DESCRIPTION
Lignocaine is 2-(diethylaminoaceto-2',6'-xylidide; C₁₄H₂₂N₂O. It is a stable, colourless, crystalline solid whose hydrochloride salt is readily soluble in water. CAS 6108-05-0. Its chemical structure is:

![Chemical Structure of Lignocaine](image)

Lignocaine Hydrochloride Injection is a sterile solution of lignocaine hydrochloride in water. The solution also contains sodium chloride. The injection is available as 1% and 2% solutions.

PHARMACOLOGY
Lignocaine stabilises the neuronal membrane and prevents the initiation and transmission of nerve impulses, thereby effecting local anaesthetic action. The onset of action is rapid and the blockade may last from 1 to 1.5 hours.

In the heart, lignocaine reduces automaticity by decreasing the rate of diastolic (phase 4) depolarisation. Lignocaine is considered as a class 1 (membrane stabilising) antiarrhythmic agent. The duration of the action potential is decreased due to blockade of the sodium channel and the refractory period is shortened.

Lignocaine is rapidly distributed to all body tissues; about 65% is protein bound. Lignocaine crosses the placenta. The half life is 1.6 hours. About 80% of the dose is metabolised in the liver; less than 10% is excreted unchanged in the urine.

INDICATIONS
For local or regional anaesthesia by infiltration; for regional intravenous anaesthesia and nerve blocks such as major plexus blocks and epidural anaesthesia.

Treatment or prophylaxis of life-threatening ventricular arrhythmias, including those associated with myocardial infarction, general anaesthesia in patients predisposed to ventricular arrhythmias, digitalis intoxication, or following resuscitation from cardiac arrest.
CONTRAINDICATIONS

Known history of allergy or hypersensitivity to lignocaine or other amide-type local anaesthetics such as prilocaine, mepivacaine or bupivacaine. See also Interactions with Other Medicines.

Stokes-Adams syndrome or severe degrees of sinoatrial, atrioventricular or intraventricular block.

Lignocaine suppresses ventricular pacemaker activity and the result may be ventricular arrhythmias, including in those undergoing epidural anaesthesia.

Serious diseases of the CNS or of the spinal cord such as meningitis, spinal fluid block, cranial or spinal haemorrhage, tumors, poliomyelitis, syphilis, tuberculosis or metastatic lesions of the spinal cord.

Patients with myasthenia gravis, severe shock, or impaired cardiac conduction.

Local anaesthetic techniques must not be used when there is inflammation and/or sepsis in the region of the proposed injection and in the presence of septicaemia.

Epidural and spinal anaesthesia in patients with uncorrected hypotension and in patients with coagulation disorders or receiving anti-coagulation treatment.

PRECAUTIONS

1. RESUSCITATIVE EQUIPMENT AND MEDICINES, INCLUDING OXYGEN, SHOULD BE IMMEDIATELY AVAILABLE WHEN LIGNOCAINE IS USED TO MANAGE POSSIBLE LIGNOCAINE-INDUCED REACTIONS INVOLVING THE CARDIOVASCULAR, RESPIRATORY OR CENTRAL NERVOUS SYSTEM EFFECTS. (see ADVERSE EFFECTS)

2. Constant ECG monitoring is essential for the proper IV administration of lignocaine. Signs of excessive depression of cardiac conductivity, such as prolongation of PR interval and QRS complex should be followed by prompt cessation of the IV infusion.

3. In emergency situations, when a ventricular rhythm disorder is suspected, and ECG equipment is not available, a single dose may be administered when the physician in attendance has determined that the potential benefit outweighs the risks.

4. Mortality. In the Cardiac Arrhythmia Suppression Trial (CAST), a long-term multi-centred randomised double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmia, who had myocardial infarction more than six days but less than two years previously, an
excess mortality and non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730), compared with that seen in patients assigned to matched placebo treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months.

While there are no comparable mortality trial data for other Class I antiarrhythmic agents post-myocardial infarction or in other clinical settings, meta-analyses of small scale clinical trials of these agents in similar populations suggest a trend towards increased mortality compared to placebo and no evidence of benefit.

All Class I antiarrhythmic agents share the capacity to produce slowing of conduction velocity which can promote tachycardias via re-entry mechanisms.

Therefore, the prophylactic use of Class I antiarrhythmic drugs following myocardial infarction is potentially hazardous. Indeed the use of these agents for other than life-threatening arrhythmias or severe symptoms due to arrhythmias is not recommended.

5. Lignocaine should be used with caution in patients with severe shock, bradycardia, hypokalaemia, cardiac conduction disturbances (see CONTRAINDICATIONS), severe digitalis intoxication. In the case of bradycardia complicated by ventricular tachyarrythmia, Lignocaine might be combined with atropine or an atropine-like medicine or pacemaker treatment.

