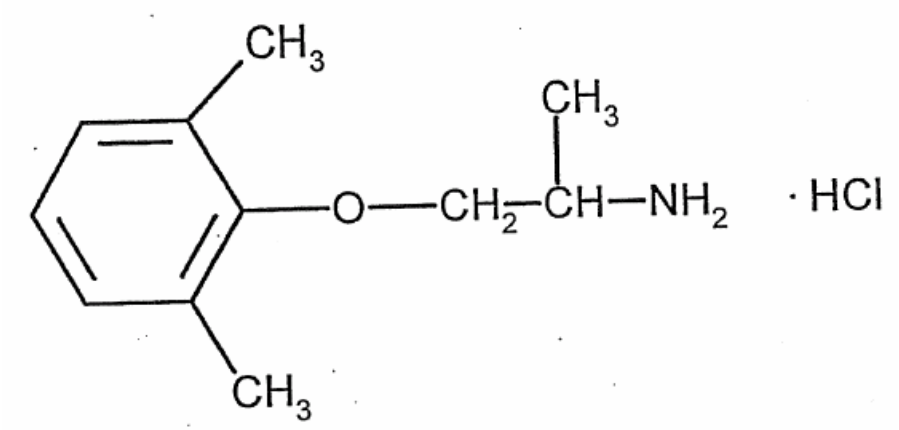
MEXITIL®

for the management of ventricular arrhythmias

NAME OF THE MEDICINE

Mexiletine hydrochloride. The chemical name for mexiletine hydrochloride is 1-methyl-2-(2-6-xylyloxy)ethylamine hydrochloride. The molecular formula is $C_{11}H_{17}NO.HCl$ and the molecular weight is 215.73. The CAS number for mexiletine hydrochloride is 5370-01-4. Mexiletine hydrochloride has the following structural formula:



DESCRIPTION

Mexitil structurally resembles the local anaesthetic agent lignocaine.

Mexiletine hydrochloride is a white to off-white crystalline substance. It is freely soluble in water, methanol and absolute ethanol and sparingly soluble in chloroform and methylene chloride.

In addition to mexiletine hydrochloride, Mexitil capsules contain the following ingredients - magnesium stearate, maize starch, colloidal anhydrous silica, gelatin and the colouring agents CI173015 indigocarmine, titanium dioxide and CI45430 erythrosine. Mexitil M50 capsules also contain the following colouring agent, CI77499 iron oxide black.

PHARMACOLOGY

Mexitil structurally resembles the local anaesthetic agent lignocaine, however Mexitil is absorbed to therapeutically active levels from the gastrointestinal tract and can therefore be given orally. Mexitil can also be differentiated from lignocaine by its longer duration of action.

Mexitil is virtually completely absorbed following oral administration with peak plasma concentrations occurring within 2-4 hours. Delayed or incomplete absorption is associated with myocardial infarction and the use of narcotic analgesics.

The therapeutic plasma range is 1-2 micrograms/mL and in healthy volunteers the half-life of Mexitil in plasma is approximately 10 hours. The plasma half-life varies according to the status of the patient and has been found to extend up to 20 hours in some patients.

Studies have shown that at serum concentrations of 0.2-2.3 micrograms/mL the mean binding to serum proteins is 56 ± 5.3%. The amount bound is relatively insignificant with respect to the total amount of drug in the body and so reduces the risk of interactions caused by displacement of Mexitil from plasma proteins by other drugs.

Mexitil is extensively metabolised in man primarily by oxidative and reductive processes and is eliminated as unchanged drug and metabolites. Nine metabolites have been detected, the major ones being parahydroxymexiletine, hydroxymethylmexiletine and their corresponding alcohols.

Mexitil and its metabolites are excreted mainly via the urine. 10-15% is excreted in the urine as unchanged drug within 72 hours of oral administration.

