KAMACAINE 0.5%

Bupivacaine HCl Injection, USP

DESCRIPTION:

Bupivacaine Hydrochloride USP, is 2-piperidinecarboxamide, 1-butyl-N-(2,6 dimethylphenyl) monohydrochloride, a white crystalline powder that is freely soluble in 95% ethanol, soluble in water, and slightly soluble in chloroform or acetone.

Bupivacaine 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.

KAMACAINE 0.5% INJECTION - is available as a sterile isotonic solution containing 5 mg bupivacaine HCl in each ml.

It may contain sodium hydroxide and/or hydrochloric acid to adjust the pH to between 4.0 to 6.5.

KAMACAINE 0.5% injection is indicated for the production of peripheral nerve block, and caudal and lumbar epidural blocks. Solutions of **KAMACAINE** may be autoclaved once.

The single dose vial solution contains no bacteriostatic or antimicrobial agent. Therefore, unused portions should be discarded after use.

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. 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 arrhythmia and to 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 intravascular injection of bupivacaine. Therefore, 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 adrenaline 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 **KAMACAINE**, permitting the use of moderately larger total doses and sometimes prolonging the duration of action. The onset of action **with KAMACAINE** is rapid and anesthesia is long-lasting. The duration of anesthesia is significantly longer with **KAMACAINE** 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 duration of anesthetic effect is prolonged by the addition of epinephrine 1:200,000.

Local anesthetics are bound to plasma proteins in varying degrees. Generally, the lower the plasma concentration of drug the higher the percentage of drug bound to plasma proteins. 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

(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. Bupivacaine 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, non ionized 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 profile of bupivacaine 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 liver where it is metabolized.

After 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 three to six hours.

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 bupivacaine in adults is 2.7 hours and in neonates 8.1 hours.

Amide-type local anesthetics such as bupivacaine 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. Pipecoloxylidine is the major metabolic of bupivacaine. 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, bupivacaine does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

INDICATION AND USAGE

KAMACAINE is indicated for the production of local or regional anesthesia or analgesia for surgery, oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures. Only the 0.25% and 0.5% concentrations are indicated for obstetrical anesthesia (See **WARNINGS**). Experience with nonobstetrical surgical procedures in pregnant patients is not sufficient to recommend use of 0.75% concentration of bupivacaine in these patients.

KAMACAINE is also indicated for spinal anesthesia for surgery (e.g. lower limb surgery lasting 3-4 hours where profound muscular relaxation is desired or needed).

KAMACAINE is not recommended for intravenous regional anesthesia (Bier block). (See **WARNINGS**).

The routes of administration of **KAMACAINE**	
Peripheral nerve block	0.5%
Lumbar epidural	0.5%
Caudal	0.5%
Spinal	0.5%
Epidural test dose	0.5% with adrenaline 1:200,000

(see **DOSAGE AND ADMINISTRATION** for additional information).

Standard textbooks should be consulted to determine the accepted procedures and techniques for the administration of **KAMACAINE**.

CONTRAINDICATIONS

KAMACAINE is contraindicated in obstetrical paracervical block anesthesia. Its use by this technique has resulted in fetal bradycardia and death.

KAMACAINE is contraindicated in patients with a known hypersensitivity to it or any local anesthetic agent of the amide-type or to other components of bupivacaine solutions.

WARNINGS

Local anesthetics should 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, PRECAUTIONS and OVERDOSAGE**). 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.

It is essential that aspiration for blood or cerebrospinal fluid (where applicable) be done prior to injecting any local anesthetic, both the original dose and all subsequent doses, to avoid intravascular or subarachnoid injection. However, a negative aspiration does not insure against an intravascular or subarachnoid injection.

Until further experience is gained in children younger than 12 years, administration of **KAMACAINE** in this age group is not recommended.

Mixing or the prior or intercurrent use of any other local anesthetic with **KAMACAINE** cannot be recommended because of insufficient data on the clinical use of such mixtures. There have been reports of cardiac arrest and death during the use of Bupivacaine for intravenous regional anesthesia (Bier block). Information on safe dosages and techniques of administration of **KAMACAINE** in this procedure is lacking. Therefore, **KAMACAINE** is not recommended for use by this technique.

PRECAUTIONS

General

The safety and effectiveness of local 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, ADVERSE REACTIONS, and OVERDOSAGE**). During major regional nerve blocks, the patient should have I.V. 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 to avoid high plasma levels and serious adverse effects. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should be used when feasible.

Epidural Anesthesia: During epidural administration of **KAMACAINE**, concentrated solutions (0.5%) should be administered in incremental doses of 3 to 5 ml. with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Injections should be made slowly with frequent aspirations before and during the injection to avoid intravascular injection. Syringe aspirations should also be performed before and during each supplemental injection in continuous (intermittent) catheter techniques. An intravascular injection is still possible even if aspirations for blood are negative.

