

Bupivacaine Hydrochloride

Introduction: Bupivacaine HCl injections are sterile isotonic solutions that contain a local anesthetic agent with and without epinephrine (as bitartrate) 1:200,000 and are administered parenterally by injection.

Mechanism of action: Local anesthetics bind selectively to the intracellular surface of sodium channels to block influx of sodium into the axon. As a result, depolarization necessary for action potential propagation and subsequent nerve function is prevented. The block at the sodium channel is reversible. When drug diffuses away from the axon, sodium channel function is restored and nerve propagation returns. Epinephrine prolongs the duration of the anesthetic actions of bupivacaine by causing vasoconstriction (alpha adrenergic receptor agonist) of the vasculature surrounding the nerve axons. This prevents the diffusion of bupivacaine away from the nerves resulting in a longer retention in the axon.

Pharmacology:

Onset of action: Infiltration and nerve block: 2-20 minutes

Duration: Infiltration: 1 hour; Nerve block: 5-7 hours

Half-life elimination, serum: Adults: 1.5-5.5 hour

Indications: Bupivacaine HCl is indicated for the production of local or regional anesthesia or analgesia for surgery, for oral surgery procedures, for diagnostic and therapeutic procedures, and for obstetrical procedures. Only the 0.25% and 0.5% concentrations are indicated for obstetrical anesthesia.

Experience with non-obstetrical surgical procedures in pregnant patients is not sufficient to recommend use of the 0.75% concentration in these patients. Bupivacaine HCl is not recommended for intravenous regional anesthesia (Bier Block).

The routes of administration and indicated Bupivacaine HCl concentrations are:

| | |
|------------------------|---|
| local infiltration | 0.25% |
| peripheral nerve block | 0.25%, 0.5% |
| retrobulbar block | 0.75% |
| sympathetic block | 0.25% |
| lumbar epidural | 0.25%, 0.5% and 0.75% (non-obstetrical) |
| caudal | 0.25%, 0.5% |

Use only the single dose ampules and single dose vials for caudal or epidural anesthesia; the multiple dose vials contain a preservative and, therefore, should not be used for these procedures.

Dosage: Dosages of Bupivacaine HCl should be reduced for young, elderly and/or debilitated patients and 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.

In recommended doses, Bupivacaine HCl produces complete sensory block, but the effect on motor function differs among 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.

0.5% 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. Most useful for epidural block in abdominal operations requiring complete muscle relaxation, and for retrobulbar anesthesia. Not for obstetrical anesthesia.

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.

Use in Epidural Anesthesia: During epidural administration of Bupivacaine HCl, 0.5% and 0.75% solutions should be administered in incremental doses of 3 mL to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. In obstetrics, only the 0.5% and 0.25% concentrations should be used; incremental doses of 3 mL to 5 mL of the 0.5% solution not exceeding 50 mg 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 the single dose ampules and single dose vials for caudal or epidural anesthesia; the multiple dose vials contain a preservative and therefore should not be used for these procedures.

| Type of Block | Conc. | Each Dose | | Motor Block ¹ |
|--------------------|-----------------------|------------|------------|--------------------------|
| | | (mL) | (mg) | |
| Local Infiltration | 0.25% ⁴ | up to max. | up to max. | |
| Epidural | 0.75% ^{2, 4} | 10-20 | 75-150 | complete |
| | 0.5% ⁴ | 10-20 | 50-100 | moderate to complete |
| | 0.25% ⁴ | 10-20 | 25-50 | partial to moderate |
| Caudal | 0.5% ⁴ | 15-30 | 75-150 | moderate to complete |
| | 0.25% ⁴ | 15-30 | 37.5-75 | moderate |
| Peripheral Nerves | 0.5% ⁴ | 5 to max. | 25 to max. | moderate to complete |

| | | | | |
|--------------------------|--------------------|-----------|----------------------|----------------------|
| | 0.25% ⁴ | 5 to max. | 12.5 to max. | moderate to complete |
| Retrobulbar ³ | 0.75% ⁴ | 2-4 | 15-30 | complete |
| Sympathetic | 0.25% | 20-50 | 50-125 | |
| Epidural ³ | 0.5% | 2-3 | 10-15 | |
| Test Dose | w/epi | | 10-15 µg epinephrine | |

Side effects:

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 the pupils.

Cardiovascular System Reactions: High doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heartblock, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and cardiac arrest.

Allergic: Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic or to other formulation ingredients, such as the antimicrobial preservative methylparaben contained in multiple-dose vials or sulfites in epinephrine-containing solutions. 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).

Neurologic: The incidences of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration, and the physical status of the patient. Many of these effects may be related to local anesthetic techniques, with or without a contribution from the drug. Neurologic effects following epidural or caudal anesthesia may include spinal block of varying magnitude (including high or total spinal block); hypotension 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 of which may have slow, incomplete, or no recovery; headache; backache; septic meningitis; meningismus; slowing of labor; increased incidence of forceps delivery; and cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.

Precautions:

Epidural Anesthesia: During epidural administration of Bupivacaine HCl, 0.5% and 0.75% solutions should be administered in incremental doses of 3 mL 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.

Use in Head and Neck Area: Small doses of local anesthetics injected into the head and neck area, including retrobulbar, dental, 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. Dosage recommendations should not be exceeded.

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.

Use in Dentistry: Because of the long duration of anesthesia, when Bupivacaine HCl 0.5% with epinephrine 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.

Pregnancy Category C: 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.

Nursing Mothers: Bupivacaine has been reported to be excreted in human milk suggesting that the nursing infant could be theoretically exposed to a dose of the drug.

Pediatric Use: Until further experience is gained in pediatric patients younger than 12 years, administration of Bupivacaine HCl in this age group is not recommended. Continuous infusions in children have been reported to result in high systemic levels of bupivacaine and seizures; high plasma levels may also be associated with cardiovascular abnormalities.

Geriatric Use: Patients over 65 years, particularly those with hypertension, may be at increased risk for developing hypotension while undergoing anesthesia with Bupivacaine HCl.

Contraindications: Bupivacaine HCl is contraindicated in obstetrical paracervical block anesthesia. Bupivacaine HCl is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type or to other components of Bupivacaine HCl solutions.

How supplied: Customized as per request.