PRODUCT MONOGRAPH

[Pr]BUPIVACAINE HYDROCHLORIDE INJECTION, USP
(Bupivacaine Hydrochloride)

2.5 mg/mL, 5 mg/mL and 7.5 mg/mL

Local Anesthetic

Hospira Healthcare Corporation
5400 Cote-de-Liesse
Town of Mount Royal (QC), CANADA
H4P 1A5

DATE OF PREPARATION:
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Control # 090308

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THERAPEUTIC CLASSIFICATION

Local Anesthetic

ACTION AND CLINICAL PHARMACOLOGY

Bupivacaine stabilizes the neuronal membrane and prevents both the generation and the conduction of nerve impulses, thereby exerting a local anesthetic action.

The onset of action is rapid, and anesthesia is long lasting. The advantage of bupivacaine over other local anesthetics is in the prolonged duration of effective anesthesia. It is to be noted however, that the duration of action of a local anesthetic is dependent on a number of factors including site of injection, route of administration, concentration and volume. 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.

Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems. At blood concentrations achieved with 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 to cardiac arrest. 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 with bupivacaine than other local anesthetics.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression or both. Apparent central stimulation is usually 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 centres. 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, concentration of drug administered and the route of administration.

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 minutes, followed by a decline to insignificant levels during the next 3 to 6 hours.

The plasma elimination half-life of bupivacaine in adults is 2.7 hours (range 1.2 to 4.6 hours). In infants the half-life ranges from 6 to 22 hours, thus it is significantly longer than in adults. Half-life is also prolonged in the elderly.

Local anesthetics are bound to plasma proteins in varying degrees. The highly lipophilic agents, such as bupivacaine, are far more highly protein-bound than the more hydrophilic compounds. Bupivacaine is approximately 95% protein-bound in normal adults. If plasma protein concentration are decreased, more of the free drug will be available to exert activity.

Because of its amide structure, bupivacaine is metabolized primarily in the liver. The major metabolite of bupivacaine is pipecoloxylidine, a dealkylated derivative. Patients with hepatic disease may be more susceptible to the potential toxicities of the amide-type local anesthetics. The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by renal perfusion and factors affecting urinary pH. Only 5% of bupivacaine is excreted unchanged in the urine.

Local anesthetics appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by the degree of plasma protein binding, the degree of ionization, and 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.
Bupivacaine, with a high protein binding capacity (95%), has a low fetal/maternal ratio (0.2 to 0.4).

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

INDICATIONS

BUPIVACAINE HYDROCHLORIDE INJECTION is indicated for the production of local or regional anesthesia and analgesia in infiltration procedures, peripheral nerve blocks, retrobulbar block, caudal and epidural blocks.

Isotonic solutions of bupivacaine are not recommended for subarachnoid (spinal) blocks.*

CONTRAINDICATIONS

BUPIVACAINE HYDROCHLORIDE INJECTION is contraindicated in persons with known hypersensitivity to local anesthetics of the amide type, or other components of bupivacaine solutions.

Bupivacaine is contraindicated in severe shock and in heart block and when there is inflammation and/or sepsis near the proposed injection site.

Bupivacaine is contraindicated for intravenous regional anesthesia (Bier Block). Reports of cardiac arrest and death have occurred with the use of bupivacaine for intravenous regional anesthesia (Bier block).

Spinal Use*: With the exception of certain serious diseases of the central nervous system or of the lumbar vertebral column, most anesthesiologists consider the following conditions to be only **relative contraindications** to spinal anesthesia. The decision as to whether or not spinal anesthesia should be used for an individual case depends on the physician's appraisal of the advantages as opposed to the risks and on his/her ability to cope with the complications that may arise.

- Disease of the cerebrospinal system, such as meningitis, spinal fluid block, cranial or spinal hemorrhage, increased intracranial pressure, tumors and syphilis.

Note:** ***Bupivacaine Spinal (0.75% Hyperbaric Solution in 5% Dextrose Injection) is currently not available.

- Shock. This should be treated before any anesthetic is administered. However, in emergency operations, spinal anesthesia may at times be considered the method of choice.

- Profound anemia, cachexia and when death is imminent.

- Sepsis with positive blood cultures.

