Lidocaine HCl 2% and Epinephrine 1:50,000 Injection

(Lidocaine hydrochloride and epinephrine injection, USP)

Rx only

Solutions for local anesthesia in Dentistry

DESCRIPTION

Lidocaine Hydrochloride and Epinephrine, USP is a sterile isotonic solution containing a local anesthetic agent, Lidocaine Hydrochloride, and a vasoconstrictor, Epinephrine (as bitartrate) and are administered parenterally by injection. Both solutions are available in single dose cartridges of 1.7 mL (See INDICATIONS AND USAGE for specific uses).

The solutions contain Lidocaine hydrochloride which is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-monohydrochloride and has the following structural formula:

\[
\text{C}_2\text{H}_5\text{NH}-\text{CO}-\text{CH}_2-\text{NHCH}_3\]

Epinephrine is ( \(-\) )-3,4-Dihydroxy-\(-\alpha\) -(Methylamino) methyl] benzylic alcohol and has the following structural formula:

\[
\text{C}_9\text{H}_13\text{NO}_3\cdot \text{C}_4\text{H}_6\text{O}_6 \quad \text{M.W. 333.3}
\]

COMPOSITION OF AVAILABLE SOLUTIONS

<table>
<thead>
<tr>
<th>PRODUCT IDENTIFICATION</th>
<th>FORMULA</th>
<th>SINGLE DOSE CARTRIDGE</th>
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<tbody>
<tr>
<td>Lidocaine hydrochloride (as the bitartrate)</td>
<td></td>
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<tr>
<td>Concentration (%)</td>
<td>Dilution (mg/mL)</td>
<td>Potassium metabisulfite (mg/mL)</td>
</tr>
<tr>
<td>2</td>
<td>1:100,000</td>
<td>6.5</td>
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<tr>
<td>2</td>
<td>1:50,000</td>
<td>6.5</td>
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The pH of all solutions are adjusted to USP limits with sodium hydroxide.

CLINICAL PHARMACOLOGY

Mechanism of action

Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of nerve impulses, thereby effecting local anesthetic action.

Onset of action/duration of anesthesia

When used for infiltration anesthesia in dental patients, the time of onset averages less than two minutes for Lidocaine and Epinephrine Injections. Lidocaine and Epinephrine Injections provide an average pulp anesthesia of at least 60 minutes when used for nerve blocks. Approximate time to loss of consciousness is 2 to 2.5 hours. When used for infiltration anesthesia approximately 2 to 4 minutes. Lidocaine and Epinephrine Injections provide pulp anesthesia averaging at least 50 minutes with an average duration of soft tissue anesthesia of 3 to 3.4 hours.

Hemodynamic effects

Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressures. These changes may be attributable to a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system and/or the beta-adrenergic receptor stimulating action of epinephrine when present.

Pharmacokinetics and metabolism

Information derived from diverse formulations, concentrations and uses reveals that the lidocaine is completely absorbed following parenteral administration. Its rate of absorption depending, for example, upon various factors such as the site of administration and the presence or absence of a vasoconstrictor agent. Except for intravascular administration, the highest blood levels are obtained following intracutaneous nerve block and the lowest after subcutaneous administration.

The plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentration of 1 to 4 µg of free base per mL, 60 to 80 percent of lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein.

Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion. Lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidney. Bioconversion includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amine linkage, and conjugation. N-dealkylation, a major pathway of bioconversion, yields the metabolites mono hydroxy-lidocaine and glucuronide. The pharmacodynamic/toxicologic actions of these metabolites are similar to, but less potent than those of lidocaine. Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-

Lidocaine.

Studies of lidocaine metabolism following intravenous bolus injections have shown that the elimination half-life of this agent is typically 1.5 to 2.0 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 60 µg free base per mL. In the rhesus monkey, arterial blood levels of 18-21 µg/mL have been shown to be the threshold for convulsive activity.

INDICATIONS AND USAGE

Lidocaine and Epinephrine, USP is indicated for the production of local anesthesia for dental procedures by nerve block or infiltration techniques. Only selected procedures for these techniques as described in standard textbooks are recommended.

