

CARDINOL LA

Propranolol hydrochloride

Presentation

CARDINOL LA capsules contain spheroids of the beta-adrenoreceptor blocking medicine Propranolol hydrochloride which have a sustained release coating to provide long action.

CARDINOL LA capsules each contain 160 mg propranolol hydrochloride BP. CARDINOL LA is presented as size 1 gelatin capsules with a clear colourless body and opaque, green cap containing cream and white pellets.

Uses

Actions

Propranolol is a competitive antagonist at both the beta₁ and beta₂-adrenoreceptors. It has no agonist activity at the beta-adrenoreceptor but has membrane stabilising activity at concentrations exceeding 1 to 3 mg/litre, though such concentrations are rarely achieved during oral therapy. Competitive beta-adrenoreceptor blockade has been demonstrated in man by a parallel shift to the right in the dose-heart rate response curve to beta-agonists such as isoprenaline.

The sustained release preparation of propranolol maintains a higher degree of beta₁-blockade 24 hours after dosing compared with conventional propranolol.

Propranolol, as with other beta-adrenoreceptor blocking medicines, has negative inotropic effects, and is therefore contraindicated in uncontrolled heart failure.

Propranolol is a racemic mixture and the active form is the S(-) isomer. With the exception of inhibition of the conversion of thyroxine to triiodothyronine it is unlikely that any additional ancillary properties possessed by R(+) propranolol, in comparison with the racemic mixture will give rise to different therapeutic effects.

Propranolol is effective and well-tolerated in most ethnic populations, although the response may be less in black patients.

Pharmacokinetics

Propranolol is completely absorbed after oral administration and peak plasma concentrations occur 1 to 2 hours after dosing in fasting patients. The liver removes up to 90% of an oral dose with an elimination half-life of 3 to 6 hours. Propranolol is widely and rapidly distributed throughout the body with highest levels occurring in the lungs, liver, kidney, brain and heart. Propranolol is highly protein bound (80 to 95%). Following oral dosing with the sustained release preparation of propranolol the blood profile is flatter than after conventional propranolol but the half-life is increased to between 10 and 20 hours.

Since the half-life may be increased in patients with significant hepatic or renal impairment, care should be taken when starting treatment and selecting the initial dose.

Indications

CARDINOL LA indicated for the following:

1. Control of hypertension.
2. Management of angina pectoris.

3. Long term prophylaxis after recovery from acute myocardial infarction.

Dosage and Administration

Adults

Hypertension

The starting dose is one capsule daily, taken either morning or evening. An adequate response is seen in most patients at this dosage. If necessary, it can be increased to two capsules and a further reduction in blood pressure can be attained if a diuretic or other antihypertensive agent is given in addition to CARDINOL LA.

Angina

An adequate response is usually obtained with one capsule daily either morning or evening, dependant on patient convenience.

Post Myocardial Infarction

Treatment should start between days 5 and 21 after myocardial infarction with one 40 mg propranolol tablet four times a day for 2 or 3 days.

In order to achieve maximum compliance the total daily dosage of 160 mg propranolol may thereafter be given as a single CARDINOL LA capsule. Compliance is extremely important as beta-blockade may have to be continued indefinitely.

Elderly

Evidence concerning the relation between blood level and age is conflicting. With regard to the elderly, the optimum dose should be individually determined according to clinical response.

Children

CARDINOL LA is not recommended for use in children.

Contraindications

CARDINOL LA must not be used if there is a history of bronchial asthma or bronchospasm.

CARDINOL LA as with other beta-adrenoreceptor blocking medicines must not be used in patients with any of the following:

Known hypersensitivity to the substance; bradycardia; cardiogenic shock; hypotension; metabolic acidosis; after prolonged fasting; severe peripheral arterial circulatory disturbances; second or third degree heart block; sick sinus syndrome; untreated phaeochromocytoma; uncontrolled heart failure; Prinzmetal's angina.

Warnings and Precautions

Although contraindicated in uncontrolled heart failure, CARDINOL LA may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.

CARDINOL LA should not be used in combination with calcium channel blockers with negative inotropic effects (eg. verapamil, diltiazem), as it can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or SA or AV conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-blocker nor

the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

CARDINOL LA should not be used in patients with Prinzmetal's angina and beta-1 selective agents should be used with care.