6. Since antiarrhythmic medicines may be ineffective in patients with hypokalaemia, serum potassium levels should be normalised prior to Lignocaine administration. Hypoxia and acid-base disturbances should also be corrected as these factors may potentiate ventricular arrhythmias.

7. The IV dose of Lignocaine should not exceed 100mg in a single injection, and no more than 200 – 300 mg in a one hour period (see DOSAGE AND ADMINISTRATION) as a hypotensive response is sometimes observed with IV administration of lignocaine.

8. Patients with reduced hepatic blood flow or function, and those on prolonged infusions of lignocaine, have a longer lignocaine half life and lower clearance resulting in accumulation of lignocaine. Patients with congestive cardiac failure have a reduced clearance. In patients with renal failure, accumulation of lignocaine and its metabolites may develop during prolonged or repeated administration. These patients may therefore require a reduction in dosage.

9. Patients with a chronic elevation in cardiac output or a drug-induced induction of hepatic microsomal enzymes will have a reduced elimination half-life of lignocaine and may therefore require a higher dosage.
10. Debilitated, elderly or acutely ill patients should be given reduced doses commensurate with their age and physical status.

11. Dosage reduction may be required during concomitant use with propranolol, metoprolol or cimetidine as there is a possibility of reduced elimination of lignocaine.

12. Use with caution in patients with genetic predisposition to malignant hyperthermia as the safety of amide local anaesthetic agents in these patients has not been fully assessed.

13. Blood lignocaine concentrations should be measured in patients in shock who may have markedly reduced lignocaine clearance, on prolonged infusions of greater than 24 hours duration especially in patients with cardiac or hepatic failure, those who are refractory to the usual dosage given, and in the presence of ambiguous signs and symptoms of lignocaine toxicity. Severe reactions are often preceded by somnolence and paraesthesia, therefore these symptoms should not be dismissed.

14. Caution should be observed in patients with cardiac decompensation and hypotension or posterior diaphragmatic infarction with a tendency towards development of heart block.

15. When high doses are used and the patient’s myocardial function is impaired, combination with other medicines which reduce the excitability of cardiac muscle requires caution.

16. Theoretical evidence suggests that lignocaine may have porphyrogenic properties. The clinical significance of this is unknown. Caution should be exercised if intravenous Lignocaine is administered to patients with acute porphyria.

The lignocaine is in a single use MIN-I-JET® prefilled syringe. Once the unit is assembled and used, any remaining portion of the solution must be discarded with the entire unit.

Carcinogenicity/Mutagenicity/Impairment of Fertility

A metabolite of lignocaine, 2, 6-dimethylamiline (2,6-Xylidine), has tumorigenic potential in man.

A two-year old toxicity study of 2,6-xylidine, a metabolite of lignocaine, has shown that in both male and female rats, 2-6-xylidine in daily doses of 900 mg/m² (150 mg/kg) resulted in carcinomas and adenomas of the nasal cavity. No nasal tumours were observed in the low dose (15 mg/kg) or control animals. In addition, the compound also caused subcutaneous fibromas and/or fibrosarcomas in male and female rats (significant at 150 mg/kg).

The genotoxic potential of 2,6-xylidine has been studied with mixed results: Positive results were reported in assays for gene mutations (weakly positive in the Ames test with metabolic activation in
the mouse lymphoma assay) and chromosomal damage (chromosomal aberrations in Chinese hamster ovary cells at concentrations at which the drug precipitated from solution). No evidence of genotoxicity was found in in vivo assays for chromosomal damage (micronucleus assay) and DNA damage (unscheduled DNA synthesis). Covalent binding studies of DNA from liver and ethmoid turbinates in rats indicate that 2,6-xylidine may be genotoxic under certain conditions in vivo.

**Use in pregnancy (Category A)**

Although lignocaine has been used extensively for surgical procedures during pregnancy with no reports of ill effects to the mother or foetus, there are no adequate or well-controlled studies in pregnant women of the effect of lignocaine on the developing foetus.

The safe use of lignocaine during pregnancy has not been established with respect to possible adverse effects upon foetal development. Therefore, lignocaine MIN-I-JET® should only be used in pregnancy if the expected medical benefits outweigh any potential risk.

Foetal bradycardia frequently follows paracervical block and may be associated with foetal acidosis. Foetal heart rate should always be monitored during paracervical anaesthesia. When the recommended dose is exceeded, the incidence of foetal bradycardia increases.

**Use in lactation**

The amount of lignocaine appearing in breast milk from nursing mother receiving parenteral lignocaine is unlikely to lead to a significant accumulation of the parent drug in the breast fed infant. The remote possibility of an idiosyncratic or allergic reaction in the breast fed infant from lignocaine remained to be determined.

Lignocaine is excreted in breast milk. The clinical significance of this is unknown.

