group Leader-HFD-160 and James Mann, M.D.,
Director of Surgical-Dental Drug Products-HFD-160

SUMMARY:

The first time that I learned that this application and my recommendations were not as uncontroversial as I had thought was on or about 1 June 1982, when I was summoned to the office of James M. Bilstad, M.D., Assistant to the Acting Director for New Drug Evaluation. He had discovered many ways to shorten the prescribing information and still say the same thing. He also wanted the organization of the ADVERSE REACTIONS section of the prescribing information changed. I recognize some of these changes from the Memorandum dated 23 June 1982 and the related attachment and I note new issues raised in that Memorandum.

I would first like to offer some general background about how the recommendations contained in my review dated 19 February 1982 were written. I took the draft of the soon to be printed Class Labeling for Local Anesthetics and re-did it as appropriate for a formulation specifically intended for intrathecal injection (the Class Labeling was tailor made for local infiltration, peripheral nerve block and epidural anesthesia and contained much information which does not come into play during the administration of spinal anesthesia). I may have done so hastily, because back last February I considered this to be a simple application worthy of quick approval from a clinical point of view; I was also fully aware of the clinical talents at Sterling Drug Company and anticipated additional discussion after they received the approvable letter.

Considerable work, spread over around 5 years, went into the Class Labeling for Local Anesthetics. First, several drafts were prepared by a consulting firm and each was gone over by me, Staff Pharmacologist and Staff Chemist; Dr. P.H. Russell joined me in commenting on the later editions. Editorial comments were sought from a member of our Anesthetic and Life Support Drugs Advisory Committee with extensive editorial experience (Edmond S. Munson, M.D., Prof. of Anes., Univ. of Florida, Editor of ANESTHESIOLOGY and Past Editor of ANESTHESIA & ANALGESIA). Later I had good reason to present adverse experiences to the advisory committee and many were concerned with mismanagement of dose related toxicity and underventilation from whatever cause, despite apparently satisfactory prescribing information. The entire committee had a shot at retouching the writing on preparation, early recognition and management of adverse reactions. It was hoped that some practitioners would read this document and realize the error of their ways, either making the necessary corrections in their institution and practice or abandoning use of local anesthetics.

Page 1A

I will now go over the points in the Memorandum dated 23 June 1982 and reply, hoping thus to see an "approvable" letter. In so doing, I feel under intense time pressure because this application is 249 days old today.

1. The first comment has to do with the fact that a Biopharm Review was not available when this package was sent to HFD-100 and what we should do about that fact.

Reply: Having obtained a 30 day time extension on this application, in the hope of fulfilling approval requirements, we none the less felt obliged to forward this application to HFD-100 on or about 11 May 1982, at the age of 203 days. A Biopharm review, dated 20 and 21 May 1982 in various places, was later received. This review, signed by Bernard E. Cabana and Edward D. Purch, recommended granting waiver of an in vivo bioavailability study. This makes it unanimous (see below), and thus I recommend no commitment from the sponsor for the approvable letter.

The question is asked: "Do we need a completed Biopharm review for a drug like this?"

It is my opinion that a Biopharm review is counterproductive for a drug like this. Pharmacological effect (spinal anesthesia) can take place with only trace plasma levels being noted. Remember that the dose is only about one-tenth that needed for epidural anesthesia and that injection is intended into a space of slow systemic absorption.

2. The 23 June 1982 Memorandum objects to the duration of motor blockade contained in the potential package insert.

Reply: All duration figures are approximate, subject to patient and practitioner variation and method of evaluation.

The best study was conducted by Daniel C. Moore, M.D., Mason Clinic, Seattle, and an internationally known authority on clinical application of nerve block. His test of recovery was pretty thorough (time until the patient could run the heel of one foot accurately up the skin covering the anterior surface of the tibia of the other leg from ankle to knee without the heel wavering, with both legs). I have now gone over the tables in his publication (see page 284 of Volume 1.1, NDA 18-692). The mean duration of motor blockade in lower extremities following administration of 12 mg Marcaine Spinal was 202 minutes or 3.3666 hours; when epinephrine 0.2 mg was added to 12 mg Marcaine Spinal, the mean duration of motor blockade was 279 minutes or 4.65 hours. The range was such that I feel rounding off is indicated.

Change (CLINICAL PHARMACOLOGY): [REDACTED] is added."

