

Lignocaine Hydrochloride Injection BP 2%

1 NAME OF THE MEDICINE

Lidocaine (lignocaine) hydrochloride monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of Lignocaine Injection contains 20 mg lidocaine (lignocaine) hydrochloride monohydrate.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Lignocaine Injection is a clear, colourless, sterile, isotonic, preservative-free solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lidocaine (lignocaine) is indicated for production of local or regional anaesthesia by nerve block, infiltration injection, caudal or other epidural blocks.

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.

4.2 Dose and method of administration

Dosage

As a local anaesthetic for infiltration and nerve block:

The dosage varies and depends upon the area to be anaesthetised, vascularity of the tissues, number of neuronal segments to be blocked, individual tolerance and the technique of anaesthesia. The lowest dose needed to provide effective anaesthesia should be administered. For specific techniques and procedures, refer to standard textbooks.

It is recommended that the dose of lidocaine (lignocaine) at any one time should not exceed 3 mg/kg. However, the dose administered must be tailored to the individual patient and procedure, and the maximum doses here quoted should be used as a guide only.

The normal recommended dose of lidocaine (lignocaine) for various anaesthetic procedures in an average, healthy 70 kg adult patient are as follows:

Procedure	Concentration (%)	Volume (mL)	Dose (mg)
Infiltration	1.0	20	200
PERIPHERAL NERVE BLOCKS			
Paravertebral	1.0	3 - 5	30 – 50

Pudendal (each side)	1.0	10	100
Paracervical	1.0	10	100
SYMPATHETIC NERVE BLOCK			
Cervical (stellate ganglion)	1.0	5	50
Lumbar	1.0	10	100
EPIDURAL BLOCKS (2-3 mL per segment)			
Thoracic	1.0	10 - 20	100 – 200
Lumbar - analgesia	1.0	10 - 20	100 – 200
- anaesthesia	2.0	5 - 10	100 – 200
Caudal - obstetric analgesia	1.0	10 - 20	100 – 200

The doses suggested above are only a guide. Toxic levels vary widely between patients so doses should be individualised and blood levels should be monitored.

Epidural injections should be administered slowly with frequent aspirations. Subarachnoid and intravascular injections are two of the most serious complications of this technique. If blood or spinal fluid become manifest during aspiration, the needle must be withdrawn and relocated.

The technique of epidural anaesthesia should only be attempted by physicians skilled in this area and readiness for emergencies must be ensured. During spinal anaesthesia the positioning of the patient is very important and the patient's pulse and blood pressure should be monitored. During thoracic, lumbar and caudal epidural anaesthesia, a marked fall in blood pressure and/or intercostal paralysis may be seen, possibly due to the use of excessive doses, improper positioning of the patient or accidental disposition of the anaesthetic within the subarachnoid space. Hypotension and bradycardia may occur as a result of sympathetic blockade.

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.

Adults: The dose should not exceed 200 mg. For spinal anaesthesia, the dose should not exceed 100 mg.

Children: For children, a reduced dosage based on body weight or surface area should be used. The dosage should be calculated for each patient individually and modified in accordance with the physician's experience and knowledge of the patient. Early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia.

In order to minimise the possibility of toxic effects, the use of Lignocaine Injection 1% solution is recommended for most anaesthetic procedures involving paediatric patients.

The dose should not exceed 3 mg/kg.

For intravenous use in cardiac arrhythmias:

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

Adults: The usual dose is lidocaine (lignocaine) 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 lidocaine (lignocaine) 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 five minutes. No more than 200 to 300 mg of lidocaine (lignocaine) should be administered during a one 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 lidocaine (lignocaine) may be administered at a rate of 1 to 4 mg/minute (20 to 50 mcg/kg/minute). Intravenous infusions must be given under ECG monitoring to avoid potential overdosage and toxicity. The infusion should be terminated 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 the infusion beyond 24 hours. As soon as possible, patients should be changed to an oral antiarrhythmic agent for maintenance therapy.

Paediatrics: For children, a reduced dose based on body weight or surface area should be used. It is recommended that the 1% solution be used to minimise the possibility of toxic effects. Experience with lidocaine (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 micrograms/kg/min.

Geriatrics: A reduction in dosage may be necessary for elderly patients, particularly those with compromised cardiovascular and/or hepatic function.

