Local anesthetic for dental use

Xylocaine 2%
with Adrenaline 1: 80000 injection

Lidocaine hydrochloride, Epinephrine injection

CONTRAINDICATIONS

(This drug is contraindicated in the following patients)

Patients with past history of hypersensitivity to components of this drug or amide local anesthetics.

The use of Xylocaine with Adrenaline is contraindicated for anesthesia of fingers, toes, tip of nose, ears and penis.

Xylocaine with adrenaline should not be given intravenously.

COMPOSITION AND CHARACTERISTICS

Xylocaine 2% with Adrenaline 1: 80000 Injection			Per 1 mL	Per vial (1.8mL)
Ingredient/Quantity	Active ingredient	Lidocaine hydrochloride	20mg	36mg
		Epinephrine	0.0125 mg	0.0225 mg
	Additives	Hydrochloric acid	0.4 μL	0.72 μL
		Sodium chloride	6 mg	10.8 mg
		Sodium pyrosulfite	0.55 mg	0.99 mg
		pH adjustment agent	Proper quantity	Proper quantity
Dosage form			Injection	
Color/Characteristic			Colorless and clear liquid	
pH			3.3-5.0	
Osmotic pressure ratio (to saline)			Approx. 1	

INDICATION(S)

Xylocaine 2% with Adrenaline 1:80,000 is a local anaesthetic solution for use in dental infiltration anaesthesia and all dental nerve block techniques.

DOSAGE AND ADMINISTRATION

Infiltration - the usual dose is 1 ml.
Nerve block - the usual dose is 1.5 to 2ml.

The recommended maximum dose for Xylocaine when given with adrenaline is 500mg.

Children and elderly or debilitated patients require smaller doses.

PRECAUTIONS FOR USE

1. This drug should be used with caution in the following patients:
   - Patients with cardiac conduction disturbance.
   - Patients with impaired respiratory function.
   - Patients with severe hepatic or renal dysfunction.
   - Patients with hypertension, cardiac disease, hyperthyroidism, or cerebrovascular insufficiency.
   - Patients with past history of vasospasm.
2. Facilities for resuscitation should be available when local anesthetics are administered.
3. Use the smallest necessary dosage. The injection rate should be as slow as possible.
4. Confirm that the injection needle is not inserted in the blood vessel. Xylocaine with Adrenaline should not be given intravenously.
5. Premedication with sedatives or some analgesics used during surgery may increase risk of respiratory depression. In situations whereby such premedications are required, these drugs should be started at a small dose, and additional dosages given only if necessary.
6. Administration of Xylocaine with Adrenaline may increase the risk for aspiration and intraoral bite.

DRUG INTERACTIONS

Lidocaine is metabolized primarily by hepatic metabolizing enzymes, CYP1A2 and CYP3A4.

Xylocaine with Adrenaline should be administered with care when coadministered with the following drugs.

Drug names	Clinical symptoms and treatments, etc.	Mechanism and risk factors
Inhalation anesthetics containing halogen: halothane	Tachycardia, arrhythmia, and very rarely cardiac arrest may occur.	These drugs increase the sensitivity of cardiomuscular adrenaline receptors.
Tricyclic antidepressants: MAO inhibitors such as imipramine, etc.	The blood pressure may be increased.	These drugs inhibit catecholamine reuptake at the adrenergic nerve ending to increase the concentration of catecholamine at the receptors, enhancing the adrenergic neurostimulation.
Non-selective β-blockers: propranolol, etc.	Vasoconstriction, increase in blood pressure, and tachycardia may occur.	These drugs block β-receptors, to make epinephrine predominate to stimulate α receptors, resulting in increase in the vascular resistance.
Antipsychotic agents (butyrophenones and dibenzothiazine): haloperidol and chlorpromazine, etc. α-Blockers	Excessive decrease in blood pressure may occur.	α-Blocking action of these drugs makes epinephrine predominate to stimulate α receptors, to increase the vascular resistance.
Drug names	Clinical symptoms and treatments, etc.	Mechanism and risk factors
Oxitocic: ergot alkaloids including oxitocin, etc. and ergometrine, etc.	Increase in blood pressure may occur	Combination use may enhance vasoconstrictor action.
Amiodarone, etc. in Class III antiarrhythmic agents	Cardiac function-depressing action may be enhanced.	The anesthetic action may be enhanced.

