

PRODUCT MONOGRAPH

XYLOCARD[®] 100 mg

20 mg/mL

(lidocaine hydrochloride injection USP)

Antiarrhythmic

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THERAPEUTIC CLASSIFICATION

Antiarrhythmic

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mode of action of the antiarrhythmic effect of XYLOCARD (lidocaine hydrochloride) appears to be similar to that of procaine, procainamide, and quinidine. Ventricular excitability is depressed and the stimulation threshold of the ventricle is increased during diastole. The sinoatrial node is, however, unaffected. In contrast to the latter three drugs, XYLOCARD in therapeutic doses does not produce a significant decrease in arterial pressure or in cardiac contractile force. In larger doses, XYLOCARD may produce circulatory depression, but the magnitude of the change is less than that found with comparable doses of procainamide. Neither drug appreciably affects the duration of the absolute refractory period.

Onset of Action

The onset of action following a single intravenous injection varies from 45 to 90 seconds. Duration of action is 10 to 20 minutes.

INDICATIONS AND CLINICAL USE

The intravenous administration of XYLOCARD (lidocaine hydrochloride) is indicated in the treatment of ventricular tachycardia occurring during cardiac manipulation, such as surgery or catheterization, or which may occur during acute myocardial infarction, digitalis toxicity, or other cardiac diseases.

CONTRAINDICATIONS

XYLOCARD (lidocaine hydrochloride) is contraindicated in patients with:

1. Known hypersensitivity to local anesthetics of the amide type, such as prilocaine, mepivacaine or bupivacaine, or to other components of the solution;
2. Adams-Stokes syndrome, or severe degrees of sinoatrial, atrioventricular or intraventricular block.

The safety of XYLOCARD in the treatment of arrhythmias in children has not been established.

WARNINGS

Constant ECG monitoring is essential for the proper administration of XYLOCARD (lidocaine hydrochloride) intravenously. Signs of excessive depression of cardiac conductivity, such as prolongation of PR interval and QRS complex, and the appearance of aggravation of arrhythmias, should be followed by prompt cessation of the intravenous infusion.

It is mandatory to have emergency resuscitative equipment and drugs immediately available to manage possible adverse reactions involving the cardiovascular, respiratory, or central nervous systems.

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 benefits outweigh the possible risks. If possible, emergency resuscitative equipment and drugs should be available.

PRECAUTIONS

XYLOCARD (lidocaine hydrochloride) should be used with caution in patients with bradycardia, severe digitalis intoxication, first or second degree heart block in the absence of a pacemaker, or hypokalaemia (see CONTRAINDICATIONS and WARNINGS).

In unconscious patients circulatory collapse should be watched for, since CNS effects may not be apparent as an initial manifestation of toxicity.

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

Intravenous administration of XYLOCARD is sometimes accompanied by a hypotensive response, and, in overdosage, this may be precipitous. For this reason the intravenous dose should not exceed 100 mg in a single injection, and no more than 200-300 mg in a one hour period (see DOSAGE and ADMINISTRATION).

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

Repeated doses of XYLOCARD 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 and acutely ill patients should be given reduced doses commensurate with their age and physical condition. XYLOCARD should also be used with caution in patients with epilepsy, impaired cardiac conduction, bradycardia, impaired hepatic function or renal function and in severe shock.

Use in the Elderly

A reduction in dosage may be necessary for elderly patients, particularly those with compromised cardiovascular and/or hepatic function and/or prolonged infusion. Elderly patients should be given reduced doses corresponding to their age and physical status.

Impaired Renal Function

Caution should be employed in the repeated use of XYLOCARD in patients with severe renal disease, since possible accumulation of lidocaine or its metabolites may lead to toxic phenomena.

Impaired Hepatic Function

Caution should be employed in the repeated use of XYLOCARD in patients with severe liver disease, since possible accumulation of lidocaine or its metabolites may lead to toxic phenomena.

Use in Pregnancy

It is reasonable to assume that lidocaine has been used, mainly as a local anesthetic, by a large number of pregnant women and women of child-bearing age. No specific disturbances to the reproductive process have so far been reported, e.g., no increased incidence of malformations. However, care should be taken during early pregnancy when maximum organogenesis takes place.

There are no adequate and well-controlled studies with intravenous administration of lidocaine in pregnant women.

Use in Nursing Mothers

Lidocaine is excreted in the breast milk, but in such small quantities that there is generally no risk of affecting the infant at therapeutic dose levels.