(b) (4)

To: [REDACTED]

(b) (4)

3. The 23 June 1982 Memorandum questions circulatory CONTRAINDICATIONS to Spinal Anesthesia.

Reply: This was derived from the sponsor's PRECAUTIONS. The problem is unique to the acute onset of sympathetic tone relaxation secondary to properly administered spinal anesthesia. In the face of adequate blood volume and adequate interstitial fluid, drops in blood pressure to an intolerable level rarely occur and are easily managed with intravenous fluids and vasopressors, such as ephedrine, when they do occur. Patients with coronary artery disease should ordinarily be able to compensate, if only at the price of increasing heart rate; this is a matter of clinical judgement and spinal anesthesia may be indicated after weighing the risks versus the potential benefits.

Anesthesia for transurethral resection of the prostate is a perfect example: 1. Spinal anesthesia is generally preferred because it is easier to diagnose perforation of the bladder and water intoxication (the signs of water intoxication are bradycardia and hypertension, which can be masked by general anesthetic drugs and adjuvants). 2. Candidates for transurethral resection of the prostate frequently have coronary artery disease, symptomatic. 3. The level of anesthesia required for such a procedure is relatively low and will usually be associated with less circulatory changes than usual for that reason. Some clinicians may also find patients with valve disease who could still benefit from sympathetic relaxation or who, for other reasons, might better tolerate spinal anesthesia than general anesthesia for some surgery.

There is less room for individual judgement in the case of complete heart block. These patients are unable to compensate for peripheral sympathetic tone relaxation by increasing their heart rate. Larger doses would bring the effect of local anesthetics on ventricular conduction into play, possibly resulting ventricular escape and a ventricular pacemaker. In addition, the use of vasopressors to manage hypotension would pose unusual risk of ventricular arrhythmias both from elevation of blood pressure, if excessive, and increased myocardial irritability. This CONTRAINDICATION originated in the prescribing information regarding lidocaine for cardiac arrhythmias and, now hard to trace, has found its way into other local anesthetic package inserts. I recommend retaining the CONTRAINDICATION regarding complete heart block for these reasons.

The decision as to whether or not to use spinal anesthesia in patients with poor cardiac output secondary to coronary artery disease, valvular disease and arrhythmias must generally be made after weighing the potential benefits in a particular situation against the potential risk. In the interest of preserving individual judgement, where there is room for such judgement, I recommend no new addition(s) to the CONTRAINDICATIONS section of the potential package insert.

4. An objection is raised to listing known hypersensitivity to amide-type local anesthetics in the CONTRAINDICATIONS section of the package insert.

Reply: We placed this in the Class Labeling on the basis of current knowledge. The fact is that we simply have insufficient data to support use of one amide-type local anesthetic in a patient known to manifest allergy to another drug in this group and it would appear wise to refrain from such practice. Cross sensitivity has been reported (P.W. Shields, Australian Dental Journal 17: 51-53, 1972). Part of the problem is that allergic reactions to amide-type local anesthetics are rare, in comparison to allergic reactions to ester-type local anesthetics. I would recommend retaining this CONTRAINDICATION unless additional data is reviewed which supports removing it. This has been the past stand of most sponsors and our own staff, a fact well known to practitioners of medicine and law.

5. The Acting Director for New Drug Evaluation wishes us to consider changing the first WARNING.

Reply: This first WARNING comes from the review of many improperly managed adverse experiences and it was prepared in the hope that some practitioners unprepared to diagnose and manage complications, or unequipped for the same, might realize their limitations and refrain from such practice. Now that this is public knowledge, from Advisory Committee Meetings, and now that the Advisory Committee has taken active part in this particular WARNING, I feel that a change in this wording is unwise. I recommend that the wording remain as it is.

6. On page 2 of the "approvable" letter, change "...expiration..." to "...aspiration..." (eleventh line of typing from the top of the page).

7. This comment raises questions about impaired cardiovascular function, from the bottom of page two of the "approvable" letter as final typed (revised and retyped) on 7 May 1982.

This discussion about hepatic and cardiovascular disease is derived from experience with lidocaine for the treatment of cardiac arrhythmias and has to do with the rate of infusion in such cases versus the rate of infusion in patients with arrhythmias who have normal cardiac output and are free of liver disease. Older wording would have said to use with caution in patients with hepatic disease and patients with cardiovascular disease. I simply felt that a few sentences of clarification were indicated. The last sentence was intended to place this in proper perspective because of the lower dosages employed for spinal anesthesia.