ADVERSE REACTIONS

None of use-results surveillance, etc., has been conducted, yet, and the incidence of adverse reactions is unknown.

(1) Clinically significant adverse reactions

1) **Shock**: Bradycardia, arrhythmia, decreased blood pressure, respiratory depression, cyanosis, or disturbance to consciousness may occur, leading to cardiac arrest on rare occasions. In addition, anaphylactic shock has been reported to occur on rare occasions. The patient should be carefully monitored, and should be appropriately managed.
2) **Disturbance to consciousness, tremor, and convulsion**: Overdose symptoms such as disturbance to consciousness, tremor, and convulsion may appear. The patient should be carefully monitored, and administration should be discontinued immediately. (Refer to "Overdosage")
3) **Abnormal feeling, perception disturbance, and movement disorder**: The contact of the injection needle with the nerves may trigger transient abnormal feeling. It should be noted that nerve injury caused by injection needle, the drug, or ischemia may lead to neurological disorders such as continuous abnormal feeling, pain, perception disturbance, and movement disorder on rare occasions.
4) **Malignant hyperpyrexia**
Serious malignant hyperpyrexia accompanied by symptoms such as tachycardia, arrhythmia, fluctuation in blood pressure, drastic increase in body temperature, muscle stiffness, cyanosis, hyperpnea, diaphoresis, acidosis, hyperkalemia, and myoglobinuria may occur on rare occasions. If these symptoms of malignant hyperpyrexia are observed during treatment with this drug, the treatment should be discontinued immediately, and appropriate measures such as intravenous administration of dantrolene sodium, general cooling, hyperventilation with pure oxygen, and correction of acid-base equilibrium be provided as required. In addition, renal failure may occur following malignant hyperpyrexia, and the urine output should be monitored and appropriate treatment provided as needed.

(2) Other adverse reaction(s)

	Incidence unknown
CNS	Sleepiness, anxiety, excitement, blurred vision, vertigo, and headache, etc.
Circulatory organs	Palpitation, tachycardia, and increase in blood pressure, etc.
Digestive tract	Nausea and vomiting, etc.
Hypersensitivity	Skin symptoms like urticaria, and edema, etc.
Injection site	Ulcer and necrosis, etc.

USE IN THE ELDERLY

Elderly patients may be highly sensitive to action of adrenaline contained in this drug. This drug should be used in the elderly with caution.

USE DURING PREGNANCY, DELIVERY OR LACTATION

Although there is no evidence from animal studies of harm to the foetus, as with all drugs, lidocaine should not be given in early pregnancy unless the benefits are considered to outweigh the risks.

OVERDOSAGE

Symptoms of overdosage may occur within a few minutes, especially when mistakenly injected into a vein. The primary symptoms are related to the CNS and cardiovascular system.

Symptoms and signs:

CNS symptoms: Early symptoms include anxiety, excitement, talkativeness, perioral paralysis, glossal numbness, light-headed feeling, hyperacusis, tinnitus, visual disturbance, and tremor. As these symptoms progress, loss of consciousness or systemic convulsion may develop, leading to codevelopment of hypoxemia and hypercapnia. In more severe cases, respiratory arrest may result.

Cardiovascular symptoms: Decrease in blood pressure, bradycardia, decrease in contraction of cardiac muscle, decrease in cardiac output, depression of conducting system, ventricular arrhythmia such as ventricular tachycardia and fibrillation, cardiovascular collapse, and cardiac arrest may occur.

Treatments: Artificial ventilation may be required to maintain adequate respiration. Diazepam or ultrashort-acting barbiturates (thiopental sodium, etc.) may be administered if tremor or convulsion occurs. Vasopressors may be used to depress overactive cardiac functions. Cardiac compression should be started immediately for cardiac arrest.