- High Blood Pressure. Spinal anesthesia should be well tolerated if particular care is taken to prevent a sudden or appreciable fall in blood pressure.

- Low Blood Pressure. The use of suitable pressor agents and methods of controlling the diffusion of the anesthetic should remove the principal objection to spinal anesthesia in patients with low blood pressure.

- Highly nervous and sensitive persons. Preoperative medication should overcome this difficulty.

- Visceral perforation, bowel strangulation, acute peritonitis. Some surgeons object to contraction of the gastrointestinal musculature; others, however, consider, the associated arrest of peristalsis an advantage. With gastrointestinal hemorrhage, spinal anesthesia should be used with caution or may even be contraindicated.

- Cardiac decompensation, massive pleural effusion, and increased intraabdominal pressure (e.g. full-term pregnancy, massive ascites, large tumor). High spinal anesthesia should not be used in patients with these conditions unless the Trendelenburg position can be omitted or the intraabdominal pressure released slowly.

WARNINGS

RESUSCITATIVE EQUIPMENT, OXYGEN AND DRUGS SHOULD BE IMMEDIATELY AVAILABLE WHENEVER ANY LOCAL ANESTHETIC DRUG IS USED.

THE HIGHEST (0.75%) CONCENTRATION OF ISOTONIC BUPIVACAINE (BUPIVACAINE HYDROCHLORIDE) INJECTION IS NOT RECOMMENDED FOR OBSTETRICAL ANESTHESIA. THERE HAVE BEEN REPORTS OF CARDIAC ARREST WITH DIFFICULT RESUSCITATION OR DEATH FOLLOWING ITS USE FOR EPIDURAL ANESTHESIA IN OBSTETRICAL PATIENTS. RESUSCITATION HAS BEEN DIFFICULT OR IMPOSSIBLE DESPITE APPARENTLY ADEQUATE PREPARATION AND APPROPRIATE MANAGEMENT. CARDIAC ARREST HAS OCCURRED AFTER CONVULSIONS RESULTING FROM SYSTEMIC TOXICITY, PROBABLY FOLLOWING UNINTENTIONAL INTRAVASCULAR INJECTION.

Bupivacaine should not be used in obstetrical paracervical block anesthesia. Its use in this technique has resulted in fetal bradycardia and death.

It is essential that aspiration for blood or cerebrospinal fluid be done prior to injecting any local anesthetic, both the original dose and all subsequent doses, to avoid intravascular or subarachnoid injection. During the performance of spinal anesthesia, a free flow of cerebrospinal fluid 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.

Mixing or the prior or intercurrent use of any other local anesthetic with bupivacaine is not recommended because of insufficient data regarding the interaction and safety of such mixtures.

Prior use of chloroprocaine may interfere with subsequent use of bupivacaine. Because of this, and because safety of intercurrent use of bupivacaine and chloroprocaine has not been established, such use is not recommended.

PRECAUTIONS

General: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen and resuscitative drugs should be available for immediate use. During major nerve blocks, the patient should have a functioning I.V. line in place, providing ready access to the circulation, for the administration of emergency drugs should an adverse reaction occur.

The lowest dosage that gives effective anesthesia should be used, to avoid high plasma levels and serious systemic side effects. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should be used when feasible.

The following precautions apply to all local anesthetics: Select needles of proper length and bevel for the technique employed. Inject slowly with frequent aspirations and if blood is aspirated, relocate the needle. Inadvertent intravascular injection may cause serious complications. Absorption is more rapid when injections are made into highly vascular tissues. In caudal or epidural anesthesia, abandon the method if the subarachnoid space has been entered, as shown by aspiration of spinal fluid. However, a negative aspiration is not 100% reliable.

Injection of repeated doses of bupivacaine may cause a significant increase in blood levels due to accumulation of the drug or its metabolites or slow metabolic degradation. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly and acutely ill patients may require reduced doses commensurate with age and physical condition. Local anesthetics should also be used with caution in patients with hypotension or heart block.

The decision to use a local anesthetic containing a vasoconstrictor in patients with peripheral vascular disease, will depend on the physician's appraisal of the relative advantages and risks.

