

PRODUCT MONOGRAPH

 **BETALOC[®]**

(metoprolol tartrate)

50 mg and 100 mg Tablets

200 mg DURULES[®]

5 mL ampoule 1 mg/mL

β -Adrenoceptor Blocking Agent

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(metoprolol tartrate)

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200 mg DURULES®

5 mL ampoule 1 mg/mL

PHARMACOLOGICAL CLASSIFICATION

β -Adrenoceptor Blocking Agent

ACTIONS AND CLINICAL PHARMACOLOGY

BETALOC (metoprolol tartrate) is a β -adrenoceptor blocking agent. *In vitro* and *in vivo* animal studies have shown that it has a preferential effect on β_1 -adrenoreceptors, chiefly located in cardiac muscle. This preferential effect is not absolute, however, and at higher doses, BETALOC also inhibits β_2 -adrenoreceptors, chiefly located in the bronchial and vascular musculature. It is used in the treatment of hypertension, angina pectoris and to reduce mortality in patients with myocardial infarction.

The mechanism of the antihypertensive effect has not been established. Among the factors that may be involved are:

- a) competitive ability to antagonize catecholamine-induced tachycardia at the β -receptor sites in the heart, thus decreasing heart rate, cardiac contractility and cardiac output;
- b) inhibition of renin release by the kidneys;
- c) inhibition of the vasomotor centers.

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction and in blood pressure, metoprolol 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. However, in patients with heart failure, beta-adrenoceptor blockade may increase oxygen requirements by increasing left ventricular fibre length and end-diastolic pressure.

The mechanisms involved in reducing mortality in patients with acute myocardial infarction are not fully understood.

Pharmacokinetics

In man, absorption of BETALOC is rapid and complete, with oxidative metabolism occurring in the liver primarily via cytochrome P450 2D6. Plasma levels following oral administration, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

Intersubject plasma levels achieved are highly variable after oral administration, although they show good reproducibility within each individual. Peak plasma concentrations are attained after approximately 1.5-2 hours with conventional metoprolol formulations, and after approximately 4-5 hours with sustained-release formulations. Upon repeated oral administration, the percentage of the dose systemically available is higher than after a single dose and also increases dose-dependently. Ingestion together with food may raise the systemic availability of an oral dose by approximately 30-40%. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol undergoes oxidative metabolism in the liver primarily by the CYP2D6 isoenzyme. Elimination is mainly by biotransformation in the liver, and the plasma half-life averages 3.5 hours (extremes: 1 and 9 hours). The total clearance rate is approximately 1 L/min and the protein binding rate is approximately 5-10%. Less than 5% of an oral dose of BETALOC is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance.

The systemic availability and half-life of BETALOC in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. The excretion of metabolites, however, is reduced. Significant accumulation of metabolites was observed in patients with a GFR of approximately 5 mL/min, but this accumulation does not influence the β -blocking effects of metoprolol. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

Elderly subjects show no significant changes in the plasma concentrations of metoprolol as compared with young persons. However, plasma concentrations of the major pharmacologically active metabolites were higher in the elderly.

Liver cirrhosis may increase the bioavailability of metoprolol and reduce its total clearance.

Pharmacodynamics

Significant β -blocking effect (as measured by reduction of exercise heart rate) occurs within one hour after oral administration, and its duration is dose-related. For example, a 50% reduction of the maximum registered effect after single oral doses of 20, 50, and 100 mg occurred at 3.3, 5.0 and 6.4 hours, respectively, in normal subjects. After repeated oral dosages of 100 mg twice daily, a significant reduction in exercise systolic blood pressure was evident at 12 hours.

Following intravenous administration of BETALOC, the half-life of the distribution phase is approximately 12 minutes; the urinary recovery of unchanged drug is approximately 10%. When the drug was infused over a 10 minute period, in normal volunteers, maximum β -blockade was achieved at approximately 20 minutes. Doses of 5 mg and 15 mg yielded a maximal reduction in exercise-induced heart rate of approximately 10% and 15%, respectively. The effect on exercise heart rate decreased linearly with time at the same rate for both doses, and disappeared at approximately 5 hours and 8 hours for the 5 mg and 15 mg doses, respectively.

Equivalent maximal β -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. However, antihypertensive activity does not appear to be related to plasma levels. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to dose, selection of proper dosage requires individual titration.