During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and the effects monitored before the full dose is given. When using a continuous catheter technique, test doses should be given prior to both the original and all reinforcing doses, because plastic tubing in the epidural space can migrate into a blood vessel or through the dura. When clinical conditions permit, the test dose should contain adrenaline (10 mcg to 15 mcg have been suggested) to serve as warning of unintended intravascular injection.

If injected into a blood vessel, this amount of epinephrine is likely to produce a transient epinephrine response within 45 seconds, consisting of an increase in heart rate and/or systolic blood pressure, circumoral pallor, palpitations and nervousness in the unsedated patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, the heart rate should be monitored for a heart rate increase. Patients on beta blockers may not manifest changes in heart rate, but blood pressure monitoring can detect a transient rise in systolic blood pressure. The test dose should also contain 10 to 15 mg of bupivacaine or equivalent amount of another local anesthetic to detect an unintended intrathecal administration. This will be evidenced within a few minutes by signs of spinal block (e.g. decreased sensation of the buttocks, paresis of the legs, or, in the sedated patient, absent knee jerk). The test dose of **Bupivacaine 0.5% and Adrenaline** (15 mg of bupivacaine and 15 mcg of epinephrine). The test dose itself may produce a systemic toxic reaction, high spinal or epinephrine-induced cardiovascular effects.

Injections of repeated doses of local anesthetics may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites or to slow metabolic degradation. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients and children should be given reduced doses commensurate with their age and physical status. Local anesthetics should also be used with caution in patients with hypotension or heart block.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and patient's state of consciousness should be performed after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, incoherent speech, light-headedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully restricted quantities in areas of the body supplied by end arteries or having otherwise compromised blood supply such as digits, nose, external ear, penis etc. Patients with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result.

Because amide-type local anesthetics, such as bupivacaine, 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 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.

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 anesthetics. 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 prompt institution of the treatment, including oxygen therapy, dantrolene (consult dantrolene sodium intravenous package insert before using), and other supportive measures.

Use in Head and Neck Area: 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. Dosage recommendations should not be exceeded. (See **DOSAGE and ADMINISTRATION**).

Spinal Anesthesia regardless of the local anesthetic used, has its own contraindications which include: active disease of the central nervous system such as meningitis, poliomyelitis, intracranial hemorrhage, subacute combined degeneration of the cord due to pernicious anemia, cerebral and spinal tumors, tuberculosis of the spine, pyrogenic infection of the skin at or adjacent to the site of lumbar puncture, cardiogenic or hypovolemic shock and coagulation disorders due to ongoing anticoagulation treatment.

Precautions: Spinal anesthesia should only be undertaken by clinicians with the necessary knowledge and experience. Resuscitative equipment and drugs should be immediately available and the anesthetist should remain in constant attendance.

Spinal anesthesia with any local anesthetic can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. These may include pre-loading the circulation with crystalloid or colloid solution. If hypotension develops it should be treated with a vasopressor such as ephedrine 10-15 mg intravenously. Severe hypotension may result from hypovolemia due to hemorrhage or dehydration, or aortocaval occlusion in patients with massive ascites, large abdominal tumors or late pregnancy. Marked hypotension should be avoided in patients with cardiac decompensation.

Patients with hypovolemia due to any cause can develop sudden and severe hypotension during spinal anesthesia.

Spinal anesthesia can cause intercostal paralysis and patients with pleural effusions may suffer respiratory embarrassment. Septicemia can increase the risk of intraspinal abscess formation in the postoperative period.

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 of depression, convulsions and cardiac stimulation or depression should be assured (See also **WARNINGS**, and **Use in Head and Neck Area** above). As with other anesthetic procedures, patients should be constantly monitored following opthalmic blocks for signs of these adverse reactions, which may occur following relatively low total doses. Mixing **KAMACAINE** with other local anesthetics is not recommended because of insufficient data on the clinical use of such mixtures.

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 caudal or epidural anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the package insert of **KAMACAINE**.

Carcinogenesis, Mutagenesis and 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 bupivacaine 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 nine and five times respectively the maximum 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. This does not exclude the use of **KAMACAINE** at term for obstetrical anesthesia or analgesia (See **Labor and Delivery**).

LABOR and DELIVERY: KAMACAINE is contraindicated in obstetrical paracervical block anesthesia.

Local anestethics rapidly cross the placenta, and when used for epidural, caudal or pudendal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity (See **Pharmacokinetics** and **CLINICAL PHARMACOLOGY**). The incidence and degree of toxicity depend upon procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

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.

Epidural, caudal or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Epidural anesthesia has 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.

It is extremely important to avoid aortocaval compression by the gravid uterus during administration 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 gravid uterus displaced to the left.

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 nursing mothers.