Dose-related cardiac arrhythmias may occur if preparations containing epinephrine are employed in patients during or immediately following the administration of halothane, cyclopropane, trichloroethylene or other related 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.

Because amide-type local anesthetics, such as bupivacaine, are metabolized in the liver, these drugs should be used cautiously in patients with hepatic disease. 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.

Epidural Use: It is recommended that a test dose be administered initially and the effects monitored before the full dose is given. However, the optimal formulation and the usefulness of the test dose in obstetrics are being debated. Generally 2-3 mL of 0.50% bupivacaine containing 1:200,000 epinephrine **should be administered to check that the spinal canal or a blood vessel has not been entered while locating epidural needle or catheter.

In the event of spinal injection, clinical signs of spinal block would become evident in a few minutes. In the event of intravascular injection, a transient increase in pulse rate and/or systolic blood pressure is usually detectable with a monitor. The other symptoms and signs of "epinephrine responses" are less dependable. Concomitantly administered medications may modify these responses.

When reinforcing doses are required, the test dose should be used again to check the catheter location. However an intravascular or subarachnoid injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal or epinephrine-induced cardiovascular effects.

***Note: Bupivacaine with epinephrine solutions are currently not available.**

Use in head and Neck Area: Relatively small doses of local anesthetics injected into the head and neck area, including retrobulbar, and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. They may also be due to puncture of the dural sheath of the optic nerve during retrobulbar block with diffusion of any local anesthetic along the subdural space to the midbrain. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available.

Use in Ophthalmic Surgery: Clinicians who perform retrobulbar blocks should be aware that there have been reports of respiratory arrest following local anesthetic injection. Prior to retrobulbar block, as with all other regional procedures, the immediate availability of equipment, drugs and personnel to manage respiratory arrest or depression, convulsions, and cardiac stimulation or depression should be assured. As with other anesthetic procedures, patients should be constantly monitored following ophthalmic blocks for signs of these adverse reactions, which may occur following relatively low total doses.

A concentration of 0.75% bupivacaine is indicated for retrobulbar block; however, this concentration is not indicated for any other peripheral nerve block, including the facial nerve, and not indicated for local infiltration, including the conjunctiva.

When bupivacaine 0.75% is used for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Therefore, presence of akinesia rather than anesthesia alone should determine readiness of the patient for surgery.

Use in Pregnancy: 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, respectively, to nine and five times the maximal recommended daily human dose (400 mg).

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.

Use in labor and delivery: The highest (0.75%) isotonic concentration is not recommended for obstetrical anesthesia (see WARNINGS). This, however does not exclude the use of isotonic Bupivacaine 0.25% or 0.50% at term for obstetrical anesthesia or analgesia.

Bupivacaine is contraindicated for obstetrical paracervical block anesthesia (see WARNINGS). Local anesthetics rapidly cross the placenta and when used for epidural, caudal or pudendal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity. However, the fetal/maternal ratio for bupivacaine is relatively low (see Pharmacokinetics).

Nursing Mothers: Bupivacaine has been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from bupivacaine, a decision should be made whether to discontinue nursing or not administer bupivacaine, taking into account the importance of the drug to the mother.

Pediatric Use: The 0.25% and 0.5% solutions of bupivacaine are recommended in children **older** than 2 years. For the appropriate concentration and dosage see DOSAGE AND ADMINISTRATION section.

Until further experience is gained, the following restrictions apply to the use of bupivacaine: (a) isotonic bupivacaine solutions are not recommended for spinal use; (b) the 0.75% isotonic solution of bupivacaine is not recommended in patients younger than 12 years.

Drug Interactions: The administration of local anesthetic solutions containing epineprhine or norepinephrine 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. Administration of H_2 blockers prior to epidural anesthesia is inadvisable since toxic levels of local anesthetic may result.

ADVERSE REACTIONS

Reactions to bupivacaine are characteristic of those associated with amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intramuscular injection, or slow metabolic degradation.

The most commonly encountered adverse reactions which demand immediate countermeasures involve the central nervous system and the cardiovascular system. The adverse reactions are usually dose-related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance or from unintentional intravascular injection. In addition to systemic dose-related toxicity, unintentional subarachnoid injection of drug during the intended performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially within the head and neck region) may result in underventilation or apnea ("Total or High Spinal"). Also, hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia may occur. This may lead to secondary cardiac arrest if untreated. Factors influencing plasma protein binding, e.g., diseases which alter protein synthesis or competition of other drugs for protein binding, may diminish individual tolerance.