**Use in Children**

The safety of lignocaine in the treatment of arrhythmias in children has not been established. Through their lower enzyme capacity, neonates are at risk of methaemoglobinaemia which can become clinically overt (cyanosis).

**Use in the Elderly**

A reduction in dosage may be necessary for elderly patients with compromised cardiovascular and/or hepatic function and/or prolonged infusions.

**Use in patients with impaired hepatic function**

Patients with reduced hepatic blood flow or function, and those on prolonged infusions of lignocaine, have a longer lignocaine half life and lower clearance and may therefore require a reduction in dosage. To lessen the risk of acute toxicity, a regimen with boluses 10 – 30 min apart followed by an infusion is preferable to a single bolus followed by infusion.
Use in patients with impaired renal function
Impairment of renal function is unlikely to affect lignocaine clearance in the short term (24 hours). However, toxicity due to accumulation of lignocaine and its metabolites may develop with prolonged or repeated administration.

Interaction with other medicines

Anti-arrhythmic medicines
Local anaesthetics of the amide type, such as lignocaine, should be used with caution in patients receiving anti-arrhythmic medicines (e.g. disopyramide, procainamide, mexilitene), since potentiation of cardiac effects may occur.

Amiodarone
Amiodarone has been reported to reduce the clearance of lignocaine in two case reports, although a small prospective study of combined therapy on lignocaine pharmacokinetics found no change in clearance or other pharmacokinetic factor. This combination has been reported to precipitate seizures and lead to severe bradycardia and a long sinoatrial arrest. Until more experience with concurrent use of lignocaine and amiodarone becomes available, patients receiving the combination should be monitored carefully.

Beta-adrenoreceptor antagonists
Propranolol, nadolol and metoprolol reduce the metabolism of IV, administered lignocaine and the possibility of this effect with other beta-adrenergic blockers should be kept in mind. If these medicines are administered concurrently, the patient should be closely observed for signs of lignocaine toxicity and serum lignocaine concentrations should be carefully monitored.

Cimetidine
Cimetidine reduces the clearance of IV administered lignocaine and toxic effects due to high serum lignocaine levels have been reported when these two medicines have been administered concurrently.

Anticonvulsive agents
Phenytoin and other antiepileptic drugs such as phenobarbitone, primidone and carbamazepine appear to enhance the metabolism of lignocaine but the significance of this effect is not known. Phenytoin and lignocaine have additive cardiac depressant effects.

Fluvoxamine
Coadministration of fluvoxamine drastically reduces the elimination of lignocaine.
Inhalation anaesthetics
Lignocaine decreases the minimum effective concentration of inhalation anaesthetics, e.g. nitrous oxide.

Skeletal muscle relaxants
Lignocaine and skeletal muscle relaxants, e.g. suxamethonium, lead to excessive neuromuscular blockade; therefore, this combination must be used with caution.

Alcohol
There have been no reports of direct interaction between alcohol and lignocaine. However, acute severe alcohol intoxication can centrally depress the cardiovascular system and may thereby prolong lignocaine elimination half-life.

Potential for influence of lignocaine on the plasma levels/effects of other medicines
Lignocaine is metabolised by CYP1A2 and CYP3A4 and thus has the potential to inhibit the metabolism of medicines metabolised by these isoenzymes, thus increasing their plasma levels, however, this effect has so far not been reported.

Potential for influence of other medicines on the plasma levels/effect of lignocaine
Concomitant treatment with medicines that are substrates, inhibitors, or inducers of CYP1A2 or CYP3A4 has the potential to influence the metabolism and hence the plasma levels and effect of lignocaine.

Laboratory test effects
Creatinine
Creatinine measurements in patients with therapeutic plasma levels of lignocaine are about 15 – 35% higher when measured by an enzymatic method versus the Jaffe method. This appears to be due to assay interference from N-ethylglycine, a metabolite of lignocaine.

ADVERSE EFFECTS
Reactions to lignocaine hydrochloride are similar in character to those observed with other local anaesthetics.
Adverse experiences are, in general, dose-related and may result from high plasma levels or from a hypersensitivity, idiosyncrasy or diminished tolerance.

Serious adverse events are generally systemic in nature, the following types are those more commonly reported.
Central Nervous System
CNS manifestations are excitatory and/or depressant and may be characterised by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, disorientation, tinnitus, double or blurred vision, vomiting, sensations of heat, cold or numbness, paraesthesia, twitching, tremors, convulsions, unconciousness, psychosis, dyspnoea, respiratory depression and/or arrest, agitation, difficulty swallowing and slurred speech.

The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestations of toxicity may be drowsiness merging into unconciousness and respiratory arrest. Drowsiness following administration of lignocaine is usually an early sign of a high blood level of the drug and may occur as a result of rapid absorption. In unconscious patients, circulatory collapse should be watched for as CNS effects may not be apparent, as an early manifestation of toxicity may in some cases progress to frank convulsions and ultimately lead to respiratory depression and/or arrest. It is crucial to have resuscitative equipment and anticonvulsant medicines available to manage such patients (Overdosage – Treatment of Overdosage).