CARDINOL LA is contraindicated in severe peripheral arterial circulatory disturbances. CARDINOL LA may also aggravate less severe peripheral arterial circulatory disturbances.

Due to its negative effect on conduction time, caution must be exercised if CARDINOL LA is given to patients with first degree heart block.

CARDINOL LA may modify the signs and symptoms of hypoglycaemia (especially tachycardia). Propranolol occasionally causes hypoglycaemia, even in non-diabetic patients, eg. neonates, infants, children, elderly patients, patients on haemodialysis or patients suffering from chronic liver disease and patients suffering from overdose. Severe hypoglycaemia associated with propranolol long-acting has rarely presented with seizures and/or coma in isolated patients. Caution must be exercised in the concurrent use of CARDINOL LA and hypoglycaemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin.

CARDINOL LA may mask the signs of thyrotoxicosis.

CARDINOL LA should not be used in untreated phaeochromocytoma. However, in patients with phaeochromocytoma, an alpha-blocker may be given concomitantly.

CARDINOL LA should be used to treat the elderly with caution, starting with a lower dose.

One of the pharmacological actions of beta-adrenoreceptor blocking medicines is to reduce heart rate. In the rare instances when a treated patient develops symptoms that may be attributable to a slow heart rate, the dose may be reduced.

Abrupt withdrawal of beta-blockers is to be avoided. The dosage should be withdrawn gradually over a period of 7 to 14 days. An equivalent dosage of another beta-blocker may be substituted during the withdrawal period to facilitate a reduction in dosage below CARDINOL LA. Patients should be followed during withdrawal especially those with ischaemic heart disease.

When a patient is scheduled for surgery and a decision is made to discontinue beta-blocker therapy, this should be done at least 24 hours prior to the procedure.

The risk/benefit of stopping beta blockade should be made for each patient.

CARDINOL LA may cause a more severe reaction to a variety of allergens when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenalin used to treat the allergic reactions.

Since the half-life may be increased in patients with significant hepatic or renal impairment, caution must be exercised when starting treatment and selecting the initial dose.

CARDINOL LA must be used with caution in patients with decompensated cirrhosis.

In patients with portal hypertension, liver function may deteriorate and hepatic encephalopathy may develop. There have been reports that propranolol may increase the risk of developing hepatic encephalopathy.

Pregnancy

As with all other medicines, CARDINOL LA should not be given in pregnancy unless its use is essential. There is no evidence of teratogenicity with propranolol. However, beta-adrenoreceptor blocking medicines reduce placental perfusion, which may result in intra-uterine foetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia in

the neonate and bradycardia in the foetus) may occur. There is an increased risk of cardiac and pulmonary complications in the neonate in the post-natal period.

Lactation

Most beta-adrenoreceptor blocking medicines, particularly lipophilic compounds, will pass into breast milk although to a variable extent. Breast feeding is therefore not recommended following administration of these compounds.

Effects on ability to drive and use machines

The use of CARDINOL LA is unlikely to result in any impairment of the ability of patients to drive or operate machinery. However it should be taken into account that occasionally dizziness or fatigue may occur.

Adverse Effects

CARDINOL LA is usually well tolerated. In clinical studies, the undesired events reported are usually attributable to the pharmacological actions of propranolol.

The following undesired events, listed by body system, have been reported:

Cardiovascular

Bradycardia; heart failure deterioration; postural hypotension which may be associated with syncope; cold cyanotic extremities. In susceptible patients: precipitation of heart block; exacerbation of intermittent claudication; Raynaud's phenomenon.

CNS

Confusion; dizziness; mood changes; nightmares; psychoses and hallucinations; sleep disturbances.

Endocrine

Hypoglycaemia in neonates, infants, children, elderly patients, patients on haemodialysis, patients on concomitant antidiabetic therapy, patients with prolonged fasting and patients with chronic liver disease has been reported.

Gastrointestinal

Gastrointestinal disturbance.

Haematological

Purpura; thrombocytopenia.

Integumentary

Alopecia; dry eyes; psoriasiform skin reactions; exacerbation of psoriasis; skin rashes.