8. The wording about drug interactions is questioned.

Reply: It is true that the usual adverse experience from combined tricyclic antidepressant therapy and use of vasopressors is severe hypertension (A.J. Boakes, et. al. Brit. Med. J1. 1: 311-315, 1973). Such is not the case with phenothiazines. Administration of catecholamines in patients under the influence of phenothiazines may be followed by a paradoxical reaction of hypotension unless the infusion rate is greatly advanced. I therefore feel that this general discussion is best left unchanged.

The question is also raised as to the source of the PRECAUTION concerning concurrent use of vasopressors and ergot-type oxytocics.

Reply: See G.M. Casady, D.C. Moore and L.D. Bridenbaugh, "Postpartum Hypertension After Use of Vasoconstrictor and Oxytocic Drugs", J.A.M.A. 172: 1011-1016, 5 March 1960. This reference has been accepted as Reference No. 57 for the Class Labeling for Local Anesthetics. The older package inserts mention oxytocics and we now want to clarify that we are talking about ergot-type oxytocics, an important change.

9. A request is made to add complete heart block to the ADVERSE REACTIONS section.

Reply: The consideration in CONTRAINDICATIONS was with regard to administration of local anesthetics to patients unable to compensate for the relaxation of sympathetic tone. Dose related toxicity is related to myocardial depression and decreased cardiac output, as well as ventricular arrhythmias which may arise as a result of prolongation of the ventricular myocardium relative refractory period. I guess that heart block could be added to the list, but it would seem to be an intermediary event. Add "...heart block..." between "...bradycardia..." and "...ventricular arrhythmias..." on the top of page 5. I would avoid using the term "complete heart block" because all degrees of heart block are possible.

10. Allergic reactions to other formulation ingredients are questioned by the Associate Director for New Drug Evaluation.

- Reply:
1. Screening has to do with intracutaneous testing.
 2. After discussion with Dr. Mann (Division Director), it was decided to leave out reference to "...[REDACTED] ^{(b)(4)}..."
 3. Cross sensitivity has been reported (see reply #4) and most experts advocate proceeding as if there is enhanced risk under such circumstances.
 4. Much of the allergic discussion is now well known to both the medical and legal profession, from package inserts in circulation and advisory committee discussion, and I recommend that it be retained except for the deletion cited above.

11. This comment has to do with a request to rewrite the ADVERSE REACTIONS section of the potential "approvable" letter. I will now re-write all of the discussion, except for the discussion of "Allergy", covered above. The Federal Register of 26 June 1979 specifies the following: "In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate." I have chosen "...a combination of these, as appropriate.", nevertheless, this discussion will differ from the potential approvable letter final typed on 7 May 1982.

(For letter)

Adverse Reactions:

Change this section to read:

The most commonly encountered acute adverse experiences which demand immediate countermeasures following the administration of spinal anesthesia are hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia.

(b) (4)

Respiratory System: Respiratory paralysis or underventilation may be noted as a result of upward extension of the level of spinal anesthesia and may lead to secondary hypoxic [REDACTED] ^{(b) (4)}. Preanesthetic medication, intraoperative analgesics and sedatives, as well as surgical manipulation, may contribute to underventilation. This will usually be noted within minutes of the injection of spinal anesthetic solution, but because of differing surgical manipulation it may occur at any time during surgery or the immediate recovery period.

Cardiovascular System: Hypotension due to loss of sympathetic tone is a commonly encountered extension of the clinical pharmacology of spinal anesthesia. This is more commonly observed in patients with shrunken blood volume, shrunken interstitial fluid volume, cephalad spread of the local anesthetic and/or mechanical obstruction of venous return. Nausea and vomiting is frequently associated with hypotensive episodes following the administration of spinal anesthesia. High doses, or inadvertent intravascular injection, may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, bradycardia, heart block, ventricular arrhythmias and possibly cardiac arrest.

Central Nervous System: Respiratory paralysis or underventilation secondary to cephalad spread of the level of spinal anesthesia (see Respiratory System discussion above) and hypotension for the same reason (see Cardiovascular System (b) (4)) are the two most commonly encountered central nervous system related adverse observations which demand immediate countermeasures.