Dosage adjustment

Hepatic impairment

Although lidocaine (lignocaine) is metabolised by the liver, dosage reduction for local anaesthesia is probably not warranted. However, caution should be exercised with repeated doses or prolonged infusion.

Renal impairment

Impairment of renal function is unlikely to affect lidocaine (lignocaine) clearance in the short term (up to 24 hours). However, toxicity due to accumulation may develop with prolonged or repeated administration.

Lignocaine Injection is for one dose in one patient only. Discard any remaining contents.

4.3 Contraindications

- Allergy or hypersensitivity to local anaesthetics of the amide type or to any excipients. Detection of suspected hypersensitivity by skin testing is of limited value.
- Inflammation and/or sepsis at the proposed site of injection and/or in the presence of septicaemia.

- Patients with myasthenia gravis, severe shock or impaired cardiac conduction.
- Epidural or spinal anaesthesia in patients with
 - uncorrected hypotension or
 - coagulation disorders or receiving anticoagulants or
 - serious diseases of the central nervous system or spinal cord such as meningitis, spinal fluid block, cranial or spinal haemorrhage, tumours, poliomyelitis, syphilis, tuberculosis or metastatic lesions of the spinal cord.
- Antiarrhythmic use in patients with
 - supraventricular arrhythmia or
 - Stokes-Adams Syndrome or severe degrees of sinoatrial, atrioventricular or intraventricular block unless the patient has an artificial pacemaker.
- Lidocaine (lignocaine) suppresses ventricular pacemaker activity and may cause ventricular standstill in such patients.
- General contraindications related to epidural anaesthesia, regardless of the local anaesthetic used, should be taken into account.

4.4 Special warnings and precautions for use

General precautions:

When any local anaesthetic agent is used, resuscitative equipment and drugs, including oxygen, should be immediately available in order to manage possible adverse reactions involving the cardiovascular, respiratory or central nervous systems. Because of the possibility of hypotension and bradycardia following major blocks, an IV cannula should be inserted before the local anaesthetic is injected. Delay in proper management of dose-related toxicity, under-ventilation from any cause and/or altered sensitivity may lead to the development of acidosis, cardiac arrest and death.

Injection of repeated doses of lidocaine (lignocaine) may cause accumulation of lidocaine (lignocaine) or its metabolites and result in toxic effects. Significant increases in blood levels with each repeated dose can occur due to slow accumulation of the drug or its metabolites, or slow metabolic degradation. This is especially relevant in patients with hepatic and/or renal impairment.

Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, children and those with advanced liver disease or severe renal dysfunction, should be given reduced dosages commensurate with their age and physical status.

Since lidocaine (lignocaine) is metabolised in the liver and excreted via the kidneys, the possibility of drug accumulation should be considered in patients with hepatic and/or renal impairment (see section 4.2 Dose and method of administration).

Lidocaine (lignocaine) should be used cautiously in patients with known drug allergies or sensitivities. Patients showing allergy to ester derivatives of para-aminobenzoic acid such as procaine, benzocaine and tetracaine have not shown cross-sensitivity to agents of the amide type.

Lidocaine (lignocaine) should be given cautiously to patients with epilepsy, hepatic disease, renal disease, congestive cardiac failure, marked hypoxia, severe respiratory depression, severe shock or hypovolaemia and in patients with any form of heart block or sinus, bradycardia, cardiac conduction disturbances, severe digitalis intoxication. Lidocaine (lignocaine) should be administered with great caution to patients with impaired cardiovascular function as they may be less able to compensate for functional changes associated with the prolongation of atrioventricular conduction produced by these drugs. In patients with Stokes-Adams syndrome or Wolff-Parkinson-White syndrome extreme care should be taken to avoid accidental arteriovenous injection.

Hypokalaemia, hypoxia and disorders of acid-base balance should be corrected before treatment with lidocaine (lignocaine).

Lidocaine (lignocaine) solutions for injection are probably porphyrinogenic and should only be prescribed to patients with acute porphyria on strong or urgent indications. Appropriate precautions should be taken for all porphyric patients.

Although intra-articular continuous infusions of local anaesthetics following arthroscopic and other surgical procedures is an unapproved use, 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 paediatric and adult patients following intra-articular continuous infusions of local anaesthetics with and without adrenaline (epinephrine) acid tartrate 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 2nd 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. Therefore, Lignocaine Injection should not be used for post-operative intra-articular continuous infusion.

