4% Lidocaine Hydrochloride
Injection, USP (40 mg/mL)
AQUEOUS SOLUTION FOR TOPICAL USE AND RETROBULBAR INJECTION

Hospira

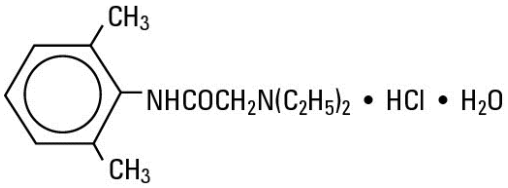
Rx only

DESCRIPTION

4% Lidocaine Hydrochloride Injection, USP is a sterile, nonpyrogenic solution containing lidocaine hydrochloride, anhydrous 40 mg/mL in water for injection. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. pH 6.5 (5.0 to 7.0).

Lidocaine has cardiac antiarrhythmic properties and is a local anesthetic of the amide-type.

Lidocaine Hydrochloride, USP is chemically designated 2-(diethylamino)-2′,6′-acetoxylidide monohydrochloride monohydrate, a white powder freely soluble in water. It has the following structural formula:



CLINICAL PHARMACOLOGY

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

Onset and duration of anesthesia: The onset of action is rapid. For retrobulbar injection, 4 mL of 4% Lidocaine Hydrochloride Injection provides an average duration of action of 1 to 1.5 hours. This duration may be extended for ophthalmic surgery by the addition of epinephrine, the usual recommended dilution being 1:50,000 to 1:100,000.

Hemodynamics: 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. The net effect is normally a modest hypotension when the recommended dosages are not exceeded.

Pharmacokinetics and metabolism: Information derived from other formulations, concentrations and usages reveals that lidocaine is completely absorbed following parenteral administration, its rate of absorption depending, for example, upon such factors such as the site of administration and the presence or absence of a vasoconstrictor agent. Lidocaine may be absorbed following topical administration to mucous membranes, its rate and extent of absorption depending upon concentration and total dose administered, the specific site of application and duration of exposure. In general, the rate of absorption of local anesthetic agents following topical application occurs most rapidly after intratracheal administration. Lidocaine is also well absorbed from the gastrointestinal tract, but intact drug appears in the circulation because of biotransformation by the liver.

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 amide

linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/toxicological 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-2,6-dimethylaniline.

Studies have shown that peak blood levels of lidocaine may occur as early as 5 minutes and as late as 30 minutes after endotracheal administration of a 4% lidocaine hydrochloride injection.

The plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 mcg of free base per mL, 60 to 80% 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.

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 central nervous system stimulants and depressants affect the central nervous system levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6.0 mcg free base per mL. In the rhesus monkey arterial blood levels of 18–21 mcg/mL have been shown to be threshold for convulsive activity.

INDICATIONS AND USAGE

4% Lidocaine Hydrochloride Injection is indicated for the production of topical anesthesia of the mucous membranes of the respiratory tract or the genito-urinary tract. It may be injected trans-tracheally to anesthetize the larynx and trachea, and it may be administered by retrobulbar injection to provide anesthesia for ophthalmic surgery.

CONTRAINDICATIONS

Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide-type.

WARNINGS

4% LIDOCAINE HYDROCHLORIDE INJECTION SHOULD BE EMPLOYED ONLY BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES THAT MIGHT ARISE AND THEN ONLY AFTER ENSURING THE *IMMEDIATE* AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY EQUIPMENT, AND THE PERSONNEL NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (see also **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.

Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary

compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.

Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue lidocaine hydrochloride and any other oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in pediatric and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness and loss of motion can be variable, but may begin as early as the second month after surgery. Currently, there is no effective treatment for chondrolysis; patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

To avoid intravascular injection, aspiration should be performed before the local anesthetic solution is injected. 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 guarantee that intravascular injection has been avoided.