Use in Neonates

Through their lower enzyme capacity, *very rarely*, neonates are at risk of methaemoglobinaemia. Methaemoglobinaemia can become clinically overt (cyanosis), and treatment with methylene blue may be considered necessary.

Use in Patients with Acute Porphyria

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

Drug Interactions

Potential for the influence of lidocaine on the plasma levels/effect of other drugs

Lidocaine is metabolized by cytochromes P4501A2 (CYP1A2) and P4503A4 (CYP3A4) and thus has the potential to inhibit the metabolism of other drugs metabolized by these isoenzymes, resulting in increased plasma levels of these. This has so far not been reported for any CYP1A2 or CYP3A4 substrate.

Potential for the influence of other drugs on the plasma levels/effect of lidocaine

Concomitant treatment with drugs 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 lidocaine. Concomitant administration with the substrate amiodarone has resulted in increased plasma levels of lidocaine resulting in toxic effects.

During concomitant administration with carbamazepine, phenobarbital, and phenytoin which are inducers of CYP3A4, decreased plasma levels of lidocaine have been reported. Primidone has also been reported to induce the metabolism of lidocaine.

Cimetidine has an unspecific inhibitory effect on CYP (including CYP 3A4) mediated metabolism. It reduces liver blood flow and thus systemic clearance of drugs that are highly extracted by the liver. Clinical experiments showed that the concomitant administration of cimetidine reduces the systemic clearance of lidocaine and increases lidocaine serum concentration by as much as 50%. Thus, therapeutic serum levels of lidocaine may rise to toxic levels when cimetidine is used concomitantly. Ranitidine has not displayed this effect.

Coadministration with inhibitors of CYP1A2, such as fluvoxamine, drastically reduced the elimination of lidocaine in healthy subjects.

CYP1A2 is the isoenzyme shown most consistently to be decreased in human cirrhosis and hence makes smaller contribution in lidocaine metabolism than in patients with normal liver function.

Concomitant treatment with metoprolol, nadolol, and propranolol have also been reported to increase the plasma levels of lidocaine resulting in toxic effects. Administration of

propranolol during infusion of lidocaine may increase the plasma concentration of lidocaine by about 30%. Patients already receiving propranolol tend to have higher lidocaine levels than controls. The combination should be avoided.

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.

ADVERSE REACTIONS

Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide type agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage or rapid absorption, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

Common adverse reactions are those from the central and peripheral nervous system. They occur in 5-10% of the patients and are mostly dose-related. The following definitions of frequencies are used: Very common ($\geq 10\%$), common (1 – 9.9%), uncommon (0.1 – 0.9%), rare (0.01 – 0.09%) and very rare ($< 0.01\%$).

Systemic reactions of the following types have been reported:

Central Nervous System

CNS manifestations are excitatory and/or depressant. Common adverse reactions are circumoral paresthesia, dizziness and drowsiness. Rare adverse reactions would include persistent dizziness, lightheadedness, nervousness, apprehension, euphoria, confusion, hyperacusis, tinnitus, blurred vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, apnea, 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 lidocaine plasma level and may occur as a consequence of rapid absorption.

Cardiovascular System

Rare cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, asystole and cardiovascular collapse which may lead to cardiac arrest. Arrhythmias, including ventricular tachycardia/ventricular fibrillation have also been reported.

Hematologic System

Very rarely, neonatal methaemoglobinaemia can occur (see Precautions).

Immune System

Allergic reactions are characterized by cutaneous lesions, urticaria, edema, or in the most severe and very rare instances, hypersensitivity including anaphylactic shock. Allergic reactions of the amide type are rare and may occur as a result of sensitivity either to the drug itself, or to other components of the formulation.

Idiosyncratic reactions have been reported at low doses in some patients. Cross-sensitivity between XYLOCARD and procainamide or XYLOCARD and quinidine have not been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms of overdose or idiosyncratic reactions are described under ADVERSE REACTIONS.

Symptoms

Central nervous system toxicity is a graded response, with symptoms and signs of escalating severity. The first symptoms are circumoral paresthesia, numbness of the tongue, lightheadedness, hyperacusis and tinnitus. Visual disturbance and muscular tremors are more serious and precede the onset of generalized convulsions. Unconsciousness and grand mal convulsions may follow, which 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. In severe cases apnea may occur. Acidosis increases the toxic effects.

Recovery is due to redistribution and metabolism of the drug. Recovery may be rapid unless large amounts of the drug have been administered.