High doses, or inadvertent intravascular injection, may lead to high plasma levels and related central nervous system toxicity characterized by excitement and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest.

(b) (4)

12. A comment is made that the first and second paragraphs on page 6 are self evident and the question is asked about whether or not they can be deleted. This has to do with management of adverse reactions: 1. The first paragraph in question has to do with the consequences of delaying treatment of adverse reactions and the fact that recovery from dose related toxicity has been reported after prolonged resuscitative efforts. 2. The second paragraph in question has to do with the fact that endotracheal intubation may be indicated during resuscitation if difficulty is encountered in the maintenance of a patent airway, etc.

Reply: These are hard learned lessons from evaluation of many adverse experience reports concerned with death or irreversible brain damage. I suggest maintaining these paragraphs. For instance: Looking at cold sheets of paper, it is easy to say that administration of oxygen by mask under pressure will usually suffice. I have talked to people who have managed local anesthetic convulsions and they warn that it is difficult to tell whether or not you are getting enough oxygen delivered to the right place because of all of the skeletal muscle activity associated with convulsions. Thus clinician-authorities advocate that endotracheal intubation may be required; they only differ on some finer points of when and how.

CONCLUSION AND RECOMMENDATION:

I have either replied or made changes in the potential package insert, or both, in response to each of the 12 questions and/or comments contained in the Memorandum dated 23 June 1982 from the Acting Director for New Drug Evaluation. This reply contains additional text which may now be used to prepare a new potential "approvable" letter for MARCAINE Spinal. I have examined the other changes made by hand in the attachment (copy of letter as final typed on 7 May 1982) to the Memorandum dated 23 June 1982 and feel that these additional changes in the package insert can be made with out los of needed prescribing information. I trust that MARCAINE Spinal will now receive quick approval.

David L. Scally, M.D.
Medical Officer, HFD-160

Pre-NDA 18-692

HFD-160

R/D DLScally 6/25/82

R/D init. by CRodriguez 6/28/82, JPMann 6/28/82

FT AK W0043K 6/30/82

DocRm 160

JUL 07 1982

MEMORANDUM Regarding Pending NDA 18-692, Under Review

Sponsor: BREON (Div. Sterling Drugs)
NYC

Name of Product: Marcaine (bupivacaine HCl 0.75% with dextrose 8.25% injection) Spinal

SUMMARY:

This Memorandum is in response to the 29 April 1982 Memo Record (Form FD 2034) from Dr. Charles Kumkumian of the Office of New Drug Evaluation to Dr. J. Mann of HFD-160 regarding the above cited product, application near completion of evaluation. Dr. Kumkumian notes that in the package insert, under HOW SUPPLIED, a statement is made that the (b)(4) in this product may show some (b)(4) discoloration (b)(4) and that it may be used if slightly discolored as long as it is free of particulate matter. He asks whether or not there is any concern about slightly colored solutions being used in spinal injections (his second question). In addition, he asks (first question) whether or not a statement should be made about how many times the product can be autoclaved. These are not exact quotes, but from the remainder of the text it will be obvious that all of these questions have been taken care of.

By way of background, it is probable that ideas of this type came from the currently approved package insert for Xylocaine for Spinal Anesthesia (lidocaine with dextrose---ASTRA). In addition, BREON markets Pontocaine (tetracaine) for spinal anesthesia, a pre 1938 drug not subject to NDA requirements; several formulations contain dextrose and discoloration is discussed in the package insert. In neither case are the words exactly the same as this application under consideration. In addition, see page 3 of the letter to the sponsor (NDA 18-692) dated 18 DEC 1981; this letter was obviously prepared before Dr. Kumkumian's inquiry or it would have been worded differently.

Encouraged by Dr. Kumkumian's note, I sought permission to contact the sponsor from my Acting Group Leader, and that permission was granted. I called Dr. Edward J. Hiross of Regulatory Affairs on or about 30 April 1982 and explained the problem; we needed a disposition of the above matter in order to complete our evaluation of this pending NDA and would like to expedite matters. He noted that he would make inquiries and that he would have Dr. (b)(4), Chemistry Staff, call me later that day. In addition, arrangements were made to discuss the problem with Dr. Karen Putterman, Medical Director of BREON, while she was here for an Advisory Committee Meeting on Anesthetic Drugs (3 May 1982); that date was especially important because Dr. Daniel Moore, main U.S.A. investigator of Marcaine Spinal (see my review dated 19 FEB 1982) would also be present.