Methemoglobinemia

Cases of methemoglobinemia have been reported in association with local anaesthetic 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 methemoglobinaemia 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. Methaemoglobin 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 (lignocaine) hydrochloride monohydrate injection 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.

Inform patients that use of local anaesthetics may cause methemoglobinaemia, 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, grey, or blue coloured skin (cyanosis); headache; rapid heart rate; shortness of breath; light-headedness; or fatigue.

Patients who are administered local anaesthetics are at increased risk of developing methemoglobinaemia when concurrently exposed to the following medicines, which could include other local anaesthetics:

- Nitrates/Nitrites such as nitric oxide, nitroglycerin, sodium nitroprusside, nitrous oxide.
- Local anaesthetics such as articaine, benzocaine, bupivacaine, lidocaine (lignocaine), mepivacaine, prilocaine, procaine, ropivacaine, tetracaine.
- Antineoplastic agents such as cyclophosphamide monohydrate, flutamide, hydroxycarbamide (hydroxyurea), ifosfamide, rasburicase.
- Antibiotics such as dapsone, nitrofurantoin, para-aminosalicylic acid, sulphonamides.
- Antimalarials such as chloroquine phosphate, primaquine.
- Anticonvulsants such as phenobarbital (phenobarbitone), phenytoin, sodium valproate.
- Other drugs such as paracetamol, metoclopramide, quinine, sulfasalazine.

For local anaesthesia

Injection should always be made slowly with frequent aspirations to avoid inadvertent intravascular injection, which can produce cerebral symptoms even at low doses.

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

Low molecular weight heparins and heparinoids - when neuraxial anaesthesia (epidural/spinal anaesthesia) is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events is increased by the use of indwelling epidural catheters, traumatic or repeated epidural/spinal puncture, and the concomitant use of drugs affecting haemostasis such as NSAIDs, platelet inhibitors or other anticoagulants. Patients should be frequently monitored for signs and symptoms of neurological impairment.

The safety and effectiveness of lidocaine (lignocaine) depends on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted regarding specific techniques and precautions for various regional anaesthetic procedures.

The lowest dosage that results in effective anaesthesia should be used to avoid high plasma levels and serious undesirable systemic side effects.

Central nerve blocks may cause cardiovascular depression, especially in the presence of hypovolaemia. Epidural anaesthesia should be used with caution in patients with impaired cardiovascular function. Epidural anaesthesia may lead to hypotension and bradycardia. Hypotension should be treated promptly with a sympathomimetic intravenously and repeated as necessary.

Local anaesthetics in general should be given cautiously (see section 4.3 Contraindications) to patients with pre-existing abnormal neurological conditions as neurological reactions may occur following administration.

Inadvertent intravascular or subarachnoid injection of small doses of local anaesthetics in 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.

Clinicians who perform retrobulbar blocks should be aware that there have been reports of cardiovascular collapse and apnoea following the use of local anaesthetic injections for retrobulbar block. Prior to retrobulbar block, necessary equipment, drugs and personnel should be immediately available, as with all other regional procedures.

Retrobulbar injections may very occasionally reach the subarachnoid space, causing temporary blindness, cardiovascular collapse, apnoea, convulsions, etc. These must be diagnosed and treated promptly.

Retro- and peribulbar injections of local anaesthetics carry a low risk of persistent ocular muscle dysfunction. The primary causes include trauma and/or local toxic effects on muscles or nerves. The severity of such tissue reactions is related to the degree of trauma, the concentration of the local anaesthetic and the duration of exposure of the tissue to the local anaesthetic. For this reason, as with all local anaesthetics, the lowest effective concentration and dose of local anaesthetic should be used. Vasoconstrictors may aggravate tissue reactions and should be used only when indicated.

The likelihood of hypotension and bradycardia following epidural or subarachnoid blockade should be anticipated and appropriate precautions taken.

For cardiac arrhythmia use

Constant ECG monitoring is essential during intravenous administration of lidocaine (lignocaine). If signs of excessive depression of cardiac conductivity (*e.g.* prolongation of the PR interval or QRS complex), aggravation of arrhythmias or other severe reactions occur, lidocaine (lignocaine) should be promptly discontinued. Severe reactions are often preceded by somnolence and paraesthesia, and these symptoms should not be ignored.