Pediatric Use: Until further experience is gained in children younger than 12 years of age, administration of KAMACAINE in this age group is not recommended. Continuous infusions of bupivacaine in children have been reported to result in high systemic levels of bupivacaine and seizures.

DRUG INTERACTIONS

Bupivacaine should be used with care in patients receiving anti-arrhythmic drugs with local anesthetic activity, as their toxic effects may be additive.

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

ADVERSE REACTIONS

Reactions to **KAMACAINE** are characteristic of those associated with other amino-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to over dosage, unintentional intravascular injection or slow metabolic degradation.

Spinal anesthesia itself can cause adverse reactions regardless of the local anesthetic agent used. These include hypotension and bradycardia due to sympathetic blockade and/or vasovagal fainting.

In severe cases cardiac arrest can occur.

High spinal anesthesia may result in paralysis of all respiratory muscles. Postoperatively a post lumbar headache can occur.

Neurological damage is a rare but well recognized consequence of regional and particularly spinal anesthesia. It may be due to several causes, e.g. direct injury to the spinal cord or spinal nerves, anterior spinal artery syndrome, injection of an irritant substance, or an injection of a non-sterile solution. This may result in localized areas of peresthesia or anesthesia, motor weakness, loss of sphincter control and paraplegia. Occasionally these are permanent. Neurological complications of this type have been reported after the use of all local anesthetic used for spinal anesthesia.

Systemic toxicity is rare with spinal anesthesia but might occur after accidental intravascular injection. Systemic adverse reactions are characterized by numbness of the tongue, light headedness, dizziness and tremors, followed by convulsions and cardiovascular disorders.

Treatment of side-effects: High or total spinal blockade causing respiratory paralysis should be treated by ensuring and maintaining a patent airway and giving oxygen by assisted or controlled ventilation.

Hypotension should be treated by the use of vasopressors, e.g. ephedrine 10-15 mg intravenously and repeated until the desired level at arterial pressure is reached, intravenous fluids, both electrolytes and colloids, given rapidly can also reverse hypotension.

Systemic: The most commonly encountered acute adverse experiences which demand immediate countermeasures are related to the central nervous system and the cardiovascular system. These adverse experiences such as convulsions and cardiovascular collapse, are generally 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 of the local anesthetic solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection of the drug during the intended performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in 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 binding, such as acidosis, systemic diseases which alter protein production or competition of other drugs for protein binding sites, may diminish individual tolerance.

Treatment of systemic toxicity: No treatment is required for milder symptoms of systemic toxicity but if convulsions occur then it is important to ensure adequate oxygenation and to arrest the convulsions if they last more than 15-30 seconds. Oxygen should be given by face mask and the respiration assisted or controlled if necessary. Convulsions can be arrested by injection of thiopentane 100-150 mg intravenously or with diazepam 5-10 mg intravenously. Alternatively, succinylcholine 50-100 mg intravenously may be given but only if the clinician has the ability to perform endotracheal intubation and to manage a totally paralyzed patient.

Central Nervous System Reactions: These are characterized by excitation 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. Other central nervous system effects may be nausea, vomiting, chills and constriction of pupils.

The incidence of convulsions associated with the use of local anesthetics varies with procedure used and the total dose administered. In a survey of studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1% of local anesthetic administration.

Cardiovascular System Reactions: High doses of unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias including ventricular tachycardia and ventricular fibrillation and cardiac arrest (See **WARNINGS, PRECAUTIONS** and **OVERDOSAGE**).

Allergic: Allergic type reactions are rare and may occur as a result of sensitivity to the local anesthetic or to other formulation ingredients. 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-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitely established.

Neurologic: The incidence of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetics 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 contribution from the drug.

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 on the amount of drug administered intrathecally and the physiological and physical effects of a dual puncture. A "high spinal" is characterized by paralysis of the legs, loss of consciousness, respiratory paralysis and bradycardia.

Neurologic effects following unintentional subarachnoid administration during epidural or caudal anesthesia may include spinal block of varying magnitude (including high or total spinal block); hypertension secondary to spinal block; urinary retention; fecal and urinary incontinence; loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities and loss of sphincter control, all which may have slow, incomplete or no recovery; headache, backache, septic meningitis; meningismus; slowing of labor; increased incidence of forceps delivery; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.

Neurologic effects following other procedures or routes of administration may include persistent anesthesia, paresthesia, weakness, paralysis, all of which may have slow, incomplete or no recovery.

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. (See **ADVERSE REACTIONS**, **WARNINGS** and **PRECAUTIONS**).

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 unintentional subarachnoid injection of drug solution, 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 to 100 mg 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 5 to 10 mg of diazepam or 50 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 ephedrine or epinephrine to enhance myocardial contractile force).