Dr. (b)(4) called me later on or about 30 April 1982. It was from him that I obtained the above cited information concerning pre-1938 formulations of Pontocaine with dextrose; he read from the currently circulated package insert of that product concerning caramelization. He planned to check his own stability data regarding autoclaving; at that time it was his impression that dextrose does not caramelize in the currently employed, more precise, autoclaving systems and that directions to the contrary are from another era. The possibility of recommending that autoclaving be performed only once was discussed and it was understood that he would consider such a request. I then noted that my end of the inquiry was mainly clinical and

that additional stability information would be referred to the Chemistry Reviewing Staff, if necessary. Additional action was deferred in anticipation of discussion with Dr. Putterman, et. al.

On 3 MAY 1982 I met with Drs. Karen Putterman and Lester Reich of BREON and Dr. Daniel C. Moore, Consultant to BREON and Senior Anesthesiologist at the Mason Clinic and Virginia Mason Hospital, Seattle (an authority on clinical application of nerve blocks). In answer to inquiries, Dr. Moore noted that in his own 400 plus cases concerned with Marcaine Spinal he always checked the autoclaved solution for appearance; none of the solutions were caramelized, otherwise discolored, and none contained particulate matter; if the situation had been otherwise, the ampul would not have been used by him and would have been discarded. I recommended to Drs. Putterman and Reich that, once they are back at the office, they inquire into the possibility of re-writing the HOW SUPPLIED (and also DESCRIPTION) sections of the package insert to recommend autoclaving only once and to discourage use of solutions which are discolored or which contain particulate matter, at least at the time of initial approval. Such an inquiry was assured and a return phone call was expected in about 24 hours.

Dr. Putterman called again after I had left for home on 4 May 1982 and I returned her call between 0900-1000 hrs, on 5 MAY 1982. She cited the 18 DEC 1982 letter by way of background; I noted that that letter issued before the Senior Chemist of the Office of New Drug Evaluation asked questions which I was unable to answer and before anyone else had expressed concern about the matter, including me. She noted that stability data, employing currently accepted autoclaving equipment and directions, revealed no caramelization, other discoloration or particulate matter after autoclaving. We arrived at the following changes in the HOW SUPPLIED section of the potential package insert:

Change the second paragraph (ii) [redacted] (b) (4)

[redacted] so that it reads:

[redacted] (b) (4) may be autoclaved once at 15-pound pressure at 121 degrees C (250 degrees F) for 15 minutes. (b) (4)

The related sentence in DESCRIPTION will be deleted in deference to the above change in HOW SUPPLIED

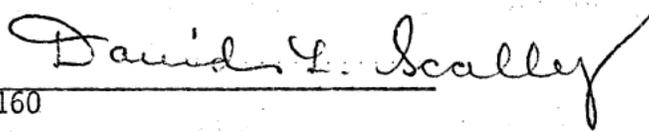
[redacted] (b) (4)
[redacted] (b) (4)

I thanked Dr. Putterman for furnishing this additional information, needed in order to assist us in completing our evaluation of this pending NDA. I noted that additional changes, such as more liberal autoclaving directions, could be reviewed by our staff after approval, should any interest be expressed in such changes; no such interest is anticipated at this time.

CONCLUSIONS AND RECOMMENDATIONS:

1. The directions for autoclaving which are the subject of Dr. Kumkumian's inquiry of 29 April 1982 can be traced back to the pre-1938 era through the package insert for Pontocaine (tetracaine hydrochloride) with Dextrose for Spinal Anesthesia, a "grandfathered" product. Current autoclaving practices do not result in caramelization, other discoloration or the formation of particulate matter. Directions can (b)(4) recommend autoclaving only once and to recommend that solutions which are discolored or which contain particulate matter should not be used clinically. The sponsor has agreed (b)(4) (see page two of this memorandum).
2. Revise the approvable letter to reflect these changes, then this application is once again approvable under SEC. 505 (b) (6) of the Federal Food, Drug and Cosmetic Act.

David L. Scally, M.D.
 Medical Officer---HFD-160



ADDENDUM: 6 MAY 1982.