CONTRAINDICATIONS

Lidocaine and Epinephrine Injections is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type or to any components of the injectable formulations.

WARNINGS

DENTAL PRACTITIONERS WHO EMPLOY LOCAL ANESTHETIC AGENTS SHOULD BE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF EMERGENCIES WHICH MAY ARISE FROM THEIR USE.

RESUSCITATIVE EQUIPMENT, OXYGEN AND OTHER RESUSCITATIVE DRUGS SHOULD BE AVAILABLE FOR IMMEDIATE USE.

To minimize the likelihood of intravascular injection, aspiration should be performed before the local anesthetic solution is injected. If blood is aspirated, the needle must be repositioned until no return of blood can be elicited by aspiration. Note, however, that the absence of blood in the syringe does not assure that intravascular injection will be avoided.

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

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The American Heart Association has made the following recommendations regarding the use of local anesthetics with vasoconstrictors in patients with ischemic heart disease: “Vasoconstrictor agents should be used in local anesthesia solutions during dental practice only when it is clear that the procedure will be shortened or the anesthesia rendered more profound. When a vasoconstrictor is indicated, extreme care should be taken to avoid intravenous injection. The minimum possible amount of vasoconstrictor should be used.” (Kaplan, EL, editor. Cardiovascular disease in dental practice, Dallas 1988, American Heart Association.)

PRECAUTIONS

General

The safety and effectiveness of lidocaine depend on proper dosage, correct technique, adequate precautions and readiness for emergencies. Consult standard textbooks for specific techniques and precautions for various regional anesthetic procedures. Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use (See WARNINGS AND ADVERSE REACTIONS).

The lowest dose that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose. The lowest effective dose should be used in patients with impaired cardiovascular function. Lidocaine anesthesia containing a vasoconstrictor should be used with caution in areas of the body supplied by end arteries or having otherwise compromised blood supply. Patients with peripheral vascular disease and those with hypertensive vascular disease should be used with caution in patients with severe shock or heart block. Lidocaine should also be used with caution in patients with impaired cardiovascular function. Local anesthetic solutions containing a vasoconstrictor should be used with caution in areas of the body supplied by end arteries or having otherwise compromised blood supply. Patients with peripheral vascular disease and those with hypertensive vascular disease should be given reduced doses commensurate with their age and physical condition.

If vasodilation occurs to reduce patient apprehension, reduced doses should be used since local anesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect. Young children should be given minimal doses of each agent.

Lidocaine should be used with caution in patients with severe shock or heart block. Lidocaine should also be used with caution in patients with impaired cardiovascular function. Local anesthetic solutions containing a vasoconstrictor should be used with caution in areas of the body supplied by end arteries or having otherwise compromised blood supply. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasovasospastic response. Ischemic injury (such as exacerbating or ulcerating lesions) or necrosis may result. Preparations containing a vasoconstrictor should be used with caution in patients during or following administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such conditions.

Cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient’s state of consciousness should be monitored after each local anesthetic injection. Restlessness, anxiety tinnitus, dizziness, blurred vision, tremors, depression or drowsiness should alert the practitioner to the possibility of central nervous system toxicity. Signs and symptoms of depressed cardiovascular function may commonly result from a vasovagal reaction, particularly if the patient is in an upright position; placing the patient in the recumbent position is recommended when an adverse response is noted after injection of a local anesthetic (See ADVERSE REACTIONS - Cardiovascular System). Vasovagal reactions may elicit a range of clinical manifestations, from prodrome signs of pre-syncope (e.g. light-headedness, pallor, nausea, sweating, visual disturbances, weakness) to brief loss of consciousness (i.e. syncope).

