Lopressor®

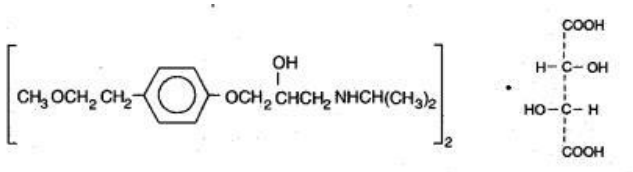
metoprolol tartrate injection, USP

Rx only

Prescribing Information

DESCRIPTION

Lopressor, metoprolol tartrate USP, is a selective beta$_1$-adrenoreceptor blocking agent, available in 5-mL ampuls for intravenous administration. Each ampul contains a sterile solution of metoprolol tartrate USP, 5 mg, and sodium chloride USP, 45 mg, and water for injection USP. Metoprolol tartrate USP is (±)-1-(Isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol L-(+)-tartrate (2:1) salt, and its structural formula is:



Metoprolol tartrate USP is a white, practically odorless, crystalline powder with a molecular weight of 684.82. It is very soluble in water; freely soluble in methylene chloride, in chloroform, and in alcohol; slightly soluble in acetone; and insoluble in ether.

CLINICAL PHARMACOLOGY

Mechanism of Action

Lopressor is a beta$_1$-selective (cardioselective) adrenergic receptor blocker. This preferential effect is not absolute, however, and at higher plasma concentrations, Lopressor also inhibits beta$_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Clinical pharmacology studies have demonstrated the beta-blocking activity of metoprolol, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Hypertension

The mechanism of the antihypertensive effects of beta-blocking agents has not been fully elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

Angina Pectoris

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, Lopressor reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris.

Myocardial Infarction

The precise mechanism of action of Lopressor in patients with suspected or definite myocardial infarction is not known.

Pharmacodynamics

Relative $beta_1$ selectivity is demonstrated by the following: (1) In healthy subjects, Lopressor is unable to reverse the $beta_2$-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective ($beta_1$ plus $beta_2$) beta blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, Lopressor reduces FEV_1 and FVC significantly less than a nonselective beta blocker, propranolol, at equivalent $beta_1$-receptor blocking doses.

Lopressor has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at doses much greater than required for beta blockade. Animal and human experiments indicate that Lopressor slows the sinus rate and decreases AV nodal conduction.

When the drug was infused over a 10-minute period, in normal volunteers, maximum beta blockade was achieved at approximately 20 minutes. Equivalent maximal beta-blocking effect is achieved with oral and intravenous doses in the ratio of approximately 2.5:1. There is a linear relationship between the log of plasma levels and reduction of exercise heart rate.

In several studies of patients with acute myocardial infarction, intravenous followed by oral administration of Lopressor caused a reduction in heart rate, systolic blood pressure and cardiac output. Stroke volume, diastolic blood pressure and pulmonary artery end diastolic pressure remained unchanged.

Pharmacokinetics

Absorption: The estimated oral bioavailability of immediate release metoprolol is about 50% because of pre-systemic metabolism which is saturable leading to non-proportionate increase in the exposure with increased dose.

Distribution: Metoprolol is extensively distributed with a reported volume of distribution of 3.2 to 5.6 L/kg. About 10% of metoprolol in plasma is bound to serum albumin. Metoprolol is known to cross the placenta and is found in breast milk. Metoprolol is also known to cross the blood brain barrier following oral administration and CSF concentrations close to that observed in plasma have been reported. Metoprolol is not a significant P-glycoprotein substrate.

Metabolism: Lopressor is primarily metabolized by CYP2D6. Metoprolol is a racemic mixture of R- and S- enantiomers, and when administered orally, it exhibits stereo selective metabolism that is dependent on oxidation phenotype. CYP2D6 is absent (poor metabolizers) in about 8% of Caucasians and about 2% of most other populations. Poor CYP2D6 metabolizers exhibit several-fold higher plasma concentrations of Lopressor than extensive metabolizers with normal CYP2D6 activity thereby decreasing Lopressor's cardioselectivity.

Elimination: Elimination of Lopressor is mainly by biotransformation in the liver. The mean elimination half-life of metoprolol is 3 to 4 hours; in poor CYP2D6 metabolizers the half-life may be 7 to 9 hours. Approximately 95% of the dose can be recovered in urine. In most subjects (extensive metabolizers), less than 10% of an intravenous dose are excreted as unchanged drug in the urine. In poor metabolizers, up to 30% or 40% of oral or intravenous doses, respectively, may be excreted unchanged; the rest is excreted by the kidneys as metabolites that appear to have no

beta blocking activity. The renal clearance of the stereo-isomers does not exhibit stereo-selectivity in renal excretion.

Special Populations

Geriatric patients: The geriatric population may show slightly higher plasma concentrations of metoprolol as a combined result of a decreased metabolism of the drug in elderly population and a decreased hepatic blood flow. However, this increase is not clinically significant or therapeutically relevant.