4% Lidocaine Hydrochloride Injection should be used with extreme caution if there is sepsis or severely traumatized mucosa in the area of application, since under such conditions there is the potential for rapid systemic absorption.

PRECAUTIONS

General: The safety and effectiveness of lidocaine 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** 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, because of slow accumulation of the drug or its metabolites. 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. Lidocaine should also be used with caution in patients with severe shock or heart block.

Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully circumscribed quantities 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 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, since cardiac arrhythmias may occur under such conditions.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be accomplished after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Since amide-type local anesthetics are metabolized by the liver, lidocaine should be used with caution 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. Lidocaine should also be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Use in Ophthalmic Surgery: When local anesthetic solutions are employed for retrobulbar block, lack of corneal sensation should not be relied upon to determine whether or not the patient is ready for surgery since corneal sensation usually precedes clinically acceptable external ocular muscle akinesia.

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

Lidocaine should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

Use in the 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. 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. 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**).

Information for Patients: When topical anesthetics are used in the mouth, the patient should be aware that the production of topical anesthesia may impair swallowing and thus enhance the danger of aspiration. For this reason, food should not be ingested for 60 minutes following use of local anesthetic preparations in the mouth or throat area. This is particularly important in children because of their frequency of eating.

Numbness of the tongue or buccal mucosa may enhance the danger of unintentional biting trauma. Food and chewing gums should not be taken while the mouth or throat area is anesthetized.

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; light-headedness; or fatigue.

Clinically significant drug interactions: The administration of local anesthetic solutions containing epinephrine or nor-epinephrine to patients receiving monoamine oxidase inhibitors, tricyclic antidepressants or phenothiazines may produce severe, prolonged hypotension or hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Drug/Laboratory test interactions: The intramuscular injection of lidocaine may result in an increase in creatine phosphokinase levels. Thus, the use of this enzyme determination, without isoenzyme separation, as a diagnostic test for the presence of acute myocardiac infarction may be compromised by the intramuscular injection of lidocaine.

Patients who are administered local anesthetics are at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics:

Examples of Drugs Associated with Methemoglobinemia:

Class	**Examples**
Nitrates/Nitrites	nitric oxide, nitroglycerin, nitroprusside, nitrous oxide
Local anesthetics	articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine
Antineoplastic agents	cyclophosphamide, flutamide, hydroxyurea, ifosfamide, rasburicase
Antibiotics	dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides
Antimalarials	chloroquine, primaquine
Anticonvulsants	phenobarbital, phenytoin, sodium valproate
Other drugs	acetaminophen, metoclopramide, quinine, sulfasalazine

Carcinogenesis, mutagenesis, impairment of fertility: Studies of lidocaine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Use in Pregnancy: Teratogenic Effects. Reproduction studies have been performed in rats at doses 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 are not always predictive of human response. General consideration should be given to this fact before administering lidocaine to women of childbearing potential, especially during early pregnancy when maximum organogenesis takes place.

Labor and delivery: Lidocaine is not contraindicated in labor and delivery. Should 4% Lidocaine Hydrochloride Injection be used concomitantly with other products containing lidocaine, the total dose contributed by all formulations must be kept in mind.

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 children should be reduced, commensurate with age and body weight (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Adverse reactions following the administration of lidocaine are similar in nature to those observed with other amide local anesthetic agents. These adverse reactions are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption or inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Serious adverse reactions are generally systemic in nature. The following types are those most commonly reported:

Central nervous system: Central nervous system manifestations are excitatory and/or depressant and may be characterized by light-headedness, 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 excitatory 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.

Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

Cardiovascular system: Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

Allergic: Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions. 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: The incidences of adverse 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.

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 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 thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to use of local anesthetics, with these

anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).

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 cardiopulmonary resuscitative measures should be instituted.

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.

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

The intravenous LD_{50} of lidocaine hydrochloride in female mice is 26 (21–31) mg/kg and the subcutaneous LD_{50} is 264 (203–304) mg/kg.