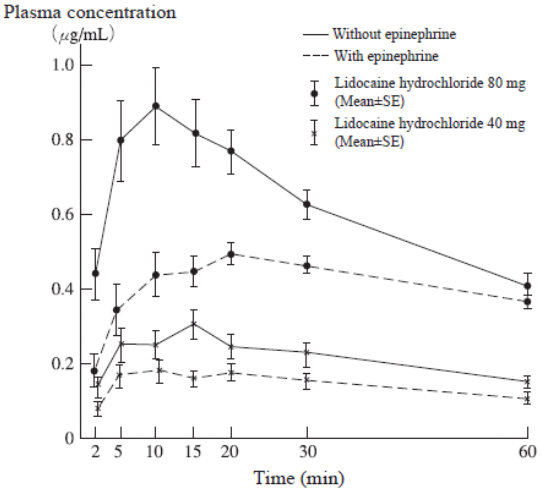
INSTRUCTIONS FOR ADMINISTRATION

(1) This product is for single-use only.
(2) Disinfect the head of cartridge (aluminium cap) membrane with alcohol before use.
(3) The injection should be administered as slow as possible.
(4) This drug may erode metals, and it is advised that the injection needle should not be in contact with the solution for prolonged periods.
(5) Dispose this product appropriately.

PHARMACOKINETICS

1. Absorption and pharmacokinetics

In healthy subjects in whom 2 or 4 mL of 2% lidocaine solution (lidocaine hydrochloride 40 or 80 mg) was used independently or in combination with epinephrine (1:80,000) for mandibular conduction anesthesia or buccal infiltration anesthesia, the plasma maximum concentration of lidocaine in combination use with epinephrine was significantly lowered as compared to the monotherapy with lidocaine solution, significantly prolonging the time to the maximum concentration.[1)]



Time course of plasma concentration of lidocaine in healthy subjects who received conduction and infiltration anesthesia with 2 or 4 mL of 2% lidocaine solution (lidocaine hydrochloride 40 or 80 mg).

Parameters / Dosage groups	Cmax (μg/mL)	Tmax (min)
Without epinephrine	0.93±0.10	11.4±1.4
With epinephrine	0.56±0.05	18.9±2.2

The terminal half-life in the elderly subjects intravenously administered lidocaine hydrochloride 50 mg was 140 min, which was longer as compared to 81 min in young subjects.[2)]

2. Distribution[3)]

The protein binding rate of lidocaine at a concentration of 2 μg/nL was about 65%, where the binding partner was α_1-acid glycoprotein and albumin. The concentration ratio of blood to plasma was about 0.8, suggesting that distribution in blood cells is small. In pregnant women who received epidural injection of lidocaine, the concentration ratio of umbilical vein blood to mother plasma was 0.5 to 0.7, indicating that lidocaine hydrochloride passes through the placenta.

3. Metabolism[4)]

Lidocaine is metabolized to N-deethylated form, monoethyl glycine-xylidide (MEGX), and further to glycinexylidide (GX) and 2,6-xylidine primarily in the liver, and 70% of the dosage is excreted in urine as 4-hydroxy-2,6-xylidine.

4. Excretion[4)]

In Caucasian healthy subjects orally administered ^{3}H-lidocaine 250 mg, the urinary excretion of radioactivity in 24 hrs was rated at 83.8% of dosage, where the unchanged drug was rated at 2.8%.

5. Pharmacokinetics under pathological condition[5)]

In Caucasian patients with cardiac failure or renal failure intravenously administered ^{3}H-lidocaine 50 mg, the elimination half-life was comparable to that in healthy subjects, although it was prolonged about 3 times in patients with lowered hepatic function.

PHARMACOLOGY

1. **Action mechanism**: Lidocaine hydrochloride is a local anesthetic agent which blocks sodium channels in nerve membranes to reversibly depress conduction of action potential in the nerves, leading to blockage of sensory and motor nerves.
2. **Anesthetic effect and action time**: Lidocaine hydrochloride is more potent in surface, infiltration, and conduction anesthetic actions than procaine hydrochloride, and its action lasts longer than that of procaine hydrochloride. Addition of epinephrine increases the action.[6-11)]

PACKAGING

1.8 mL x 50 vials (cartridges)

STORAGE CONDITIONS

Protect from light, store at 15°C or below. Do not freeze.
Expiry: 3 years from date of manufacturing (indicated on outer carton.

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