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 together with myocardial depression from the direct effects of the local anesthetic may lead to cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur. Underventilation or apnea due to unintentional subarachnoid injection of local anesthetic solution may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur, successful outcome may require 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 hypertension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or the 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 LD_{50} in mice is 6 to 8 mg/kg and 38 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 bupivacaine hydrochloride should be reduced for elderly and debilitated patients with cardiac and/or liver disease. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should be used when feasible.

For specific techniques and procedures refer to standard textbooks.

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

The duration of anesthesia with **KAMACAINE** is such that for most indications, 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 225 mg with epinephrine 1:200.000, and 175 mg without epinephrine; more or less drug may be used depending on individualization of each case.

These doses may be repeated up to once every three hours. In clinical studies to date, total daily doses up to 400 mg have been reported. Until further experience is gained, this dose should not be exceeded in 24 hours. The duration of anesthetic effect may be prolonged by the addition of epinephrine. The dosages in the following table (Table 1) have been generally proved satisfactory and recommended as a guide for use in the average adult. These dosages should be reduced for young, elderly or debilitated patients. Until further experience is gained, **KAMACAINE** (bupivacaine hydrochloride) is not recommended for children younger than 12 years. **KAMACAINE** is contraindicated for obstetrical paracervical block anesthesia and is not recommended for intravenous regional anesthesia (Bier block).

Use in Epidural Anesthesia: During epidural administration **KAMACAINE** should be administered in incremental doses of 3 to 5 ml with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. In obstetrics, only 0.5% and 0.25% concentrations should be used; incremental doses of 3 to 5 ml of 0.5% solution not exceeding 50 to 100 mg at any dosing interval are recommended. Repeat doses should be preceded by a test dose containing epinephrine if not contraindicated. Use only single-dose vials for caudal or epidural anesthesia; the multiple dose vials contain a preservative and therefore should not be used for these procedures.

Use in Spinal Anesthesia: The doses recommended below should be regarded as a guide for use in the average adult.

The spread of anesthesia obtained with **KAMACAINE** depends on several factors, including the volume of solution and the position of the patient during and following the injection. It should be understood that the level of spinal anesthesia achieved with any local anesthesia can be unpredictable in a given patient.

Test Dose for Caudal and Lumbar Epidural Blocks: The test dose of Bupivacaine 0.5% and Adrenaline (15 mg of bupivacaine and 15 mcg of epinephrine) is recommended for use as a test dose when clinical conditions permit prior to caudal and lumbar epidural blocks. This may serve as a warning of unintended intravascular or subarachnoid injection (see **PRECAUTIONS**). The pulse rate and other signs should be monitored carefully immediately following each test dose administration to detect possible intravascular injection, and adequate time for onset of spinal block should be allotted to detect possible intrathecal injection. An intravascular or subarachnoid injection is still possible even if results of test are negative. The test dose itself may produce a systemic toxic reaction, "high spinal" or cardiovascular effects from epinephrine (See **WARNINGS** and **OVERDOSAGE**).

Unused portions of solutions must be discarded following initial use.

This product should be inspected visually for particulate matter prior to administration. Solutions which contain particulate matter should not be administered.

Table 1:
Recommended concentrations of KAMACAINE

Type of block	Concentration	Each dose (ml.)	Each dose (mg.)	Motor block[1]
Epidural	0.5%	10-20	50-100	**Moderate to Complete**
Caudal	0.5%	15-30	75-150	**Moderate to Complete**
Peripheral nerves	0.5%	5 to max.	25 to max.	**Moderate to Complete**
Epidural Test Dose[2]	0.5% w/epi*	2-3	10-15[2] 10-15 mcg/ epi*	-
Spinal	**0.5%**	**2-4**	**10-20**	-

1) With continuous (intermittent) techniques, repeat doses increase the degree of motor block. The first repeat dose of 0.5% may produce complete motor block. Intercostal nerve block with 0.25% may also produce complete motor block for intra-abdominal surgery.
2) See **PRECAUTIONS**.
* Epinephrine

Storage and Technical Procedures:

Disinfecting agents containing heavy metals, which cause release of respective ions (mercury, zinc, copper, etc.), should not be used for skin or mucous membrane disinfection as they have been related to incidents of swelling and edema. When chemical disinfecting of the container surface is desired, either isopropyl alcohol (91%) or ethyl alcohol (70%) is recommended. Many commercially available brands of rubbing alcohol, as well as solutions of ethyl alcohol not USP grade, contain denaturants which are injurious to rubber and therefore, are not to be used. It is recommended that chemical disinfection be accompanied by wiping the vial stopper with cotton or gauze that has been moistened with the recommended alcohol just prior to use.

KAMACAINE 0.5% should be stored at room temperature below 25°C.

SUPPLIED

KAMACAINE 0.5% is supplied in glass vials containing 20 ml solution of Bupivacaine HCl 0.5% (5 mg/ml), in a box of 10 vials.

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KAMADA

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