



Wivacaine™

Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection USP (as bitartrate)

(bupivacaine hydrochloride and epinephrine injection, USP)

THIS SOLUTION IS INTENDED FOR DENTAL USE.

ACTION
WIVACAIN[™] stabilizes the neuronal membrane and prevents both the generation and the conduction of the nerve impulses, thereby exerting a local anesthetic action. The onset of action following dental injections is usually 2 to 15 minutes and anesthesia may last for up to three times longer than lidocaine or mepivacaine for dental use. In many patients lasting up to seven hours. 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 is also noted that there is a potential for toxicity which may occur after the time the need for strong analgesics is reduced.

When administered in recommended doses and concentrations, WIVACAIN[™] does not ordinarily produce irritation or tissue damage, and does not cause methemoglobinemia.

PHARMACOKINETICS
Following injection of WIVACAIN[™] for caudal epidural, or peripheral nerve block in man, peak levels of WIVACAIN[™] in the blood are reached in 30 to 45 minutes, followed by a gradual decline to insignificant levels during the next three to six hours.

The plasma elimination half-life of WIVACAIN[™] in adults is 2.7 hours (range 1.2 - 4.8 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. WIVACAIN[™] is approximately 95% protein-bound in normal adults. If plasma protein concentrations are decreased, more of the free drug will be available to exert its activity.

Because of its amide structure, WIVACAIN[™] is metabolized primarily in the liver. The major metabolite of WIVACAIN[™] is pipercolidine, a desalkylated derivative. Patients with hepatic disease may be more susceptible to the potential toxicity 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.

Local anesthetics appear to cross the placenta by diffusion. The same and degree of placental protein binding. (2) the degree of fetal solubility.

Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of placental protein binding because only the free, unbound drug is available for placental transfer. WIVACAIN[™] with a high protein binding capacity (95%) had a fetal/maternal ratio (0.2 to 0.4).

INDICATIONS

WIVACAIN[™] is indicated for nerve block in dental procedures.

CONTRAINDICATIONS

WIVACAIN[™] is contraindicated in persons with known hypersensitivity to local anesthetics of the amide type, or to other components of WIVACAIN[™] solutions, (see **AVAILABILITY**).

WIVACAIN[™] is contraindicated in persons who are in heart block and when there is information and/or signs near the site of the proposed injection.

WARNINGS

LOCAL ANESTHETICS SHOULD BE EMPLOYED ONLY 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 ADEQUATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL REQUIRED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RAPID EMERGENCIES. (See **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.**)**

Small doses of local anesthetics injected into the head and neck area, as well as into the epinephrine-containing solutions, may cause systemic toxicity. Systemic toxicity may occur with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression, and/or respiratory arrest, cardiovascular stimulation or depression and cardiac arrest have been reported. Reactions resulting in fatalities have occurred on rare occasions. In a few cases, resuscitation has been difficult or impossible despite apparently adequate preparation and appropriate management. These reactions may be avoided by the following: (1) the use of smaller injections of the local anesthetic with adequate flow to the cerebral circulation; (2) 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 **DOSEAGE AND ADMINISTRATION**).

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 injection. However, a negative aspiration does not assure an intravascular injection.

Reactions resulting in fatalities have occurred on rare occasions with the use of local anesthetics, even in the absence of a history of hypersensitivity.

This solution, which contains a vasoconstrictor, should be used with extreme caution for patients whose medical history and physical evaluation suggest the existence of hypertension, arteriosclerotic heart disease, cerebral vascular dysfunction, heart block, hypertension and diabetes, as well as patients receiving drugs likely to potentiate alterations in blood pressure.

Epinephrine-containing solutions should not be injected into tissues supplied by end arteries, for example, fingers and toes, ears, the nose and the penis.

WIVACAIN[™] or other vasoconstrictors should not be used concomitantly with ergot-type vasoconstrictors because severe persistent hypertension may occur.

WIVACAIN[™] or other vasoconstrictors should not be used in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the imipramine type because severe hypertension may occur.

Mixing of the prior or subsequent use of any other local anesthetic with WIVACAIN[™] is not recommended because of insufficient data regarding the interaction and safety of such mixtures.

WIVACAIN[™] contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in individuals than in nonasthmatic people.