DOSAGE AND ADMINISTRATION

When 4% Lidocaine Hydrochloride Injection is used concomitantly with other products containing lidocaine, the total dose contributed by all formulations must be kept in mind.

The dosage varies and depends upon the area to be anesthetized, vascularity of the tissues, individual tolerance and the technique of anesthesia. The lowest dosage needed to provide effective anesthesia should be administered. Dosages should be reduced for children and for elderly and debilitated patients.

Although the incidence of adverse effects with 4% Lidocaine Hydrochloride Injection is quite low, caution should be exercised, particularly when employing large volumes and concentrations of lidocaine since the incidence of adverse effects is directly proportional to the total dose of local anesthetic agent administered.

For specific techniques and procedures refer to standard textbooks.

There have been adverse event reports of chondrolysis in patients receiving intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures. 4% Lidocaine Hydrochloride Injection is not approved for this use (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

The dosages below are for normal, healthy adults.

RETROBULBAR INJECTION: The suggested dose for a 70 kg person is 3 mL to 5 mL (120 mg to 200 mg of lidocaine hydrochloride), i.e., 1.7 mg/kg to 3 mg/kg or 0.9 mg/lb to 1.5 mg/lb body weight. A portion of this is injected retrobulbarly and the rest may be used to block the facial nerve.

TRANSTRACHEAL INJECTION: For local anesthesia by the transtracheal route 2 mL to 3 mL should be injected through a large enough needle so that the injection can be made rapidly. By injecting during inspiration some of the drug will be carried into the bronchi and the resulting cough will distribute the rest of the drug over the vocal cords and the epiglottis.

Occasionally it may be necessary to spray the pharynx by oropharyngeal spray to achieve complete analgesia. For the combination of the injection and spray, it should rarely be necessary to utilize more than 5 mL (200 mg of lidocaine hydrochloride), i.e., 3 mg/kg or 1.5 mg/lb body weight.

TOPICAL APPLICATION: For laryngoscopy, bronchoscopy and endotracheal intubation, the pharynx may be sprayed with 1 mL to 5 mL (40 mg to 200 mg of lidocaine hydrochloride), i.e., 0.6 mg/kg to 3 mg/kg or 0.3 mg/lb to 1.5 mg/lb body weight.

Maximum Recommended Dosages

Normal Healthy Adults: The maximum recommended dose of 4% Lidocaine Hydrochloride Injection should be such that the dose of lidocaine hydrochloride is kept below 300 mg and in any case should not exceed 4.5 mg/kg (2 mg/lb) body weight.

Children: It is difficult to recommend a maximum dose of any drug for children since this varies as a function of age and weight. For children of less than ten years who have a normal lean body mass and normal body development, the maximum dose may be determined by the application of one of the standard pediatric drug formulas (e.g., Clark's rule). For example, in a child of five years weighing 50 lbs, the dose of lidocaine hydrochloride should not exceed 75 mg to 100 mg when calculated according to Clark's rule. In any case, the maximum dose of lidocaine hydrochloride and epinephrine injection should not exceed 7 mg/kg (3.2 mg/lb) of body weight. When used without epinephrine, the amount of lidocaine administered should be such that the dose is kept below 300 mg and in any case should not exceed 4.5 mg/kg (2 mg/lb) of body weight.

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. Do not use unless solution is clear and container undamaged.

HOW SUPPLIED

4% Lidocaine Hydrochloride Injection, USP is supplied in the following:

Unit of Sale	Concentration
NDC 0409-4283-01 Bundle of 5 Clamcells containing 5 Single-dose Ampuls per Clamcell	4% 200 mg/5 mL (40 mg/mL)
NDC 0409-4283-15 Carton of 5 Clamcells containing 5 Single-dose Ampuls per Clamcell	4% 200 mg/5 mL (40 mg/mL)

Discard unused portion.

Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature.]

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

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