Central nervous system effects are characterized by excitation or depression. The first manifestation may be anxiety, nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constricting of the pupils, or tinnitus.

Cardiovascular manifestations of excessive plasma levels may include blood pressure changes (usually hypotension), depression of the myocardium, decreased cardiac output, heart block, bradycardia, ventricular arrhythmias including ventricular tachycardia and ventricular

fibrillation and cardiac arrest.
Neurologic reactions following epidural or caudal anesthesia may include: high or total spinal block; urinary retention; fecal and urinary incontinence, loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, and paralysis of the lower extremities and loss of sphincter control all of which may have slow, incomplete recovery; headache and backache; septic meningitis; meningismus; slowing of labour and increased incidence of forceps delivery; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.

It should be noted that reactions due to systemic absorption may be slow or rapid in onset. Those of rapid onset include respiratory depression, cardiovascular collapse and cardiac arrest. This type of reaction necessitates a high degree of preparedness since it can occur with little warning.

In some subjects, bupivacaine may produce marked peripheral vasoconstriction in unanesthetized areas which may last for several hours.

In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter or needle may occur. Subsequent adverse effects may depend partially upon the amount of drug administered intrathecally, and the physiological and physical effects of a dural puncture.

Allergic reactions are rare and may occur as a result of sensitivity to local anesthetics of the amide-type. These reactions are characterized by signs such as urticaria, pruritis, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid symptomatology (including respiratory depression, cardiovascular collapse and cardiac arrest). Cross sensitivity among members of the amide-type local anesthetic group has been reported.

SPINAL USE:*

THE MOST COMMONLY ENCOUNTERED ADVERSE REACTIONS WHICH DEMAND IMMEDIATE COUNTERMEASURES 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, one or several of the following complications or side effects may be observed during or after spinal anesthesia.

Meningitis. With the employment of an aseptic technique, septic meningitis should be practically nonexistent. Some instances of aseptic meningitis, with fever, neck rigidity, and cloudy spinal fluid, have been reported with the use of other spinal anesthetics. In such cases, the course is usually brief and benign, terminating in complete recovery.

However, in a few, permanent paralysis (sometimes terminating fatally) and sensory disturbances have been observed. This type of meningitis has also been observed in rare instances following ordinary diagnostic lumbar puncture.

Note:** **Bupivacaine Spinal (0.75% Hyperbaric Solution in 5% Dextrose Injection) is currently not available.

Palsies. These are rare and affect either the extraocular muscles or the legs and the anal and vesical sphincters (cauda equina syndrome). Paralysis of extraocular muscles usually clears up spontaneously by the third or fourth week. Cauda equina and lumbosacral cord complications (usually consisting of arachnoiditis and demyelinization) result in loss or impairment of motor and sensory function of the saddle area (bladder, rectum) and one or both legs.

The complications have occurred after the use of most, if not all, spinal anesthetics. The loss or impairment of motor function may be permanent or partial recovery may slowly occur.

Various explanations for such complications have been advanced, such as hypersensitivity or intolerance to the anesthetic agent with a resultant myelolytic or neurotoxic effect; pooling of relatively high concentrations of anesthetic solution around the cauda equina and spinal cord before diffusion; and accidental injection of irritating antiseptics or detergents (as when syringes and needles are incompletely cleansed or when ampoule storage solution enters a cracked ampoule). Hence, most anesthesiologists prefer to autoclave ampoules in order to destroy bacteria on the exterior before opening.

Headache. This may largely be prevented by using a small gauge needle to prevent spinal fluid leakage and by placing the patient in the supine position after operation and providing adequate hydration.

Nausea and vomiting. These may be due to a drop in blood pressure, undue intra-abdominal manipulation or pre-operative medication.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution.

Management of Local Anesthetic Emergencies: The first consideration in the management of the emergencies 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.