PRECAUTIONS

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 IV line in place, providing ready access to the circulation, for the administration of emergency drugs should an adverse reaction occur. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should be used when feasible.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of WIVACAIN[™] may cause significant increases in blood levels with each additional dose. Due to accumulation of the drug in its metabolites, a low maintenance dosage is recommended. Tolerance varies with the status of the patient. Deliberate, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

The following precautions apply to all local anesthetics. Select needles of proper length and gauge 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.

Because of the long duration of anesthesia, WIVACAIN[™] is used for dental injections, patients should be cautioned about the possibility of inadvertent trauma to tongue, lips and buccal mucosa and advised not to chew solid foods or test the anesthetized area by biting or probing.

Changes in serum potassium, such as excitation, disorientation, drowsiness, may be early indicators of a high blood level of the drug and may occur following inadvertent intravascular administration or rapid absorption of WIVACAIN[™].

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease. Caution is advised in administration of repeat doses of WIVACAIN[™] to patients with severe liver disease.

Local anesthetic 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.

Local anesthetic procedures should be used with caution when there is inflammation and/or sepsis in the region of the proposed injection.

Drug interactions: See **WARNINGS** concerning solutions containing a vasoconstrictor.

If fatalities are employed to reduce patient apprehension, use reduced doses, since local anesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect.

WIVACAIN[™] should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

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 chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, their 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.

INDICATION FOR PATIENTS

When appropriate, the dentist should discuss information including reactions in the Product Monograph for WIVACAIN[™].

Clinical Significant Drug Interactions: The administration of local anesthetics solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypotension. Concurrent use of these agents should generally be avoided in situations where concurrent therapy is necessary, cardiac monitoring is essential.

Concomitant administration of vasoconstrictor drugs and of ergot-type vasoconstrictor drugs may cause severe, persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce the 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 and/or the effect on fertility has not been determined. There is no evidence from human data that WIVACAIN[™] may be carcinogenic or mutagenic or that it impairs fertility.

Pregnancy: Decreased pup survival in rats and an embryonic 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. This does not exclude the use of WIVACAIN[™] at term for obstetrical analgesia/epidural anesthesia.

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. Bupivacaine has been reported to be excreted in human milk suggesting that the nursing infant could be potentially exposed to the active form of the drug. Because of the potential for serious adverse reactions in nursing infants from bupivacaine, a decision should be made whether to discontinue nursing or to not administer bupivacaine, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

Reactions to WIVACAIN[™] are characteristic of those associated with other 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 intravascular injection, or slow metabolic degradation. Other causes of reactions to these local anesthetics may be hypersensitivity, idiosyncrasy, or diminished tolerance.

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. Factors influencing plasma protein binding, e.g., diseases which alter protein synthesis or competition of other drugs for protein binding, may diminish individual tolerance.

Excessive plasma levels cause systemic reactions involving the central nervous system and the cardiovascular system. The central nervous system effects are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possible respiratory arrest.

Other central nervous system effects may be nausea, vomiting, dizziness, confusion of the pupils, or irritability. The cardiovascular manifestations of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), cardiac arrest, decreased cardiac output, heart block, bradycardia, ventricular arrhythmias including ventricular tachycardia and ventricular fibrillation. Recent clinical reports and animal studies suggest that myo-inositol may be used with the long acting amide local anesthetics such as bupivacaine.

Adverse reactions are characterized by cutaneous lesions (e.g., urticaria, edema) and other manifestations of allergy. 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 coordinated studies of 30,000 procedures carried out by 15 investigators, there were 2 severe systemic reactions. Both patients experienced convulsions as a result of inadvertent vascular injection.

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

Treatment of Overdose and Severe Reactions: Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics. The first consideration in the management of the emergency 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. Toxic effects of local anesthetics require symptomatic treatment, there is no specific cure. The dentist should be prepared to maintain an airway and assist or control respiration as well as supportive treatment of the cardiovascular system including intravenous fluids and, when appropriate, vasoconstrictors (preferably those that stimulate the myocardium).

Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate or muscle relaxant, or follow-up primarily an ultra-short acting barbiturate such as thiopental or thiamylal, if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or a short-acting muscle relaxant (succinylcholine). Intravenous muscle relaxants and barbiturates should only be administered to those familiar with their use.

Recent clinical data from patients experiencing local anesthetic-induced convulsions demonstrated rapid development of hypoxia, hypercarbia and acidosis with hyperventilation with a mixture of the onset of convulsion. 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.

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

For management of a suspected drug overdose, contact your regional Poison Control Center.