This document, and the Memorandum cited above, were also referred to the Supervisory Chemist (C. Sinopoli) and he conferred by phone with the Reviewing Chemist (S. Koch), who is on leave. It was noted that the new directions will have to be rearranged to conform with 201.57 (j) of the Code of Federal Regulations (21). Under that regulation, the Dosage and Administration of the package insert should note that parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration (see also page 5 of the latest approvable letter, which must now be revised). It would therefore seem reasonable to add the following to the approvable letter:

section

In addition, we note that changes in (b)(4), regarding how often this product may be (b)(4) and changes regarding discoloration or particulate matter as related to clinical usage were agreed to during a 5 May 1982 telephone conversation between Dr. Karen Putterman of your firm and Dr. David L. Scally of the Division of Surgical-Dental Drug Products. Please note that that the text below has been slightly altered since that conversation to conform to 21 CFR 201.57 (j):

DESCRIPTION:

The sentence regarding (b)(4) will be changed to read: (b)(4)

DOSAGE AND ADMINISTRATION:

End the DOSAGE AND ADMINISTRATION section with the following statement: "MARCAINER Spinal should be inspected visually for discoloration and particulate matter..."

APPEARS THIS WAY ON ORIGINAL

solutions which are discolored or which contain particulate matter should not be administered."

HOW SUPPLIED:

The second paragraph of this section ((b)(4)) will be changed to read:
(b)(4) may be autoclaved once at 15-pound pressure at 121 degrees C (250 degrees F) for 15 minutes. Do not administer (b)(4) which (b)(4) discolored or (b)(4) particulate matter."

(In addition, page 6 of the latest draft of an approvable letter should be changed to delete: "The DOSAGE AND ADMINISTRATION section should contain the statement on parenteral drug products particulate matter and discoloration as set forth in 201.57 (j)."
This matter has now been taken care of more specifically as it is applicable to MARCAINER Spinal.)

David L. Scally, M.D.
Medical Officer---HFD-160
6 May 1982.

David L. Scally

DLK 5/6/82

JM 5/6/82

JUL 07 1982

NDA 18-692

Sterling Drug, Inc.
Attention: Edward J. Hiross, Ph.D.
90 Park Avenue
New York, NY 10016

APR 23 1982

Gentlemen:

Please refer to your New Drug Application dated October 31, 1981 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Marcaine Spinal Injection.

As authorized by section 505(c) of the Act and as agreed to by your representative C. R. Tamarria, Ph.D. in discussing the application with Gary H. Boyer of this Division, on April 14 and 15, 1982, the time allowed for consideration of this application has been extended 30 days.

Sincerely yours,

James P. Mann, M.D.
Director
Division of Surgical-Dental
Drug Products
Bureau of Drugs

NDA 18-692
BUF-DO (HFR-2200)
HFD-160

R/D JSinger HFD-160 4/15/82
R/D Init GBoyer 4/15/82; JPMann 4/15/82
doc room 160
fianl typed mw 4/21/82
WANG 1059P

NDA 18-692

Food and Drug Administration
Rockville MD 20857

Sterling Drug, Inc.
Attention: Edward J. Hiross, Ph.D.
90 Park Avenue
New York, NY 10016

NOV 02 1981

Dr. Hiross:

We are pleased to acknowledge your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug: Marcaine^R Spinal (bupivacaine hydrochloride 0.75%
with dextrose 8.25% injection)

Date of Application: October 13, 1981

Date of Receipt: October 20, 1981

Our Reference Number: NDA 18-692

We will correspond with you further after we have had the opportunity to study the application. Should you have any questions prior to our contacting you please call:

Mr. John Singer
Consumer Safety Officer
301/443-3560

All future communications concerning this NDA should be addressed as follows:

Bureau of Drugs HFD-160
Attention: DOCUMENT CONTROL ROOM #18B03
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

James P. Mann, M.D.
Director
Division of Surgical-Dental
Drug Products
Bureau of Drugs

Food and Drug Administration
Rockville MD 20857

ACKNOWLEDGEMENT

NYK-DO (HFR-2200)

NDA 18-692

HFD-160

R/D M Wilson (HFD-160) 10/26/81

Init by: G Boyer 10/29/81; J M Singer 10/29/81 and J P Mann 10/29/81

F/T sm 10/30/81 (W0641P)

doc. rm 160

10/30/81