THE FIRST STEP IN THE MANAGEMENT OF SYSTEMIC TOXIC REACTIONS, AS WELL AS UNDERVENTILATION OR APNEA, CONSISTS OF THE IMMEDIATE ESTABLISHMENT AND MAINTENANCE OF A PATENT AIRWAY AND 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.

Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (such as epinephrine or ephedrine which enhance myocardial contractility).

If necessary, use drugs to control convulsions. A bolus i.v. injection of succinylcholine will paralyze the patient without depressing the central nervous or cardiovascular systems and facilitate ventilation. A bolus i.v. dose of diazepam or thiopental will permit ventilation and counteract central nervous system stimulation, but these drugs also depress central nervous system, respiratory, and cardiac function, add to possible depression, and may result in apnea.

Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. For specific techniques and procedures, refer to standard textbooks.

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 cardiac arrest should occur, successful outcome may require prolonged resuscitative efforts.

DOSAGE AND ADMINISTRATION

ISOTONIC SOLUTIONS ARE NOT FOR SPINAL ANESTHESIA. BUPIVACAINE SPINAL (0.75% HYPERBARIC SOLUTION IN 5% DEXTROSE INJECTION) IS CURRENTLY NOT AVAILABLE.

As with all local anesthetics, the dosage of bupivacaine varies and depends upon 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, individual tolerance, the technique of anesthesia and the physical condition of the patient. The lowest dosage and concentration needed to provide effective anesthesia should be administered. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional doses should be used when feasible.

In recommended doses, bupivacaine produces complete sensory block, but the effect on motor function differs between the three concentrations.

0.25% when used for caudal, epidural, or peripheral nerve block, produces incomplete motor block. Should be used for operations in which muscle relaxation is not important, or when another means of providing muscle relaxation is used concurrently. Onset of action may be slower than with the 0.5 or 0.75% solutions.

0.50% provides motor blockade for caudal, epidural, or nerve block, but muscle relaxation may be inadequate for operations in which complete muscle relaxation is essential.

0.75% produces complete motor block. This concentration is recommended only for epidural block (single dose) in abdominal operations requiring complete muscle relaxation without the aid of other medication, and for retrobular anesthesia. It is not recommended for epidural block in obstetrical patients.

The duration of anesthesia with bupivacaine is such that, for most procedures, a single dose is sufficient. Maximum dosage limit must be individualized in each case after evaluating the size and physical status of the patient, as well as the usual rate of systemic absorption from a particular injection site.

Most experience to date is with single doses of bupivacaine up to 175 mg without epinephrine; more or less drug may be used depending on individualization of each case. The maximum doses of bupivacaine are considered to apply to a healthy, 70 kilogram, young male; however, it is not recommended that they be exceeded in heavier persons.

At present there is insufficient clinical evidence with multiple dosage or intermittent dose techniques to permit precise recommendations for such procedures to be given. However, limited clinical experience in this area of use indicates that bupivacaine may be repeated in 3 to 6 hours; total daily doses have been up to 400 mg. The duration of anesthetic effect may be prolonged by the addition of a vasoconstricting substance, e.g. epinephrine.

The 0.75% concentration of isotonic bupivacaine is not recommended for obstetrical anesthesia or analgesia (see WARNINGS). The 0.5% and 0.25% concentrations of isotonic bupivacaine are recommended at term for obstetrical anesthesia and analgesia.

Table 1 is presented as a guide to the use of bupivacaine in adults. The doses shown have generally proved satisfactory for the average patient. They may require reduction in relation to age and the physical condition of the patient.

Note: Unused portions of solution in single dose vials must be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered.

Table 1
RECOMMENDED CONCENTRATIONS AND DOSAGE FOR ADULTS

Type of Block	Concentration	Each Dose		Motor Block [1]
		mL	mg	
Local Infiltration	0.25%	up to max.	up to max.	-
Epidural[3]	0.75%[2]	10 - 20	75 - 150	Complete
	0.50%	10 - 20	50 - 100	Moderate to Complete
	0.25%	10 - 20	25 - 50	Partial to Moderate
Epidural[3] Test dose**	0.50% w/epi.	2 - 3	10 - 15 (10 - 15 µg epinephrine)	-
Caudal	0.50%	15 - 30	75 - 150	Moderate to Complete
	0.25%	15 - 30	37.5 - 75	Moderate
Peripheral Nerves	0.50%	5 - 30	25 - 150	Moderate to Complete
	0.25%	5 - 60	12.5 - 150	Moderate to Complete
Retrobulbar	0.75%	2 - 4	15 - 30	Complete
Sympathetic	0.25%	20 - 50	50 - 125	-