Lidocaine should be used with caution in patients with hepatic disease, since amide-type local anesthetics are metabolized by the liver. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations.
Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anesthetics may trigger this reaction, and since the majority of cases of malignant hyperthermia cannot be predicted in advance, it is suggested that, in general, their use in this management be avoided. Preoperative administration of a test dose followed by observation, when the patient is subjected to a test induction of anesthesia, is recommended. Lidocaine should be used with caution in patients with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

Use in Heart-Lung Assist Cases

Small doses of local anesthetics injected into the head and neck area, including intrabulbar, dural and nodal site ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. 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, or to the local anesthetic effect on the central circulation. Intra-arterial administration of these solutions should be carefully observed and arterial blood pressure should be used to monitor arterial perfusion to the brain. If arterial blood pressure drops significantly, the patient should be observed closely for deterioration in cerebral perfusion.

Clinically Significant Drug Interactions

The intravenous LD50 of lidocaine HCl in female mice is 26 (21-31) mg/kg and the subcutaneous LD50 is 264 (203-304) mg/kg.

Central Nervous System

CNSS manifestations are excitory and/or depressant and may be characterized by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. The excitiatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lidocaine is administered to a nursing woman.

Pediatric Use:

Dosages in pediatric population should be reduced, commensurate with age, weight and physical condition (See DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS, WARNINGS AND PRECAUTIONS

Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide-type local anesthetic agents. These adverse experiences are, in general, dose-related and may result from local anesthetic absorption into the bloodstream, from a direct effect on the cardiovascular system, subcutaneous emphysema, neuritis, local anesthetic systemic toxicity, and, rarely, death. Clinical manifestations of systemic toxicity may be related to lidocaine plasma levels that exceed 5 to 9 mg/mL. Treatment of systemic toxicity should be symptomatic and supportive, administered by intravenous administration at a rate of 5 to 10 mg/L. Overdosage therapy should be instituted immediately following the administration of lidocaine.

Signs and symptoms of diminished cardiovascular function may commonly result from a cardiovascular reaction, particularly if the patient is in an upright position. Less commonly, they may result from a direct effect of the drug. Failure to recognize the premonitory signs such as widening of a pulse or sphygmogram may result in progressive cerebral hypoxia and severe or serious cardiovascular collapse. Management consists of placing the patient in the recumbent position and providing oxygen. Supportive treatment of circulatory depression may require the administration of intravenous fluids and, when appropriate, a vasopressor (e.g., ephedrine) as directed by the clinical situation.

Adverse reactions characterized by cutaneous urticaria, urticaria, edema, anaphylactoid reactions or dyspnea due to bronchoconstriction. Allergic reactions as a result of sensitivity to lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Neurologic reactions

The incidence of adverse reactions (e.g., persistent neurologic deficit) associated with the use of local anesthetics may be related to the technique employed, the total dose of local anesthetic administered, the particular drug used, and the physical condition of the patient.

Pharyngitis

Persistent parotid pangs of the lips, tongue, and oral tissues have been reported with the use of lidocaine, with slow, incomplete, or no recovery. These post-marketing events have been reported chiefly following nerve blocks in the mandible and have involved the trigeminal nerve and its branches.

OVERDOSAGE

Acute exposures from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintentional subcutaneous injection of local anesthetic solution (See ADVERSE REACTIONS, WARNINGS AND PRECAUTIONS).

Use in the Head and Neck Area

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. If cardiac arrest should occur, standard cardio-pulmonary resuscitation (CPR) should be initiated. The administration of 10 mL to 20 mL of 1:10,000 epinephrine by intravenous injection is recommended. In addition, if not contraindicated, IV and/or intraarterial administration of calcium gluconate may be beneficial in the treatment of cardiac arrest.

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DOSAGE AND ADMINISTRATION

The dosage of Lidocaine and Epinephrine Injections, USP depends on the physical status of the patient, the area of the oral cavity to be anesthetized, the vascularity of the oral tissues, and the technique of anesthesia used.

For most routine dental procedures, Lidocaine and Epinephrine 1:100,000 Injection is preferred. However, when greater depth and a more pronounced hemostasis are required, a 1:50,000 Epinephrine concentration should be used. The intravenous LD50 of lidocaine HCl is 26 (21-31) mg/kg and the subcutaneous LD50 is 264 (203-304) mg/kg.

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