In several studies of patients with acute myocardial infarction, intravenous followed by oral administration of BETALOC 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.

Studies in hypertensive and angina patients have shown plasma levels of 28-46 ng/mL 12 hours after regular tablets and 19-45 ng/mL 24 hours after BETALOC DURULES and were comparable to the peak levels after 100 mg regular tablets.

INDICATIONS AND CLINICAL USE

Hypertension

BETALOC (metoprolol tartrate) is indicated in patients with mild or moderate hypertension. It may be used alone or in combination with other antihypertensive agents. See DOSAGE AND ADMINISTRATION.

The combination of BETALOC with a diuretic or peripheral vasodilator has been found to be compatible and generally more effective than metoprolol tartrate alone. Limited experience with other antihypertensive agents has not shown evidence of incompatibility with BETALOC.

BETALOC is not recommended for the emergency treatment of hypertensive crises.

Angina Pectoris

BETALOC is indicated for the long-term treatment of angina pectoris due to ischemic heart disease.

Myocardial Infarction

BETALOC is indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality.

Treatment with intravenous BETALOC can be initiated as soon as the patient's clinical condition allows (see DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS). BETALOC I.V. should be administered by a qualified health professional who is experienced in the use of anti-hypertension I.V. agents and who has been trained in the management of patients with myocardial infarction. Alternatively, in patients with proven myocardial infarction, oral treatment can begin within 3 to 10 days of the acute event (see DOSAGE AND ADMINISTRATION). Data are not available as to whether benefit would ensue if the treatment is initiated later.

Clinical trials have shown that patients in whom the myocardial infarction was unconfirmed, received no benefit from early BETALOC therapy.

The COMMIT trial has shown that allocation to the intravenous then oral BETALOC regimen in a patient population of Chinese origin with 25% of patients in Killip Class II-III resulted in an excess of cardiogenic shock, (5.0% vs. 3.9% on placebo) mainly during the first 24 hours after admission. (See WARNINGS).

CONTRAINDICATIONS

BETALOC (metoprolol tartrate) should not be used in the presence of:

1. known hypersensitivity to metoprolol and related derivatives;
2. sinus bradycardia;
3. sick sinus syndrome;
4. second- and third-degree A-V block;
5. right ventricular failure secondary to pulmonary hypertension;
6. overt heart failure;
7. cardiogenic shock;
8. severe peripheral arterial circulatory disorders;
9. anesthesia with agents that produce myocardial depression, e.g. ether.
10. The intravenous form is also contraindicated in the presence of asthma and other obstructive respiratory diseases (for oral treatment, see PRECAUTIONS, Bronchospastic Diseases).

Myocardial Infarction Patients - Additional Contraindications

BETALOC is contraindicated in patients with a heart rate < 45 beats/min; significant heart block greater than first degree (PR interval \geq 0.24 sec); systolic blood pressure < 100 mmHg; or moderate to severe cardiac failure (see WARNINGS).

WARNINGS

Cardiac Failure

Special caution should be exercised when administering BETALOC (metoprolol tartrate) to patients with a history of heart failure. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with β -blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. The positive inotropic action of digitalis may be reduced by the negative inotropic effect of metoprolol tartrate when the two drugs are used concomitantly. The effects of β -blockers and digitalis are additive in depressing A-V conduction and may induce bradycardia. This also applies to combinations with calcium antagonists of the verapamil type or some antiarrhythmics (see Drug Interactions).

In patients without a history of cardiac failure, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure and/or hypotension (systolic blood pressure \leq 90 mmHg). Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, BETALOC therapy should be reduced or withdrawn.

Abrupt Cessation of Therapy

Patients with angina should be warned against abrupt discontinuation of BETALOC. There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation of β -blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of BETALOC is planned in patients with angina pectoris or previous myocardial infarction, the dosage should be gradually reduced over a period of at least 10 to 14 days, in diminishing doses, to 25 mg once a day for the last 6 days. During this period the patient should be carefully observed. In situations of greater urgency, metoprolol tartrate therapy should be discontinued stepwise and under conditions of closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with BETALOC be reinstated promptly, at least temporarily.

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 BETALOC therapy abruptly even in patients treated only for hypertension.