Mexitil effectively suppresses experimentally induced arrhythmias in 3 accepted animal models - ouabain-induced ventricular fibrillation, halothane/adrenaline induced ectopic beats and coronary artery ligation. At concentrations in excess of those necessary to suppress arrhythmias in man, both lignocaine and Mexitil slow the conduction velocity and there is some depression of the contraction amplitude. In contrast to lignocaine, however, Mexitil lessens the duration of the effective refractory period.

In man, Mexitil is classified as a Class I antiarrhythmic since it depresses the maximum rate of myocardial depolarisation with little or no modification of resting potentials or the duration of action potentials. Haemodynamically, Mexitil may exhibit a mild and dose related negative inotropism, not dissimilar to lignocaine. This effect is enhanced when used in situations of impaired ventricular function.

Clinical studies have shown that Mexitil effectively suppresses ventricular arrhythmias associated with myocardial infarction, ischaemic heart disease, digitalis toxicity and prosthetic heart valves. So-called idiopathic arrhythmias have also proved amenable to control. Specific abnormalities of rhythm that have been treated include ventricular ectopic beats, uni or multi-focal ectopic beats, ventricular bigemini, R on T ectopics and ventricular tachycardia, flutter and fibrillation. In a few cases, supraventricular arrhythmias have been controlled.

INDICATIONS

Documented ventricular arrhythmias, such as sustained ventricular tachycardia, which are judged to be life-threatening. Because of the proarrhythmic potential of antiarrhythmic drugs, the use of mexiletine is not recommended for lesser arrhythmias. Treatment of asymptomatic ventricular premature contractions should be avoided. In patients with structural heart disease, proarrhythmia and cardiac

decompensation are a special risk associated with antiarrhythmic drugs. Special caution should be exercised when prescribing mexiletine for these patients.

CONTRAINDICATIONS

Mexitil should not be used in the first three months following myocardial infarction or where cardiac output is limited (left ventricular stroke work of less than 35%), except in patients with life-threatening ventricular arrhythmias.

Mexitil is contraindicated in the presence of cardiogenic shock or pre-existing second or third degree AV block if no pacemaker is present.

Mexitil should not be used in known cases of hypersensitivity to mexiletine or local anaesthetics eg. lignocaine, procaine.

If Mexitil is used in the following situations, the patient should be carefully monitored: sinus node dysfunction, conduction defect, bradycardia, hypotension or cardiac, renal or hepatic failure (see also "PRECAUTIONS").

PRECAUTIONS

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 6 days but less than 2 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 10 months. While there are no comparable mortality trial data for other Class I antiarrhythmic agents post myocardial infarction, meta-analysis of small scale clinical trials of these agents in similar populations suggests a trend toward increased mortality compared to placebo.

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

In the light of this information, it is prudent to consider the prophylactic use of Class I antiarrhythmic drugs following myocardial infarction as potentially hazardous.

1. Because of the conditions in which Mexitil is used, patients will usually be under observation with particular regard to ECG and blood pressure. Routine laboratory monitoring is also advisable although disturbances of renal and hepatic function or appearance of anti-nuclear factor have not been a feature even of long term treatment.

2. Patients with sinus node dysfunction conduction defect, bradycardia, hypotension or cardiac failure will require careful monitoring. A reduction in Mexitil dosage may be required.

3. Patients with uncompensated liver cirrhosis show evidence of delayed breakdown and elimination rates of Mexitil. This may also occur in patients with severe renal failure. In these patients, the Mexitil dosage must be adjusted on an individual basis.

4. Patients in whom pathologically high liver values have been established or who have signs or symptoms of impaired liver function, should be monitored carefully.

5. Careful monitoring is also recommended in patients with convulsive disorders.

6. The duration of treatment required in any patient is variable and although no precise guide can be given, withdrawal of treatment may be attempted after a suitable period free of arrhythmia. Gradual withdrawal i.e. over 1 to 2 weeks is preferable as arrhythmias which have been satisfactorily controlled may recur.