Cardiovascular effects may be seen in cases with high systemic concentrations. Severe hypotension, bradycardia, arrhythmia and cardiovascular collapse may be the result in such cases.

Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anesthetic or is heavily sedated with drugs such as a benzodiazepine or barbiturate.

Treatment

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. 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.

An anticonvulsant should be given i.v. if the convulsions do not stop spontaneously in 15-20 seconds. Thiopental 100-150 mg i.v. will abort the convulsions rapidly. Alternatively, diazepam 5-10 mg i.v. may be used, although its action is slower. Succinylcholine 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.

Hypotension may be counteracted by giving sympathicomimetic drugs (e.g., adrenaline). Adrenergic agents of both α -adrenoceptor stimulating (e.g., metaraminol) and β -adrenoceptor stimulating type (e.g., isoprenaline) are generally effective. The bradycardia may be treated with parasympatholytic agents (e.g., atropine).

Should circulatory arrest occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance, since hypoxia and acidosis will increase the systemic toxicity of local anesthetics. Epinephrine (0.1-0.2 mg as intravenous or intracardial injections) should be given as soon as possible and repeated, if necessary.

DOSAGE AND ADMINISTRATION

Single Intravenous Injection

The usual dose is 50 to 100 mg XYLOCARD (lidocaine hydrochloride) administered under ECG and blood pressure monitoring. This dose may be administered at the rate of approximately 25 to 50 mg/min. Sufficient time should be allowed to enable a slow circulation to carry the drug to the site of action. If the initial injection of 50 to 100 mg does not produce a desired response, a second dose may be repeated after 10 minutes. **NO MORE THAN 200 TO 300 MG OF XYLOCARD SHOULD BE ADMINISTERED DURING A ONE HOUR PERIOD.**

Continuous Intravenous Infusion

Following intravenous injection, XYLOCARD may be administered by intravenous infusion at a rate of 1-2 mg/min (approximately 15-30 μ g/kg/min in the average 70 kg patient) in those patients in whom the arrhythmia tends to recur, and who are incapable of receiving oral antiarrhythmic therapy.

Intravenous infusions of XYLOCARD must be administered under constant ECG and blood pressure monitoring and with meticulous regulation of infusion rate, in order to avoid potential overdosage and toxicity.

Intravenous infusions should be terminated as soon as the patient's basic cardiac rhythm appears to be stable or at the earliest signs of toxicity. It should rarely be necessary to continue intravenous infusion beyond 24 hours. As soon as possible, and when indicated, patients should be changed to an oral antiarrhythmic agent for maintenance therapy.

Solution for intravenous infusion may be prepared by the addition of one gram of XYLOCARD (i.e., contents of ten 5 mL ampoules) to one litre of an appropriate infusion solution. Approximately a 0.1% solution will result from this procedure; that is, each mL will contain approximately 1 mg of XYLOCARD.

In those cases in which fluid restriction is medically desirable a more concentrated solution may be prepared by adding one gram of XYLOCARD (i.e., contents of ten 5 mL ampoules) to 500 mL of diluent. Approximately a 0.2% solution will result from this procedure; that is, each mL will contain approximately 2 mg of XYLOCARD.

Solutions should be prepared using aseptic technique. As with all intravenous admixtures, dilution should be made just prior to administration. Prepared solutions should be used within 12 hours.

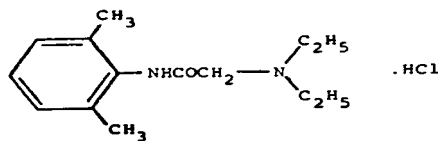
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Lidocaine hydrochloride

Chemical Name: 2-(Diethylamino)-2',6'-acetoxylidide monohydro-chloride monohydrate

Structural Formula:



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

Molecular Weight: 288.82

Description: Lidocaine hydrochloride is a white, odourless, crystalline powder which has a slightly bitter taste. It is very soluble in water and in alcohol, soluble in chloroform and insoluble in ether.

Composition/mL

XYLOCARD

100 mg

Active:

Lidocaine hydrochloride 20 mg

XYLOCARD

100 mg

Non-medicinal:

Sodium chloride 6 mg
for (isotonicity)

Water for
injection

Sodium hydroxide and/or hydrochloric acid to adjust pH to 5.0-7.0.

Stability and Storage Recommendations

Store at room temperature (15-30°C).