Neurological

Paraesthesia.

Respiratory

Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome (see Contraindications).

Special senses

Visual disturbances.

Others

Fatigue and/or lassitude (often transient); an increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear; isolated reports of myasthenia gravis have been reported in patients administered propranolol.

Discontinuance of the medicine should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions. Cessation of therapy with a beta-adrenoreceptor blocking medicine should be gradual. In the rare event of intolerance, manifested as bradycardia and hypotension, the medicine should be withdrawn and, if necessary, treatment for overdosage instituted.

Interactions

CARDINOL LA modifies the tachycardia of hypoglycaemia. Caution must be exercised in the concurrent use of propranolol-long acting and hypoglycaemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin.

Care must be exercised in prescribing a beta-adrenoreceptor blocking medicine with Class I antiarrhythmic agents such as disopyramide.

Digitalis glycosides in association with beta-adrenoreceptor blocking medicines may increase atrioventricular conduction time.

Combined use of beta-adrenoreceptor blocking medicines and calcium channel blockers with negative inotropic effects (eg. verapamil, diltiazem) can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or SA or AV conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-adrenoreceptor blocking medicine nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Concomitant therapy with dihydropyridine calcium channel blockers eg. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Concomitant use of sympathomimetic agents eg. adrenalin, may counteract the effect of beta-adrenoreceptor blocking medicines. Caution must be exercised in the parenteral administration of preparations containing adrenalin to patients taking beta-adrenoreceptor blocking medicines as, in rare cases, vasoconstriction, hypertension and bradycardia may result.

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

Concomitant use of cimetidine will increase, whereas concomitant use of alcohol will decrease, the plasma levels of propranolol.

Beta-adrenoreceptor blocking medicines may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two medicines are co-administered, the beta-adrenoreceptor blocking medicine should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-adrenoreceptor blocking medicine therapy, the introduction of beta-adrenoreceptor blocking medicine should be delayed for several days after clonidine administration has stopped (also see prescribing information for clonidine).

Caution must be exercised if ergotamine, dihydroergotamine or related compounds are given in combination with propranolol since vasospastic reactions have been reported in a few patients.

Concomitant use of prostaglandin synthetase inhibiting medicines eg. ibuprofen and indomethacin, may decrease the hypotensive effects of propranolol.

Concomitant administration of propranolol and chlorpromazine may result in an increase in plasma levels of both medicines. This may lead to an enhanced antipsychotic effect for chlorpromazine and an increased antihypertensive effect for propranolol.

Caution must be exercised when using anaesthetic agents with CARDINOL LA. The anaesthetist should be informed and the choice of anaesthetic should be the agent with as little negative inotropic activity as possible. Use of beta-adrenoreceptor blocking drugs with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

Pharmacokinetic studies have shown that the following agents may interact with propranolol due to effects on the enzyme systems in the liver which metabolise propranolol and these agents: quinidine, propafenone, rifampicin, theophylline, warfarin, thioridazine and dihydropyridine calcium channel blockers such as nifedipine, nisoldipine, nicardipine, isradipine and lacidipine. Owing to the fact that blood concentrations of either agent may be affected, dosage adjustments may be needed according to clinical judgement.

Propranolol has been reported to interfere with the estimation of serum bilirubin by the diazo method and with the determination of catecholamines by methods using fluorescence.

Overdosage

The symptoms of overdosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include: close supervision, treatment in an intensive care ward, the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any medicine still present in the gastrointestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock.

Excessive bradycardia can be countered with atropine 1 to 2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1 to 10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoreceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given.

Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-adrenoreceptor blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Bronchospasm can usually be reversed by beta-2 agonist bronchodilators such as salbutamol; large doses may be required and the dose should be titrated according to the clinical response. Oxygen or artificial ventilation may be required in severe cases.

Pharmaceutical Precautions

Blister pack: store below 30°C.

Bottle pack: store below 25°C.

Medicine Classification

Prescription Medicine.

Package Quantities

Capsule 160 mg in a 30 days calendar pack presentation and bottle of 100.

Further Information

Nil.

Name and Address

Mylan New Zealand Limited
PO Box 11-183
Ellerslie
AUCKLAND
Telephone 09-579-2792

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