(1) With continuous (intermittent) techniques in caudal and epidural block, using 0.25 and 0.50% solutions, repeat doses increase the degree of motor block. For intermittent epidural anesthesia use maximum increments of 3-5 mL of 0.50% bupivacaine with sufficient time between doses to detect any toxic effects. The first dose of 0.50% may produce complete motor block. In most intercostal nerve blocks for intra-abdominal surgery, the 0.25% concentration has produced satisfactory motor blockade.

(2) For single dose use: Not for intermittent technique. Not for obstetrical anesthesia.

(3) Use of an appropriate test dose is recommended prior to injecting the full epidural dose (see PRECAUTIONS).

***Note: Bupivacaine with epinephrine solutions are currently not available.**

PEDIATRIC DOSAGE

Until further experience is gained, the following restrictions apply to the use of bupivacaine: (a) isotonic bupivacaine solutions are not recommended for spinal use; (b) the 0.75% isotonic solution of bupivacaine is not recommended in patients younger than 12 years.

The 0.25% and 0.5% solutions of bupivacaine are recommended in children **older** than 2 years. For the appropriate suggested concentrations and dosage see Table 2.

Table 2
RECOMMENDED CONCENTRATION AND DOSAGE FOR CHILDREN

Type of Block	Concentration	mL/kg	mg/kg
Caudal	0.25% 0.5%	0.4 - 0.8 0.2 - 0.4	1 - 2 1 - 2
Lumbar/Epidural	0.25% 0.5%	0.6 - 1.0 0.3 - 0.5	1.5 - 2.5 1.5 - 2.5
Penile	0.25% 0.5%	0.1 - 0.2 0.06 - 0.1	0.3 - 0.5 0.3 - 0.5
Intercostal**	0.25% (with epinephrine) 0.5% (with epinephrine)	0.8 - 1.2 0.4 - 0.6	2 - 3 2 - 3
Local infiltration for hernia repair	0.25% 0.5%	0.2 - 0.8 0.1 - 0.4	0.5 - 2 0.5 - 2

N.B.: These bupivacaine concentrations and doses are recommended for anesthesia and/or analgesia, with the understanding that such use may be supplementary to light general anesthesia.

*****Note: Bupivacaine with epinephrine solutions are currently not available.***

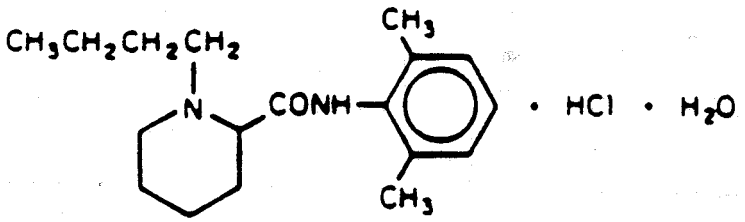
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Bupivacaine Hydrochloride, USP

Chemical Name: 2-piperidenecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate

Structural formula:



Molecular formula: $C_{18}H_{28}N_20.HCl.H_20$

Molecular weight: 342.91

Description:

Bupivacaine is chemically and pharmacologically related to the amino-acyl local anesthetics. It is a white, crystalline powder that is freely soluble in 95% ethanol, soluble in water, and slightly soluble in chloroform or acetone. The pKa of bupivacaine hydrochloride is 8.1.

Composition:

BUPIVACAINE HYDROCHLORIDE INJECTION, USP is available in sterile, isotonic solutions containing bupivacaine hydrochloride anhydrous (2.5, 5.0 or 7.5 mg/mL) in Water for Injection, sodium chloride added to adjust tonicity. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment.

Stability and Storage Recommendation:

Store at controlled room temperature (15°-30°C). Protect from freezing.

AVAILABILITY OF DOSAGE FORMS

ISOTONIC SOLUTIONS ARE NOT FOR SPINAL ANESTHESIA. BUPIVACAINE SPINAL (0.75% HYPERBARIC SOLUTION IN 5% DEXTROSE INJECTION) IS CURRENTLY NOT AVAILABLE.