Mortality

In the Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-centre, 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 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 1 antiarrhythmic agents post myocardial infarction, or in other clinical settings, meta-analysis of small scale clinical trials of these agents in similar populations suggests a trend towards increased mortality compared to placebo and no evidence of benefit.

All class 1 antiarrhythmic agents share the capacity to produce slowing of conduction velocity that can promote tachycardias via re-entry mechanisms. Therefore, the prophylactic use of class 1 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.

Patients being treated with antiarrhythmic drugs class III (e.g. amiodarone) should be under close surveillance and ECG monitoring since cardiac effects may be additive.

The safety and effectiveness of lidocaine (lignocaine) depend upon proper dosage, correct technique, adequate precautions and readiness for emergencies.

Patients with reduced hepatic blood flow or function, and those on prolonged infusions of lidocaine (lignocaine) will have a longer half-life and a lower clearance. During congestive cardiac failure, clearance will be reduced and in renal failure, accumulation of lidocaine (lignocaine) may occur. Such instances will require a reduction in dosage.

Lidocaine (lignocaine) may increase ventricular rate when it is administered to patients with atrial fibrillation. Ischaemia or necrosis may occur in patients with hypertensive vascular disease or with an exaggerated vasoconstrictor response.

Lidocaine (lignocaine) suppresses ventricular pacemaker activity and may cause severe bradycardia or asystole in patients, including those undergoing epidural anaesthesia.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

Creatinine

Creatinine measurements in patients with therapeutic plasma levels of lidocaine (lignocaine) are about 15 to 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 lidocaine (lignocaine).

Creatine kinase

The intramuscular injection of lidocaine (lignocaine) may result in an increase in creatine kinase levels for up to 48 hours. This may interfere with the diagnosis of myocardial infarction.

4.5 Interactions with other medicines and other forms of interactions

See section 4.4 Special warnings and precautions for use– Methemoglobinaemia

Antiarrhythmic drugs

Local anaesthetics of the amide type, such as lidocaine (lignocaine), should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics e.g. certain antiarrhythmic drugs such as disopyramide, procainamide or mexiletine. Use lidocaine (lignocaine) cautiously in patients receiving antiarrhythmic drugs as potentiation of cardiac effects may occur. Specific interaction studies with lidocaine (lignocaine) and antiarrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution should be advised (see section 4.4 Special warnings and precautions for use).

Beta-adrenoreceptor antagonists

Propranolol and metoprolol reduce the metabolism of intravenously administered lidocaine (lignocaine). It is possible that this effect will be repeated with other beta-adrenergic blockers. If these drugs are administered concurrently, the patient should be closely observed for signs of lidocaine (lignocaine) toxicity.

Cimetidine

The clearance of intravenously administered lidocaine (lignocaine) is reduced when it is administered in conjunction with cimetidine. Toxic effects due to high serum lidocaine (lignocaine) levels have been reported when these two drugs have been administered concurrently.

Amiodarone

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

Anticonvulsant drugs

Phenytoin, phenobarbitone, primidone and carbamazepine appear to enhance the metabolism of lidocaine (lignocaine) possibly due to an induction of microsomal enzymes, but the significance is unknown. Phenytoin and lidocaine (lignocaine) have additive cardiac depressant effects.

Skeletal muscle relaxants

Lidocaine (lignocaine) and skeletal muscle relaxants, *e.g.* suxamethonium, lead to excessive neuromuscular blockade, therefore this combination must be used with caution. Lidocaine (lignocaine) prolongs the duration of suxamethonium.

Inhalational anaesthetics

Lidocaine (lignocaine) decreases the minimum effective concentration of inhalational anaesthetics, *e.g.* nitrous oxide.

Alcohol

Acute, severe alcohol intoxication can centrally depress the cardiovascular system and may thereby prolong lidocaine (lignocaine) elimination half-life.

Structurally related local anaesthetics

Lidocaine (lignocaine) should be used with caution in patients receiving agents structurally related to local anaesthetics.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in Pregnancy - Category A

The safe use of lidocaine (lignocaine) during pregnancy has not been established. Although lidocaine (lignocaine) has been used extensively for surgical procedures during pregnancy with no reports of ill effects to mother or fetus, there are no adequate or well-controlled studies in pregnant women of the effect of lidocaine (lignocaine) on the developing fetus.