XYLOCARD solutions are preservative free and are for single use. Discard unused portion.

AVAILABILITY OF DOSAGE FORMS

Single Intravenous Injection

XYLOCARD 100 mg is available in a 5 mL glass ampoule (contains 20 mg/mL, a 2% solution).

Continuous Intravenous Infusion

5% dextrose in water is the preferred diluent.

See DOSAGE and ADMINISTRATION section for instructions regarding preparation of solutions for continuous intravenous infusion.

PHARMACOLOGY

Lidocaine hydrochloride is a well known anesthetic agent which has been used for many years for regional and topical anesthesia. However, it has been demonstrated to exert an antiarrhythmic effect by increasing the electrical stimulation threshold of the ventricle during diastole.

In decerebrated, vagotomized cats with stellate ganglia destroyed, lidocaine hydrochloride intravenous suppressed cardiac arrhythmias induced by faradic stimulation, barium chloride and epinephrine. The minimal effective dose was 0.5 mg per kg. This was 4 and 5 times less than the minimal doses of procaine and procainamide respectively.

In anesthetized open-chest dogs, lidocaine hydrochloride 5 mg per kg intravenously reduced the duration of methacholine-induced auricular arrhythmias by 55.5%. The effect of quinidine sulphate at the same dose was a reduction 46.5%. Ventricular arrhythmias induced by coronary ligation were controlled by total intravenous doses of 50 mg/kg. Convulsions and vomiting were produced and death occurred in 1 of 6 dogs at 75.5 mg/kg. In the same

preparation, interruption of the arrhythmia was obtained by an injection of 15 mg/kg directly into the ventricle. In normothermic or hypothermic dogs the same effect was obtained in ventricular fibrillation induced by mechanical stimulation.

In anesthetized dogs, intravenous infusions of 40-80 mg converted digitalis-induced ventricular arrhythmia to sinus rhythm. Also, acetylstrophanthidin-induced ventricular tachycardia was suppressed at a minimal effective dose of lidocaine hydrochloride of 1 mg/kg intravenously. Digitalis-induced ventricular tachycardia, which failed to respond to electroshock was converted to normal sinus rhythm by intravenous injection of lidocaine hydrochloride 100 mg and ventricular tachycardia, induced by ouabain, was converted to supraventricular tachycardia by intravenous injection of 1-2 mg/kg.

In unanesthetized dogs with ventricular arrhythmia induced by coronary occlusion, intravenous injections of 5-10 mg/kg suppressed the arrhythmia. This effect could be maintained by intravenous infusion with calculated lidocaine hydrochloride blood levels of 1-3 µg/mL.

Other effects in anesthetized intact dogs were depression of myocardial contractile force, heart rate and femoral arterial pressure with lidocaine hydrochloride 0.5 to 6 mg/kg intravenously. At 2.0 mg/kg intra-arterially the same effects were obtained but there was less diminution of contractile force. In both anesthetized and conscious dogs, lidocaine hydrochloride in rapid intravenous injection of 2, 4 and 8 mg/kg caused transient decrease of systolic arterial pressure, venous pressure, cardiac output, mean ejection rate, rate of development of arterial pressure, stroke work and calculated peripheral resistance. Heart rate was slightly increased. Effects were greatest at 8 mg/kg and were more pronounced and of longer duration in anesthetized dogs. There was return to basal levels in 3-5 minutes.

Absorption, Distribution and Excretion

In rats which received ¹⁴C-labelled lidocaine hydrochloride by intravenous injection, rapid uptake by all tissues was noted. Tissue distribution studies in monkeys have indicated: high affinity for lung, spleen, kidney, stomach and adipose tissue; moderate affinity for brain and most gastrointestinal organs; and low affinity for musculoskeletal tissue and skin. Similar distribution has been observed in the dog.

Studies on plasma binding in monkey and man have indicated approximately 60% plasma binding within the plasma concentration range usually seen in clinical use. However, plasma binding was markedly reduced at concentrations of lidocaine hydrochloride exceeding 10 µg/mL, presumably due to saturation of the binding sites.

Studies in rabbit and rat have demonstrated that the liver is the principal site of metabolism. In man, hepatic clearance studies have shown that approximately 70% of the lidocaine hydrochloride passing through the liver was extracted. Microsomal enzyme systems are primarily responsible for hepatic metabolism. The major degradative pathway appears to be by conversion to monoethylglycinexylidide, followed by hydrolysis to 2,6-xylidine; further conversion to 4-hydroxy-2,6-xylidine appears to occur in man.