7. As Mexitil is largely excreted renally in a pH-dependent fashion, increasing with low pH, any change to the patient's acid-base balance may require readjustment of the Mexitil dosage. Normal physiological variation in urine pH may affect the plasma half-life or steady state plasma concentrations.

8. Mexitil may potentiate tremor in patients with Parkinsonism.

9. Mexitil may impair a patient's ability to drive or operate machinery. Concomitant administration with alcohol will enhance this effect.

Use in Pregnancy Category B1

As with all drugs, care is recommended during pregnancy. Mexitil should only be used in pregnancy if the potential benefit justifies the potential risk.

Use in Lactation

Mexitil appears in breast milk in concentrations which may have an effect on the infant. If the use of Mexitil is deemed essential for the mother, an alternative method of infant feeding should be considered.

Interactions with other medicines

General

Drugs, such as the opiates, which affect gastrointestinal movement may effect the absorption of Mexitil.

Drugs which markedly acidify or alkalise urine should be avoided because they may enhance or reduce respectively, the rate of drug excretion and the plasma concentration of mexiletine.

Other Antiarrhythmic Drugs

Where there is concurrent administration of Mexitil and other antiarrhythmic drugs, a heightened effect on conduction and contractility of the heart is to be expected. Caution is, therefore, advised as animal studies indicate a synergistic effect particularly if the drugs are given intravenously.

Combinations with propranolol and quinidine have been used.

Liver Enzyme Inhibitors/Inducers

Since Mexitil is mainly metabolised by the liver, drugs which affect liver function may alter the concentration of Mexitil in the blood. In particular interactions with the two cytochrome P450 isoenzymes CYP1A2 and CYP2D6 have to be considered. Hence, the concurrent administration of Mexitil with drugs which inhibit liver enzymes may require a reduction in the dose of Mexitil. Similarly, the administration of Mexitil with drugs such as rifampicin which induce liver enzymes may require an increase in the dose of Mexitil.

Warfarin

An increased tendency to bleed has been observed when Mexitil has been administered to some patients stabilised on warfarin.

Local anaesthetic agents

Local anaesthetic toxicity may occur in patients who receive Mexitil and local anaesthetic agents concurrently.

Theophylline

Concurrent administration of Mexitil with theophylline will increase serum levels of theophylline.

Caffeine

Concurrent administration of Mexitil with caffeine will increase serum levels of caffeine.

Alcohol

See "PRECAUTIONS" (No. 9).

ADVERSE EFFECTS

Side effects are mainly related to plasma concentration and may therefore be seen during the initial phase of treatment when fluctuation may occur before the blood and tissue concentrations reach equilibrium. Delaying the next dose allows the plasma concentration to fall and usually reduces the side effects.

Mexiletine is a narrow therapeutic index drug and many adverse effects are dose related. The most common adverse effects are dose related. The most common adverse effects are related to gastrointestinal tract and CNS.

Mexiletine can exacerbate pre-existing arrhythmias and cardiac failure.

Oesophageal ulcerations may occur if Mexitil capsules are swallowed without adequate liquid and become lodged in the oesophagus.

The following side effects have been reported during the use of Mexitil:

Blood and the lymphatic system disorders
leucopenia, neutropenia, agranulocytosis, and thrombocytopenia

Immune system disorders
allergic reactions, lupus-like symptoms, drug induced hypersensitivity syndrome, potentially with fatal outcome.

Psychiatric disorders
confusion, somnolence, hallucination, psychotic disorders

Nervous system disorders
tremor, dizziness, drowsiness, nystagmus, paraesthesia, ataxia, convulsion, speech disorder, dysarthria

Eye disorders
abnormal vision, blurred vision, diplopia

Cardiac disorders
palpitations, arrhythmia, bradycardia, atrial fibrillation, all grades of AV-blockade (in isolated cases with syncope), cardiac failure, ventricular arrhythmia, worsening of arrhythmia, worsening of pre-existing heart failure

Vascular disorders
hypotension

Respiratory, thoracic and mediastinal disorders
lung infiltration, pulmonary fibrosis