Lidocaine (lignocaine) has been effectively used for obstetrical analgesia and adverse effects on the course of labour or delivery are rare. After epidural administration of lidocaine (lignocaine) to women in labour, lidocaine (lignocaine) crosses the placental barrier. However, concentrations in umbilical veins are lower than those found in the maternal circulation. It has been suggested that blood glucose levels should be checked in newborns after obstetric regional anaesthesia.

Fetal bradycardia/tachycardia frequently follows paracervical block and may be associated with fetal acidosis and hypoxia. Occasional cases of perinatal morbidity and mortality have been reported. When the recommended dose is exceeded, the risk of fetal bradycardia increases. Careful monitoring of the fetal heart rate is necessary.

***Category A:** Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.*

Use in lactation

Lidocaine (lignocaine) passes into the breast milk although it would be unlikely that the amount passing to the infant would lead to significant accumulation of the parent drug in the infant. The remote possibility of an idiosyncratic or allergic reaction in the breast fed infant from lidocaine (lignocaine) remains to be determined.

4.7 Effects on ability to drive and use machines

Depending on dosage, local anaesthetic may have a very mild effect on mental function and may temporarily impair locomotion and coordination.

4.8 Adverse effects (undesirable effects)

Adverse effects may be due to high plasma levels as a result of excessive dosage, rapid absorption, delayed elimination or metabolism or inadvertent intramuscular injection during local anaesthetic use, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

Pronounced acidosis or hypoxia may increase the risk or severity of toxic reactions. Such reactions are systemic and may involve the central nervous system and/or the cardiovascular system.

Inadvertent subarachnoid injection during anaesthetic procedures may lead to cardiovascular collapse, CNS depression and respiratory arrest.

Systemic reactions of the following type have been reported:

Central nervous system

CNS manifestations are excitatory and/or depressant and may be characterised by light-headedness, disorientation, confusion, psychosis, nervousness, agitation, drowsiness, dizziness, apprehension, euphoria, tinnitus, hyperacusis, blurred or double vision, nausea, vomiting, difficulty swallowing, dyspnoea, circumoral paraesthesia, numbness of the tongue, slurred speech, sensations of heat or cold, numbness, twitching, tremors, convulsions, unconsciousness, seizures, coma, 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 administration of lidocaine (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 drugs available to manage such patients (see section 4.9 Overdose – Management of adverse effects).

Cardiovascular system

Hypotension, cardiovascular collapse, arrhythmias including ventricular tachycardia/ventricular fibrillation, heart block, and bradycardia that may lead to cardiac arrest. Cardiac arrhythmias and hypertension have also been observed. Methaemaglobinaemia can occur following IV administration. Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with drugs such as a benzodiazepine or a barbiturate. In rare cases, cardiac arrest has occurred without prodromal CNS effects.

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

Haemodynamic

Regional anaesthesia may lead to maternal hypotension.

Allergic

Allergic reactions are characterised by cutaneous lesions, urticaria, oedema or anaphylactoid reactions. Allergy to amide type local anaesthetics is very rare. If such a reaction occurs, it should be managed by conventional means.

The detection of sensitivity by skin testing is of doubtful value.

Neurological system

Adverse neurological reactions occur rarely following the use of local anaesthetics. They may be related to the total dose administered, the particular drug used, the route of administration and the physical status of the patient. Persistent anaesthesia, paraesthesia, weakness, paralysis of the lower extremities and loss of sphincter control may occur.

In a prospective review of 10,440 patients who received lidocaine (lignocaine) for spinal anaesthesia, the incidences were reported to be about 3% each for positional headaches, hypotension and backache; 2% for shivering; and less than 1% each for peripheral nerve symptoms, nausea, respiratory inadequacy and double vision. Many of these observations may be related to local anaesthetic techniques, with or without a contribution from the local anaesthetic.

In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter may occur. Subsequent adverse effects may depend partially on the amount of drug administered subdurally. These may include spinal block of varying magnitude (including total spinal block), hypotension secondary to spinal block, loss of bladder and bowel control and loss of perineal sensation and sexual function. Persistent motor, sensory and/or autonomic (sphincter control) deficit of some lower spinal segments with slow recovery (several months) or incomplete recovery have been reported in rare instances when caudal or lumbar epidural block has been attempted. Backache and headache have also been noted following use of these anaesthetic procedures.

