Lidocaine HCl 2% and Epinephrine 1:50,000 Injection
Lidocaine HCl 2% and Epinephrine 1:100,000 Injection
(lidocaine hydrochloride and epinephrine injection, USP)

Rx only
SOLUTIONS FOR LOCAL ANESTHESIA IN DENTISTRY

DESCRIPTION

Solutions containing a local anesthetic agent, Lidocaine Hydrochloride, and a vasconstrictor, 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).

Solutions contain lidocaine hydrochloride which is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-methylchloride, and has the following structural formula:

\[
\text{C}_4\text{H}_3\text{CH} = \text{N} - \text{HCl}
\]

\[
\text{C}_4\text{H}_3\text{NO}_2\text{HCl}_2\text{H}_2\text{O} \quad \text{M.W. 268.8}
\]

CLINICAL PHARMACOLOGY

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

Onset and duration of anesthesia
When used for infiltration anesthesia in dental patients, the time of onset averages less than two minutes for each of the two forms of lidocaine hydrochloride and epinephrine injection, USP. Lidocaine HCl 2% and epinephrine 1:50,000 or lidocaine HCl 2% and epinephrine 1:100,000 provide an average pulp anesthesia of at least 60 minutes with a average duration of soft tissue anesthesia of approximately 2 to 3 hours. When used for nerve blocks in dental patients, the time of onset for both forms of lidocaine hydrochloride and epinephrine injection, USP, 1:50,000, or lidocaine HCl 2% and epinephrine 1:100,000 provide pulp anesthesia averaging at least 90 minutes with an average duration of soft tissue anesthesia of 3 to 5 hours.

Nephrotoxicity
Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. 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 usages reveals that 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. Except for intravascular administration, the highest blood levels are obtained following interosseal 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 mcg 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 kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amine linkage, and conjugation. N-dealkylation and hydroxylation of lidocaine proceeds by 4-hydroxylation, yielding the metabolites monohydroxyethylidide/ide, and hydroxymethylethylidide which are also 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-2, 6-dimethylaminobenzoic acid.

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 metabolism. The half-life may be prolonged by 2 to 5 fold in patients with liver disease. The half-life may 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 5.0 mcg per mL. In the rhesus monkey, arterial blood levels of 18-31 mcg/mL have been shown to be the threshold for convulsant activity.

INDICATIONS AND USAGE

Lidocaine hydrochloride and epinephrine injection, USP solutions are indicated for the production of local anesthesia for dental procedures by nerve block or infiltration techniques. Only accepted procedures for these techniques as described in standard textbooks are recommended.

CONTRAINDICATIONS

Lidocaine hydrochloride and epinephrine injection, USP 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 RESOURCES MUST BE AVAILABLE FOR EMERGENCIES.

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 not occur.

Local anesthetic solutions should be used with caution in patients with a history of convulsive disorders or with conditions or diseases that are characterized by increased intracranial pressure. The possibility of intracranial lesions should be considered in the region of the proposed injection.

Lidocaine hydrochloride and epinephrine injection, USP solutions contain potassium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe reactions in certain susceptible persons. The overall prevalence of sulfite sensitivity in the general population is unknown and probably very low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Lidocaine HCl 2% and epinephrine 1:100,000 injection, USP, along with other local anesthetics, is a cardiovascular depolarizer. The clinical signs of systemic lidocaine toxicity are cyanosis of the nail beds and lips, fatigue and weakness. If methemoglobinemia does not respond to administration of oxygen, administration of methylene blue intravenously 1-2 mg/kg body weight over a 5 minute period is recommended.

The American Heart Association has made the following recommendation regarding the use of lidocaine with vasconstrictors in patients with ischemic heart disease: “Vasconstrictor agents should be used in local anesthesia solutions during intravenous administration of local anesthetic. It is clear that the procedure will be shortened or the analgesia rendered more profound. When a vasconstrictor is indicated, extreme care should be taken to avoid intravascular injection. The minimum possible amount of vasconstrictor should be used.” (Kaplan, EL. editor: Cardiovascular disease in dental practice, Dallas 1986, 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. Reusable equipment, oxygen and other resuscitative drugs should be available for immediate use (See DOSAGE AND ADVERSE REACTIONS).