Renal impairment: The systemic availability and half-life of Lopressor in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

Hepatic Impairment: Since the drug is primarily eliminated by hepatic metabolism, hepatic impairment may impact the pharmacokinetics of metoprolol. The elimination half-life of metoprolol is considerably prolonged, depending on severity (up to 7.2 h).

Clinical Studies:

Hypertension

In controlled clinical studies, Lopressor has been shown to be an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics, at oral dosages of 100-450 mg daily. In controlled, comparative, clinical studies, Lopressor has been shown to be as effective an antihypertensive agent as propranolol, methyldopa, and thiazide-type diuretics, to be equally effective in supine and standing positions.

Angina Pectoris

In controlled clinical trials, Lopressor, administered orally two or four times daily, has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The oral dosage used in these studies ranged from 100-400 mg daily. A controlled, comparative, clinical trial showed that Lopressor was indistinguishable from propranolol in the treatment of angina pectoris.

Myocardial Infarction

In a large (1,395 patients randomized), double-blind, placebo-controlled clinical study, Lopressor was shown to reduce 3-month mortality by 36% in patients with suspected or definite myocardial infarction.

Patients were randomized and treated as soon as possible after their arrival in the hospital, once their clinical condition had stabilized and their hemodynamic status had been carefully evaluated. Subjects were ineligible if they had hypotension, bradycardia, peripheral signs of shock, and/or more than minimal basal rales as signs of congestive heart failure. Initial treatment consisted of intravenous followed by oral administration of Lopressor or placebo, given in a coronary care or comparable unit. Oral maintenance therapy with Lopressor or placebo was then continued for 3 months. After this double-blind period, all patients were given Lopressor and followed up to 1 year.

The median delay from the onset of symptoms to the initiation of therapy was 8 hours in both the Lopressor- and placebo-treatment groups. Among patients treated with Lopressor, there were comparable reductions in 3-month mortality for those treated early (≤8 hours) and those in whom

treatment was started later. Significant reductions in the incidence of ventricular fibrillation and in chest pain following initial intravenous therapy were also observed with Lopressor and were independent of the interval between onset of symptoms and initiation of therapy.

In this study, patients treated with metoprolol received the drug both very early (intravenously) and during a subsequent 3-month period, while placebo patients received no beta-blocker treatment for this period. The study thus was able to show a benefit from the overall metoprolol regimen but cannot separate the benefit of very early intravenous treatment from the benefit of later beta-blocker therapy. Nonetheless, because the overall regimen showed a clear beneficial effect on survival without evidence of an early adverse effect on survival, one acceptable dosage regimen is the precise regimen used in the trial. Because the specific benefit of very early treatment remains to be defined however, it is also reasonable to administer the drug orally to patients at a later time as is recommended for certain other beta blockers.

INDICATIONS AND USAGE

Myocardial Infarction

Lopressor ampuls are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality when used in conjunction with oral Lopressor maintenance therapy. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS).

CONTRAINDICATIONS

Hypersensitivity to Lopressor and related derivatives, or to any of the excipients; hypersensitivity to other beta blockers (cross sensitivity between beta blockers can occur).

Myocardial Infarction

Lopressor is contraindicated in patients with a heart rate <45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥0.24 sec); systolic blood pressure <100 mmHg; or moderate-to-severe cardiac failure (see WARNINGS).

WARNINGS

Heart Failure

Beta blockers, like Lopressor, can cause depression of myocardial contractility and may precipitate heart failure and cardiogenic shock. If signs or symptoms of heart failure develop, treat the patient according to recommended guidelines. It may be necessary to lower the dose of Lopressor or to discontinue it.

Ischemic Heart Disease

Do not abruptly discontinue Lopressor therapy in patients with coronary artery disease. Severe exacerbation of angina, myocardial infarction, and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with beta-blockers. When discontinuing chronically administered Lopressor, particularly in patients with coronary artery disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Use During Major Surgery

Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Bradycardia

Bradycardia, including sinus pause, heart block, and cardiac arrest have occurred with the use of Lopressor. Patients with first-degree atrioventricular block, sinus node dysfunction, or conduction disorders may be at increased risk. Monitor heart rate and rhythm in patients receiving Lopressor. If severe bradycardia develops, reduce or stop Lopressor.

Exacerbation of Bronchospastic Disease

Patients with bronchospastic disease, should, in general, not receive beta blockers, including Lopressor. Because of its relative $beta_1$ selectivity, however, Lopressor may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because $beta_1$ selectivity is not absolute use the lowest possible dose of Lopressor and consider administering Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval (see DOSAGE AND ADMINISTRATION). Bronchodilators, including $beta_2$ agonists, should be readily available or administered concomitantly.

Diabetes and Hypoglycemia

Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

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