BUPIVACAINE HYDROCHLORIDE INJECTION, USP is supplied in the following presentations:

0.25% - Contains 2.5 mg bupivacaine hydrochloride anhydrous per mL.
- Single-dose vials of 10 and 20 mL, (without preservative) box of 5, List L899 (1159)

0.5% - Contains 5 mg bupivacaine hydrochloride anhydrous per mL.
- Single-dose vials of 10 and 20 mL, (without preservative) box of 5, List L900 (1162)

0.75% - Contains 7.5 mg bupivacaine hydrochloride anhydrous per mL.
- Single-dose vials of 10 mL and 20 mL, (without preservative) box of 5, List L901 (1165)

Note: Do not use if the color of solution is pinkish or darker than slightly yellow or if a precipitate is present.

PHARMACOLOGY

Bupivacaine is chemically and pharmacologically related to the amino-acyl 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.

Local anesthetics block the generation and the conduction of nerve impulses, - 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.

Metabolic studies in the rat and monkey were performed using a subcutaneous injection of H^3-

labelled bupivacaine. Radioactivity was rapidly distributed in all tissues, with maximum concentrations occurring 15 minutes or one hour after injection. Highest concentrations were seen in pancreas, lung, liver, and kidney. Within 24 hours, the monkey had excreted 80% of the dose in urine and 28% in feces. Hydroxylation is the main metabolic pathway in the rat, whereas amide hydrolysis is the principal route in the monkey.

TOXICOLOGY

Shown in Table 3 are the acute toxicity (LD_{50}) data after intravenous and subcutaneous administration in mice and rats.

Table 3
LD_{50} of bupivacaine hydrochloride

Route of Administration	Rate of Administration (mL/sec)	Species	LD_{50} (mg/kg) ± S.E.
i.v.	0.1	Mice (N = 36)	7.3 ± 1.0
i.v.	0.01	Mice (N = 20)	10.4 ± 0.5
i.v.	0.1	Rats (N = 36)	5.6 ± 0.2
s.c.	-	Mice (N = 36)	53 ± 5
s.c.	-	Mice (N = 40)	48 ± 3

The site of toxicity of local anesthetic agents is chiefly the central nervous system and the cardiovascular system. At high intravenous doses in mice, rats, and dogs, overstimulation resulted in depression and respiratory arrest. For the cardiovascular effects there was a decrease in blood pressure, and a direct depression of the myocardium affecting both conduction and contraction.

Bupivacaine produced seizures in rhesus monkey when serum levels reached the 4.5 - 5.5 μg/mL range.

No significant pathologic changes were observed following sub-lethal doses of bupivacaine in the rat, rabbit, dog and monkey, except for dose-related inflammatory reaction in the muscle tissue at the injection sites.

In vivo studies in the rat indicated that twice daily injections into the same muscle for seven days produced muscle fibrillation and atrophy. When bupivacaine administration was stopped, the muscles recovered, and within 10 days they were restored to normal conditions.

After intracutaneous administration to rabbits for sensitivity testing no immediate or delayed allergic responses were observed.

Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine was administered in doses comparable to nine and five times respectively the maximal recommended daily human dose (400 mg).

REFERENCES

1. Aberg G. Toxicological and local anaesthetic effects of optically active isomers of two local anaesthetic compounds. Acta Pharmacol Toxicol 1972; 31: 273-286.

2. Abboud TK, Chul KK, Noveihed R, Kuhnert BR. Epidural bupivacaine for cesarean section - maternal and neonatal effects. Anesth Analog. 1983;62:914-919.

3. Beazley JM, Taylor G, Reynolds F. Placental transfer of bupivacaine after paracervical block. Obstet., Gynec. 1972;39:2-6.

4. Blaise G. and Roy WL. Spinal anaesthesia for minor paediatric surgery. Can. Anesth. Soc. J. 1986; 33(2):227-230.

5. Broadman LM, Hannallah RS, Norden JM, McGill WA. "Kiddie Caudals" Experience with 1154 consecutive cases without complications. Anesth. Analg. 1987;66:S18.