Peripheral nerve injury and arachnoiditis have been observed.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

4.9 Overdose

In anaesthesia, acute emergencies associated with the use of lidocaine (lignocaine) are normally related to high plasma levels, or unintended subarachnoid injection (see sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects (undesirable effects)).

With accidental intravascular injections, the toxic effect will be obvious within one to three minutes. With overdosage, peak plasma concentrations may not be reached for 20 to 30 minutes depending on the site of injection, and toxic signs will be delayed. Toxic reactions mainly involve the central nervous and cardiovascular systems.

Symptoms

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

Acute toxicity: CNS toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are circumoral paraesthesia, numbness of the tongue, lightheadedness, hyperacusis and tinnitus. Visual disturbance and muscular tremors are more serious and precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour.

Unconsciousness and grand mal convulsions may follow. These may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases, apnoea may occur. Acidosis increases the toxic effects of local anaesthetics.

Recovery is due to redistribution of the local anaesthetic drug from the central nervous system and metabolism. Recovery may be rapid unless large amounts of the drug have been injected.

Cardiovascular toxicity: Cardiovascular toxicity indicates a more severe situation. Hypotension, bradycardia, decreased cardiac output, heartblock, arrhythmia and even ventricular arrhythmias, ventricular fibrillation and cardiac arrest may occur as a result of huge systemic concentrations of local anaesthetics.

Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with drugs such as a benzodiazepine or a barbiturate. In rare cases, cardiac arrest has occurred without prodromal CNS effects.

Management of adverse effects

Treatment of toxicity should be to discontinue administration of lidocaine (lignocaine). Institute emergency resuscitative procedures and administer the emergency drugs necessary to manage the situation. Adequate ventilation of the patient (including oxygen if necessary) should be ensured and convulsions should be arrested if present. Adequacy of the circulation should then be evaluated, bearing in mind that drugs used to treat convulsions depress the circulation when administered intravenously.

For severe convulsions, small increments of diazepam or a short acting barbiturate such as thiopentone should be administered. Suxamethonium will stop the muscle convulsions rapidly but will require tracheal intubation and controlled ventilation, and should only be used by those familiar with these procedures. If ventricular fibrillation or cardiac arrest occurs, effective cardiovascular resuscitation treatment must be instituted and maintained for a prolonged period if necessary. Optimal oxygenation and ventilation, and circulatory support as well as treatment of acidosis are of vital importance. If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, chronotropic and or inotropic agents should be considered. Children should be given doses commensurate with age and weight.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class

Local anaesthetic of the amide type and antiarrhythmic drug.

Mechanism of action

Lidocaine (lignocaine) stabilises all potentially excitable membranes and prevents the initiation and transmission of nerve impulses. This produces a local anaesthetic effect. Onset of action is rapid and blockade may last from 60 - 90 minutes. Studies of the effects of therapeutic concentrations of lidocaine (lignocaine) on the electrophysiological properties of mammalian Purkinje fibers have shown that lidocaine (lignocaine) attenuates phase 4 diastolic depolarisation, decreases automaticity, and causes a decrease or no change in excitability and membrane responsiveness. Action potential duration and effective refractory period of Purkinje fibers are decreased, while the ratio of effective refractory period to action potential duration is increased. Action potential duration and effective refractory period of ventricular muscle are also decreased. Effective refractory period of the AV node may increase, decrease, or remain unchanged, and atrial effective refractory period is unchanged. Lidocaine (lignocaine) raises the ventricular fibrillation threshold. No significant interactions between lidocaine (lignocaine) and autonomic nervous system have been described and, consequently, lidocaine (lignocaine) has little or no effect on autonomic tone.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Lidocaine (lignocaine) has a rapid onset and a medium duration of action. The onset of action is 1 to 5 minutes following infiltration and 5 to 15 minutes following other types of administration.

The rate of absorption depends upon the dose, the route of administration and the vascularity of the injection site. Intercostal blocks give the highest peak plasma concentrations (approximately 1.5 microgram/mL for every 100 mg injected), while abdominal subcutaneous injections give the lowest (approximately 0.5 microgram/mL per 100 mg injected). Epidural and major nerve block produce peak plasma levels intermediate between these.