DOSEAGE AND ADMINISTRATION

As with all local anesthetics, the dosage varies and depends upon the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, individual tolerance, and the technique of anesthesia. The lowest dosage needed to provide effective anesthesia should be administered. For specific techniques and procedures, refer to standard textbooks.

WIVACAIN[™] is recommended for dental nerve block in the maxillary and mandibular area when a longer duration of local anesthetic action is desired, such as for oral surgical procedures generally associated with significant postoperative pain. The average dose of 1.8 mL (0.9 mg) injection will usually suffice an occasional second dose of 1.8 mL (0.9 mg) may be used if necessary to produce adequate anesthesia for up to 15 minutes onset time. The lowest effective dose should be employed and time should be allowed between injections. It is recommended that the total dose for all injection sites, spread out over a single dental setting, should not ordinarily exceed 50 mg (1.8 mL) injection of WIVACAIN[™]. Injections should be made slowly and carefully with frequent aspirations. WIVACAIN[™] is not recommended for children under 12 years of age.

Parental drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

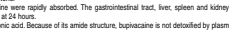
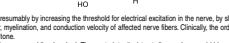
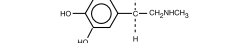
DISINFECTION OF CARTRIDGES

As in the case of any cartridge, the diaphragm should be disinfected before needle puncture. Immerse only the metal cap in undiluted isopropyl alcohol or 70% ethyl alcohol USP for at least 15 minutes. Only enough cartridges for one day's use should be stored in the alcohol.

AVAILABILITY
Each mL of solution in WIVACAIN[™] dental cartridge contains: bupivacaine hydrochloride 5.0 mg, epinephrine bitartrate 0.0091 mg, and as non medicinal ingredients sodium metabisulfite 0.5 mg; monoethyglycol 0.001mL, acetic acid 2.0 mg, etabate calcium diiodom 0.1 mg, sodium lactate and sodium chloride to make isotonic in Water for Injection. Store between 15°C and 25°C (59°F and 77°F). DO NOT PERMIT TO FREEZE. This solution should be protected from light and cannot be substituted.

PHARMACOLOGY

Bupivacaine is chemically and pharmacologically related to the amino-acyl local anesthetics with the chemical name 2-Piperidine-carboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride. It is a white, crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone, and has the following structural formula:



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.

In metabolic studies in the rat, subcutaneous doses of C¹⁴-labeled bupivacaine were rapidly absorbed. The gastrointestinal tract, liver, spleen and kidney showed relatively high concentrations. Radioactivity in adipose tissue was high immediately after drug administration but decreased rapidly and was not detected at 24 hours.

The principal route of biotransformation in the rat is by conjugation with glucuronic acid. Because of its amide structure, bupivacaine is not detoxified by plasma esterases.

TOXICOLOGY

Acute LD₅₀ determinations in the mouse and rat were as follows:

	Route of Administration	Species	Acute LD ₅₀ (mg/kg) ± S.E.
Bupivacaine HCl 0.5 %	IV	Mouse	71 ± 0.6
	IV	Rat	6.2 ± 0.5
	S.C.	Mouse	63 ± 7
Bupivacaine HCl 0.5 % and Epinephrine	IV	Mouse	6.5 ± 0.4
	IV	Rat	5.6 ± 0.4
	S.C.	Mouse	66 ± 8
Bupivacaine HCl 0.75% (Hypertonic)	S.C.	Rat	21 ± 8
	IV	Mouse	6.2 ± 0.4

At high intravenous doses in mice and rats symptoms of toxicity included CNS stimulation followed by convulsions. Central stimulation is followed by depression and death is usually due to respiratory depression. Dogs tolerated single intramuscular doses of up to 10 mg/kg, with and without epinephrine.

Bupivacaine produced seizures in rhesus monkeys when serum levels reached the 4.5-5.5 mg/L range.

No significant pathologic changes were observed following sublethal doses of bupivacaine in the rat, rabbit, dog and monkey, except for dose related inflammatory reactions in the muscle tissue at the injection sites. In inhibition studies in the rabbit, healing of the intramuscular lesions was well advanced or complete within seven days after the injection.

Uteral and other reported dose-toxicity changes in the rat following repeated intramuscular injection in the same site. They commented, however, that the conditions under which these changes occurred are not likely to be encountered in the clinical use of the drug.

No immediate or delayed adverse reactions were observed in the guinea pig after sensitivity testing. No evidence of drug-induced teratogenic effects was observed in rat and rabbit given subcutaneous injections of bupivacaine.

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

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