Gastrointestinal disorders
heartburn, dyspepsia, nausea, vomiting, oesophageal ulceration , hiccoughs, retching, taste perversion

Hepato-biliary disorders
hepatocellular damage, hepatic function abnormal, hepatic necrosis

Skin and subcutaneous tissue disorders

rash, erythroderma, Stevens-Johnson-Syndrome

General disorders

hot flush

Investigations

antinuclear antibodies positive, liver function test abnormal

DOSAGE AND ADMINISTRATION

The dosage of Mexitil must be individualised on the basis of response and tolerance, both of which are dose related. Satisfactory control can be achieved in most patients with a 3 times daily dose every 8 hours. It is important that Mexitil capsules are swallowed with ample liquid, preferably with the patient in an upright position. It is advisable to take Mexitil after food.

Mexitil 200 mg capsules are the standard dosage form for adult use. To assist dosage titration the 50 mg capsule is available, designated as Mexitil M 50. The following regimen is suggested as a guideline. However, dosage may need to be modified if the age, weight or clinical status of the patient dictates.

a) Loading dose:

Give 400 mg Mexitil. An initial loading dose of 400 mg is usually adequate.

b) Maintenance dose:

Give 200–250 mg Mexitil 3 times daily commencing 2 hours after the loading dose. The usual daily dose is between 600–800 mg in divided doses. However, if the therapeutic effect is achieved but side effects are troublesome, dosage may be reduced, since as little as 100 mg 3 times daily has been shown to produce effective plasma levels in some patients.

General Notes

a) The loading dose regime is designed to compensate for the rapid phase of tissue distribution which occurs.

b) Side effects are more likely to be encountered during the initial tissue loading phase.

c) If the optimal therapeutic effect is not achieved, the dosage may be increased, side effects permitting. For example, an additional dose of 200 mg may be given 2 hours after the loading dose, starting the standard maintenance dose of 200–250 mg 3 times daily 2 hours later.

d) The 50 mg capsule is available in order that a more precise dose titration may be undertaken should this be required. Smaller increments will also reduce the incidence of side effects.

Adjustment of Mexitil treatment
In patients with decompensated liver cirrhosis and in those with severe renal failure a dose reduction should be considered on an individual basis.

Adjustment of antiarrhythmic treatment in patients suffering from ventricular arrhythmias may only be carried out by monitoring (e.g. ECG, blood pressure) and where the appropriate cardiological emergency equipment is available. It is recommended that this control be carried out over a period of at least 24 hours.

OVERDOSAGE

Symptoms
Cardiac arrest and convulsions occurred as a result of severe overdose in addition to symptoms listed under side effects such as nausea, paraesthesia, drowsiness, confusion, bradycardia and hypotension.

Therapy
General symptomatic and supportive treatment according to the current state of the art is advisable. The use of atropine i.v is suggested to reverse any bradycardia and hypotension, with electrical pacing if necessary. Animal studies using toxic doses have shown that benzodiazepines (diazepam) reduce CNS side effects, including convulsions. In the event of convulsions the intravenous administration of diazepam may be indicated. Refer also to pH related changes in renal excretion under heading "PRECAUTIONS".

For further advice on management of overdosage, please contact the Poisons Information Centre.

PRESENTATION AND STORAGE CONDITIONS

Mexitil 200 mg Capsules
Red/red hard gelatin capsule, imprinted with the notation ‘200 mg’ and the company symbol, each capsule containing 200 mg mexiletine hydrochloride. Blister packs of 100 capsules. Store below 30°C.

Mexitil M 50 Capsules
Red/purple hard gelatin capsule, imprinted with the notation ’50 mg’ and the company symbol, each capsule containing 50 mg mexiletine hydrochloride. Blister packs of 100 capsules. Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited
ABN 52 000 452 308
85 Waterloo Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration (TGA): 15 June 2006

Date of latest amendment: 04 March 2008