Absorption of lidocaine (lignocaine) from the epidural space occurs in two phases; the first phase is in the order of 9 minutes and the second is approximately 82 minutes. The slow absorption is the rate limiting step in the elimination of lidocaine (lignocaine), which also explains the apparent elimination half-life following epidural injection being longer than after intravenous administration.

Distribution

The plasma binding of lidocaine (lignocaine) is dependent on drug concentration, and

the fraction bound decreases with increasing concentration. At free base concentrations of 1 to 4 microgram/mL, 60 to 80% of lidocaine (lignocaine) is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein.

Lidocaine (lignocaine) crosses the blood-brain and placental barriers by passive diffusion. Since the degree of plasma protein binding in the fetus is less than that in the mother, although free lidocaine (lignocaine) concentrations will be the same, the total plasma concentration will be greater in the mother.

Lidocaine (lignocaine) has a total plasma clearance of 0.95 L/minute, a volume of distribution at steady state of 91 L, an elimination half-life of 1.6 hours and an estimated hepatic extraction ratio of 0.65. Approximately 90% of a parenteral dose of lidocaine (lignocaine) is rapidly metabolised in the liver by de-ethylation to form monoethylglycinexylidide (MEGX) and glycinexylidide (GX) followed by cleavage of the amide bond to form xylidine and 4-hydroxyxylidine, which are excreted in the urine. Less than 10% of a dose is excreted unchanged in the urine.

Elimination

The principal metabolites, MEGX and GX, also possess pharmacological activity. The rate of metabolism of lidocaine (lignocaine) appears to be limited by hepatic blood flow that may be reduced in patients after acute myocardial infarction and/or congestive heart failure. The rate of lidocaine (lignocaine) metabolism may also be reduced in patients with hepatic tissue necrosis, possibly because of altered perfusion.

The duration of action depends upon the concentration used, the dose given, the nerves to be blocked and the status of the patient. The 2% solution will produce an effect for 1.5 to 2 hours when given epidurally, and up to 5 hours when given as a peripheral nerve block. When used in a 1% concentration there is less effect on motor nerve fibres and the duration of effect is shorter.

5.3 Preclinical safety data

Genotoxicity

The genotoxic potential of 2,6-xylidine has been studied with mixed results: positive results were reported in assays of gene mutations (weakly positive in the Ames test with metabolic activation and in the mouse lymphoma assay) and chromosomal damage (chromosomal aberrations in Chinese hamster ovary cells at concentrations at which the drug is precipitated from solution). No evidence of genotoxicity was found *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*.

Carcinogenicity

A two year oral toxicity study of 2,6-xylidine, a metabolite of lidocaine (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. The compound also caused subcutaneous fibromas and/or fibrosarcomas in male and female rats (significant at 150 mg/kg).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injections

6.2 Incompatibilities

Although no specific incompatibilities have been reported the introduction of any additive requires caution. Do not administer unless the solution is clear.

6.3 Shelf life

Please refer to outer carton for expiry date.

6.4 Special precautions for storage

Please refer to outer carton for storage condition.

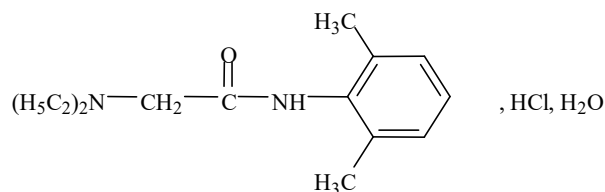
Local anaesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precautions should be taken to avoid prolonged contact between Lignocaine Injection solutions and metal surfaces such as metal bowls, cannulae and syringes with metal parts.

6.5 Nature and contents of container

Lidocaine (lignocaine) injection is available in LDPE ampoule with 2% 100 mg in 5 mL (sterile) Steriluer® (50s).

6.6 Physicochemical properties

Chemical structure



Chemical name: 2-diethylamino-2',6'-dimethylacetanilide hydrochloride monohydrate

Molecular formula: $C_{14}H_{22}N_2O \cdot HCl \cdot H_2O$

Molecular weight: 288.8

CAS number

6108-05-0

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