6. Bromage PR. An evaluation of bupivacaine in epidural analgesia for obstetrics. Canad. Anesth. Soc. J. 1969;16:46-56.

7. Bromage PR. A comparison of bupivacaine and tetracaine in epidural analgesia for surgery. Canad. Anesth. Soc. J. 1969;16:37-45.

8. Browne RA, Catton DV. Use of bupivacaine in labour. Canad. Anesth. Soc. J. 1971;18:23-32.

9. Brown DT, Beamish D, Wildsmith JAW. Allergic reaction to an amide local anesthetic. Br J Anesth 1981;53:435-437.

10. Carolan JA, Cerasoli JR, and Houle TV. Bupivacaine in retrobulbar anesthesia. Ann. Ophthalmol. August, 1974;6:843.

11. Cartwright PD. Maternal heart rate changes with a plain epidural test dose. Anesthesiology 1986;65:226-228.

12. Corke BC, Spielman FJ. Problems associated with epidural anesthesia in obstetrics. Obstet gynecol 1985;65(6):837-839.

13. Covino BG. Pharmacology of local anesthetic agents. Ratio Drug Ther 1987;21(8):1-9.

14. Dain SL, Rolbin SH, Hew EM. The epidural test dose in obstetrics: Is it necessary?

Can. J. Anesth. 1987;34:601-605.

15. Dalens B, Tanguy A, Haberer JP. Lumbar epidural anesthesia for operative and postoperative pain relief in infants and young children. Anesth. Analg 1986; 65:1069-73.

16. Downing JW. Bupivacaine - A clinical assessment in lumbar extradural block, J. Anesth. 1969;41:427-432.

17. Fargas-Babjak A, McChesney J, Morison DH. The efficacy of bupivacaine 0.75 percent as an epidural test dose. Canada. Anesth. Soc. J. 1980;27(5):500-501.

18. Feldman HS, Arthur GR, Covino BG. Toxicity of intravenously administered local anesthetic of intravenously administered local anesthetic agents in the dog. Cardiovascular and central nervous system effects. New York: Rain Press, 1986;395-404.

19. Gills JP, Rudisill JE. Bupivacaine in cataract surgery. Ophthalmic 1974;5:67-70.

20. Gillies IDS, Morgan M. Accidental total spinal analgesia with bupivacaine anesthesia 1973;28:441-445.

21. Goehl TJ, Davenport JB, Stanley MJ. Distribution, biotransformation and excretion of bupivacaine in the rat and the monkey. Xenobiotical 1973; 3(12):761-772.

22. Hannington-Kiff JG. Treatment of intractable pain by nerve block. Lancet 1971;2:1392-1394.

23. Henn F, Brattsand R. Some pharmacological and toxicological properties of a new long-acting local analgesic, LAC-43 (Marcaine*), in comparison with mepivacaine and tetracaine. Acta Anaesthesiol Scand (Suppl.) 1966;XXI:9-30.

24. Moore DC, Bridenbaugh LD, Thompson GE, Balfour RI, Horton WG. Bupivacaine: a review of 11,080 cases. Anesth Analog 1978;57:42-53.

25. Munson ES, Tucker WK, Ausinsch B, Malagodi MH. Etidocaine, bupivacaine and lidocaine seizure thresholds in monkeys. Anesthesiology 1975;42(4):471-478.

26. Reynolds, F. Metabolism and excretion of bupivacaine in man: A comparison with mepivacaine. Br J Anesth 1971;43:33-37.

27. Sokoll MD, Sonesson B, Thesleff S. Denervation changes produced in an innervated skeletal muscle by long-continued treatment with a local anesthetic. Eur J Pharmacol 1968;4:179-187.

28. Thomas J, Climie CR, Mather LE. The maternal plasma levels and placental transfer of bupivacaine following epidural analgesia. Br J Anaesth 1969;41:1035-1040.

29. Wilkinson GR, Lund PC. Bupivacaine levels in plasma and cerebrospinal fluid following peridural administration. Anesthesiology 1970;33(5):482-486.

30. Winnie AP, LaVallée DA, Sosa BP, Masud KZ. Clinical pharmacokinetics of local anaesthethics. Can Anaesth Soc J 1977;24(2):252-262.