The lowest dosage 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 due to slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Overdosed, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical condition.

If sedatives are employed 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 vasoconstrictor response. Ischemic injury (such as embolization or altering lesion) or necrosis may result. Preparations containing a vasoconstrictor should be used with caution in patients during or following the administration of potent general anesthetic agents. Patients undergoing surgery that 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 agent. (See ADVERSE REACTIONS - Cardiovascular System). Vasovagal reactions may elicit a range of clinical manifestations, from prostrating signs of pre-syncope (e.g., lightheadedness, pallor, nausea, sweating, visual disturbances, weakness) to brief loss of consciousness (i.e., syncope). Lidocaine should be used with caution in patients with hepatic anesthetics 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 need for supplemental oxygen and a vasocaudator cannot be predicted in advance, it is suggested that a standard agent of such-toxic and/or stressful agents should be administered during anesthesia.

Lidocaine should be used with caution in patients with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzoic acid and like compounds) have not shown cross sensitivity to lidocaine.

Use in the Head and Neck Area
Small doses of lidocaine injected into the head and neck area, including retrobulbar, dental and submucosal localization blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Convulsion, 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 systemic absorption. Patients receiving local anesthetic should have their circulation 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).

Clinically significant drug interactions

The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors, tricyclic antidepressants or phenothiazines may produce severe prolonged hypotension or cardiac arrest. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential. Concurrent administration of vasopressor drugs and ergot-type oxytocic drugs may cause severe, persistent hypertension or cardiomyocellular accidents.
As the Lidocaine HCl 2% and epinephrine 1:100,000 and the Lidocaine HCl 2% and epinephrine 1:50,000 solutions both contain a vasoconstrictor (epinephrine), concurrent use of either with a beta-adrenergic blocking agent (propranolol, timolol, etc.) may result in dose-dependent hypertension and bradycardia with possible heart block.

PREGNANCY
Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats dosed up to 6.6 times the human dose and have revealed no evidence of harm to the fetus caused by lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Animal reproduction studies in pregnant animals do not always predict the outcome in pregnant women, especially during early pregnancy when maximum organogenesis takes place.

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, body weight and physical condition (See DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS
Adverse experiences following the administration of lidocaine are similar in nature to those observed with other local anesthetic agents in the following order: CNS manifestations, cardiovascular system, pupillary changes, gastrointestinal manifestations, allergic manifestations.

CNS manifestations are excitatory and/or depressant and may be characterized by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tremors, blurred or double vision, vomiting, sensations of heat, cold or numbness, flushing, hirsutism, convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness, progressing to unconsciousness and respiratory arrest.

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Cardiovascular system manifestations in lidocaine are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest. In addition, the beta-adrenergic receptor-stimulating action of epinephrine may lead to excitatory cardiovascular changes, such as tachycardia, palpitations, and hypertension.

Signs and symptoms of depressed cardiovascular function may commonly result from a vasovagal 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 sweating, a feeling of faintness, changes in pulse or sensorium may result in progressive cerebral hypoxia and sequela or serious cardiovascular catastrophe. Management consists of placing the patient in the recumbent position and providing resupportive therapy. Should cardiovascular collapse persist despite adequate respiratory support and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiorphan or thiobutyls) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to use, with local anesthetics, with these anticonvulsant drugs. Supportive treatment of cardiovascular depression may require administration of intravenous fluids and, when appropriate, a vasopressor (e.g., epinephrine) as directed by the clinical situation.

Allergic reactions are characterized by cutaneous lesions, urticaria, edema, anaphylactic 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, the route of administration, and the physical condition of the patient.

PERSISTENT parenchymal damage to the lungs, 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 been associated with the trigeminal nerve and its branches.

OVERDOSAGE
Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subcutaneous 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 top priority in the management of convulsions consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask.

Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiorphan or thymylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to use, with local anesthetics, with these anticonvulsant drugs. Supportive treatment of cardiovascular depression may require administration of intravenous fluids and, when appropriate, a vasopressor (e.g., epinephrine) as directed by the clinical situation.

Not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradyarrhythmias, and cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be employed immediately, 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.

Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

The intravenous LD50 of lidocaine HCl in female mice is 26 (21-31) mg/kg and the subcutaneous LD50 is 264 (209-304) mg/kg.

DOSAGE AND ADMINISTRATION
The dosage of lidocaine HCl 2% and epinephrine 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. The useful volume of solution that results in effective local anesthesia should be administered; time should be allowed between injections to observe the patient for manifestations of an adverse reaction. For specific techniques and procedures of a local anesthesia in the oral cavity, refer to standard textbooks.

For most routine dental procedures, lidocaine HCl 2% and epinephrine 1:100,000 is preferred. However, when greater depth and a more pronounced hemostasis are required, lidocaine HCl 2% and epinephrine 1:50,000 should be used.

Dosage requirements can be determined on an individual basis. In oral infiltration and/or mandibular block, initial doses of 1.0 - 5.0 mL (1/2 to 2 1⁄2 cartridges) of lidocaine HCl 2% and epinephrine 1:50,000 or lidocaine HCl 2% and epinephrine 1:100,000 are usually effective.

In children over 2 years of age, care may necessary administer more than one-half cartridge (0.9-1.2 mL or 18-20 mg of lidocaine) per procedure to achieve local anesthesia for a procedure involving a single tooth. In maxillary infiltration, this amount will often suffice to the treatment of two or three teeth. In the mandibular block, however, satisfactory anesthesia achieved with this amount of drug, will allow treatment of the teeth of an entire quadrant. Aspiration is indicated in all cases to prevent unwanted retrograde spread.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Solutions that are discolored and/or contain particulate matter should not be used; and any unused portion of a cartridge of lidocaine hydrochloride and epinephrine injection, USP should be discarded.

- Lidocaine hydrochloride 2% and Epinephrine 1:50,000 injection is available in cartons containing 5 blisters of 10 x 1.7 mL cartridges (NDC 31382-262-05).
- Lidocaine hydrochloride 2% and Epinephrine 1:100,000 injection is available in cartons containing 5 blisters of 10 x 1.7 mL cartridges (NDC 31382-898-05).

Store at controlled room temperature, below 25°C (77°F). Protect from light. Do not permit to freeze.

REVISED: For protection from light, retain in box until time of use. Once opened, the box should be reclosed by closing the end flap.

Do not use if color is pinkish or darker than slightly yellow or if it contains a precipitate.

Sterilization: Storage and technical Procedures
1. Cartridges should not be autoclaved, because the closures employed cannot withstand autoclaving temperatures and pressures.

2. If chemical disinfection of anesthetic devices is desired, either isopropyl alcohol (91%) or 70% ethyl alcohol is recommended. Many commercially available brands of rubbing alcohol, as well as solutions of ethyl alcohol not of U.S.P. grade, contain denaturants that are injurious to rubber and, therefore, are not to be used. It is recommended that chemical disinfection be accomplished just prior to use by wiping the cartridge cap thoroughly with a pledge of cotton that has been moistened with recommended alcohol.

3. Certain metallic ions (mercury, zinc, copper, etc.) have been related to swelling and edema after local anesthesia in dentistry. Therefore, chemical disinfectants containing or releasing these ions are not recommended. Antiseptic toothpastes usually contain and should be removed or some similar agents that may be capable of releasing metal ions. Because of this, aluminum sealed cartridges should not be kept in such solutions.

4. Quaternary ammonium salts, such as benzalkonium chloride, are electrolytically incompatible with aluminum. Cartridges of lidocaine hydrochloride and epinephrine injection, USP are sealed with aluminum caps and therefore should not be immersed in any solution containing these salts.

5. To avoid leakage and breakage during injection, be sure to penetrate the rubber diaphragm when loading the syringe. An off-center penetration produces an oval shaped puncture that allows leakage around the needle. Other causes of leakage and breakage include badly worn syringes, aspirating syringes with bent hampers, the use of syringes not designed to take 1.7 mL cartridges, and inadvertent freezing.

6. Cracking of glass cartridges is most often the result of an attempt to use a cartridge with an extended plunger. An extended plunger loses its lubrication and can be forced back into the cartridge only with difficulty. Cartridges with extended plungers should be discarded.

7. Store at controlled room temperature, below 25°C (77°F).

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