Up to 10% of administered lidocaine hydrochloride may be excreted in the urine as unchanged drug. Although biliary secretion and intestinal absorption of lidocaine hydrochloride metabolites have been reported in rats, there is no evidence of biliary secretion in man.

The pharmacokinetics of lidocaine hydrochloride has been studied in normal subjects and in patients.

Following a single intravenous injection, or termination of a continuous intravenous infusion, declining plasma concentration follows a biphasic curve. Plasma half-lives of 8 to 15 minutes have been reported for the initial phase. Various studies have reported the mean half-life at the terminal phase to be in the range 1.2 to 1.9 hours. The minimum effective antiarrhythmic plasma concentration of lidocaine hydrochloride has been reported to be in the range of 1.0 to 1.2 µg/mL; concentrations higher than 5-6 µg/mL are associated with an increased risk of toxicity.

TOXICOLOGY

Acute Toxicity

| SPECIES | SEX | ROUTE | LD ₅₀ (mg/kg) |
|------------|-------|-------|--------------------------|
| mice | F | i.v. | 17.9 |
| mice | F | i.p. | 164 |
| mice | F | i.m. | 200 |
| mice | M | i.m. | 154 |
| rat | F | i.v. | 19.7 |
| rat | M | i.v. | 21.4 |
| dog | M & F | i.m. | 100 |
| guinea pig | F | i.m. | 73 |
| guinea pig | M | i.m. | 67 |
| rabbit | M | i.m. | 450 |

Acute intravenous studies were performed in rabbits which received six serial injections of 1, 2, 3, 4 or 5 mg/kg at 15 minute intervals. At the 2 mg/kg dose level, slight depression was seen, beginning with the third injection. At 3 mg/kg there was depression and rigid extension of limbs after the last 5 injections. At 5 mg/kg there was severe depression and rigid limb extension after each injection; loss of righting reflex and convulsions began with the second injection and there was gasping for breath after each of the last injections.

Dogs were given intravenous incremental doses at 30 minute intervals until death occurred. Doses of 0.1 to 3.0 mg/kg were tolerated with minimal CNS or cardiovascular effects. Convulsions, mydriasis, salivation, urination and defecation were observed after 10 mg/kg.

Respiratory arrest and death occurred in one dog after 30 mg/kg; cardiovascular collapse, respiratory arrest and death occurred in remaining animals after 100 mg/kg. Mean arterial blood pressure and heart rate increased briefly, beginning at 3.0 mg/kg, and decreased after 100 mg/kg. Myocardial conduction time was not significantly changed prior to 100 mg/kg administration.

Acute local responses were studied in rats and rabbits following single intramuscular injections of 2%, 4%, 6%, 8% and 10% solutions of lidocaine hydrochloride. Microscopic examination revealed inflammatory changes with all solutions. In general, reactions produced by 2% solutions were least, although lesions seen with all other concentrations were of similar degree.

In rabbits sacrificed seven days after intramuscular administration, there was evidence of marked muscle fiber regeneration; after 30 days there was virtually complete resolution of inflammatory changes at the site of injection.

Subacute Toxicity

In one study, dogs received daily intravenous injections according to the following schedule: 0.1 mg/kg for 7 days, 0.3 mg/kg for 7 days, 1 mg/kg for 7 days and 3 mg/kg for 21 days. Mild transient convulsions were seen in one dog at the high dose level. No other signs of toxicity were observed. Gross and microscopic examination at autopsy did not reveal any drug related effects.

In a second study, dogs received daily intravenous injections of 2.5, 5 or 10 mg/kg for 28 days. No overt symptoms were observed at the low dose level. At the 5 mg/kg level there was transient sedation, ataxia, head tremor, prostration and emesis. At the 10 mg/kg level there were severe tremors, muscular weakness, ataxia, prostration and convulsions, although animals recovered within 5-10 minutes. No ECG or hemochemistry changes were seen. No evidence of drug-related pathology was seen at autopsy. Injection sites showed inflammatory changes in drug and saline-treated animals.

In rats which received daily intravenous doses of 1.5, 4.5 or 15.0 mg/kg for 14 days, overt effects were observed only at the 15.0 mg/kg level, at which convulsions and death occurred. Increased blood glucose levels were seen in male rats at all dose levels. At autopsy, no changes were attributed to drug treatment. Mild inflammatory changes were seen at injection sites.

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