Cardiovascular
Cardiovascular manifestations are usually depressant and are characterised by bradycardia, hypotensions, and cardiovascular collapse, which may lead to cardiac arrest. Methaemoglobinaemia can occur following IV administration, particularly in neonates. Arrhythmias including ventricular tachycardia/ventricular fibrillation.

Allergic
Allergic reactions are characterised by cutaneous lesions, urticaria, oedema or anaphylactoid reactions. Allergy to amide-type local anaesthetics is very rare.

DOSAGE AND ADMINISTRATION

Local anaesthesia
The dose varies depending upon the area to be anaesthetised, vascularity of the tissues, number of neuronal segments to be blocked, individual tolerance and the anaesthetic technique. The lowest dose needed to provide effective anaesthesia should be used.

Injection should be made slowly and with frequent aspiration to guard against intravascular injection, which may produce toxic effects. Care should be exercised in performing epidural anaesthesia to prevent intravascular or subarachnoid injection of the large dose of anaesthetic.

For continuous epidural or caudal anaesthesia and paracervical block for obstetric analgesia the maximum dose should not be repeated at intervals of less than 1.5 hours.
During spinal anaesthesia the positioning of the patient is very important (see PRECAUTIONS) and the patient's pulse and blood pressure should be monitored.

**Adults:** the dose should not exceed 200 mg.

For spinal anaesthesia, dose should not exceed 100 mg.

**Children:** the dose should not exceed 3 mg/kg.

In children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia.

**Intravenous use in cardiac arrhythmias**

Patients with congestive heart failure or cardiogenic shock may require smaller bolus doses.

**Adults:** the usual dose is 50 to 100 mg administered intravenously under ECG monitoring. The dose may be injected at a rate of approximately 25 to 50 mg (2.5 to 5.0 mL of the 1% solution or 1.25 to 2.5 mL of the 2% solution) per minute. A sufficient period of time should be allowed to enable a slow circulation to carry the drug to the site of action. If the initial dose of 50 to 100 mg does not produce the desired response, a second dose may be given after 5 minutes. No more than 200 - 300 mg of lignocaine should be administered during a 1 hour period.

Following a single injection in those patients in whom arrhythmia tends to recur and who are incapable of receiving oral antiarrhythmic therapy, intravenous infusions of lignocaine may be administered at a rate of 1 to 4 mg/minute (20 to 50 microgram/kg/minute). Intravenous infusions must be given under ECG monitoring to avoid potential overdosage and toxicity. The infusion should be reassessed as soon as the patient’s cardiac rhythm appears to be stable or at the earliest signs of toxicity. It should rarely be necessary to continue intravenous infusions of Min-I-Jet Lignocaine for prolonged periods. As soon as possible, patients should be changed to an oral antiarrhythmic agent for maintenance therapy.

**Children:** experience with lignocaine is limited. A suggested paediatric dose is a loading dose of 0.5 to 1 mg/kg repeated if necessary up to 3-5 mg/kg, followed by continuous infusions of 10 to 50 microgram/kg/minute.

**Elderly:** the dose may need to be reduced depending on age and physical state.
OVERDOSAGE

Symptoms
Reactions due to overdose with lignocaine are systemic and involve the central nervous, respiratory and cardiovascular systems. Effects include medullary depression, tonic and clonic convulsions and cardiovascular collapse (see ADVERSE REACTIONS).

In children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia.

Cardiovascular toxicity
In anaesthetised or unconscious patients, signs of CNS toxicity may not be apparent. Thus, cardiovascular toxicity, (esp. cardiovascular depression) may be the first indication of Lidocaine toxicity in these patients.
In rare cases, cardiac arrest has occurred without prodromal CNS effects.

Treatment
Institute emergency resuscitative procedures and administer the drugs necessary to counteract each appropriate abnormality. For severe convulsions, small increments of diazepam or an ultra-short acting barbiturate (thiopentone) should be given. If the patient is anaesthetised, a short acting muscle relaxant may be given intravenously. Patency of the airway and adequacy of ventilation must be assured. Should circulatory depression occur, vasopressors such as metaraminol may be used.

Contact the Poison Information Centre on 131 126 for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

PRESENTATION
Lignocaine Hydrochloride Injections are available in single use prefilled MIN-I-JET® syringes containing 100 mg lignocaine hydrochloride in 5 mL (2% solution).

STORAGE
Store below 25°C.

POISON SCHEDULE OF THE MEDICINE
Schedule 4 – Prescription Only Medicine
Name and Address of
Sponsor: CSL Limited, ABN 99 051 588 348
45 Poplar Road, Parkville
Victoria 3052 Australia