Oculomucocutaneous Syndrome

Various skin rashes and conjunctival xerosis have been reported with β -blockers, including metoprolol tartrate. Oculomucocutaneous syndrome, a severe syndrome whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one β -adrenergic-blocking agent (practolol). This syndrome has not been observed with BETALOC or any other such agent. However, physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

Severe Sinus Bradycardia

Severe sinus bradycardia may occur with the use of BETALOC from unopposed vagal activity remaining after blockade of β_1 -adrenergic receptors. Very rarely a pre-existing A-V conduction disorder of moderate degree may become aggravated, possibly leading to A-V block. In such cases, dosage should be reduced. Atropine, isoproterenol or dobutamine should be considered in patients with acute myocardial infarction.

Thyrotoxicosis

Although metoprolol has successfully been used for the symptomatic (adjuvant) therapy of thyrotoxicosis, possible deleterious effects from long-term use of BETALOC have not been adequately appraised. β -blockade may mask the clinical signs of continuing hyperthyroidism or complications, and give a false impression of improvement. Therefore, abrupt withdrawal of metoprolol tartrate may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

Myocardial Infarction Patients - Additional Warnings

Acute Intervention

During acute intervention in myocardial infarction, intravenous metoprolol should only be used by experienced staff under circumstances where resuscitation and monitoring equipment are available.

Cardiac Failure

Depression of the myocardium with BETALOC may lead to cardiac failure (see general WARNINGS above). Special caution should be exercised when administering BETALOC to patients with a history of cardiac failure or those with a minimal cardiac reserve. Should failure occur, treatment should be as described in WARNINGS.

Severe Sinus Bradycardia

See General Warnings for severe sinus bradycardia.

A-V Conduction

BETALOC slows A-V conduction and may produce significant first- (PR interval ≥ 0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, BETALOC should be discontinued and atropine (0.25 - 0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension

If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, BETALOC should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or A-V block, treatment should be directed at reversing these (see above).

Patients of Chinese Origin with Acute Myocardial Infarction

It has been shown that allocation to the intravenous then oral BETALOC regimen resulted in a significant increase in the development of cardiogenic shock [5% BETALOC vs. 3.9% placebo] mainly during the first 24 hours after admission in a Chinese population with 25% of patients in Killip Class II-III.

PRECAUTIONS

Bronchospastic Diseases

Patients with bronchospastic diseases should, in general, not receive β -blockers. Because of its relative β_1 -selectivity, however, BETALOC (metoprolol tartrate) may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since β_1 -selectivity is not absolute, a β_2 -stimulating agent should preferably be administered concomitantly, and the lowest possible dose of BETALOC should be used. In these circumstances it would be prudent initially to administer BETALOC 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).

Because it is unknown to what extent β_2 -stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should not be used prophylactically in patients with proven or suspected acute myocardial infarction. If bronchospasm not related to congestive heart failure occurs, BETALOC should be discontinued. A theophylline derivative or a β_2 -agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and β_2 -agonists may produce serious cardiac arrhythmias.

Diabetes and Hypoglycemia

BETALOC should be administered with caution to diabetic patients subject to spontaneous hypoglycemia (most of these patients are insulin treated). β -adrenergic blockers may mask the premonitory signs and symptoms of acute hypoglycemia, but this is mainly attributed to unselective β -adrenergic blockers.

Liver Function

BETALOC should be used with caution in patients with impaired liver function. Liver function tests should be performed at regular intervals during long-term treatment. Dose adjustment is normally not needed in patients suffering from liver cirrhosis because metoprolol has low protein binding (5-10%). When there are signs of serious impairment of liver function (e.g., shunt-operated patients) a dose reduction should be considered.

Allergen Immunotherapy

There may be increased difficulty in treating an allergic type reaction in patients on β -blockers. In these patients, the reaction may be more severe due to pharmacologic effects of the β -blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other these doses can be associated with excessive alpha-adrenergic stimulation with consequent hypertension, reflex bradycardia and heart-block, and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of β -agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

Patients Undergoing Surgery

It is not advisable to withdraw β -adrenoceptor blocking drugs prior to surgery in the majority of patients especially in those with risk of overt or silent coronary heart disease. However, care should be taken to avoid using anesthetic agents that may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg i.v.).

Some patients receiving β -blocking drugs have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported.

Acute initiation of high-dose metoprolol to patients undergoing non-cardiac surgery should be avoided, since it has been associated with bradycardia, hypotension and stroke including fatal outcome in patients with cardiovascular risk factors.

Since metoprolol is a competitive inhibitor of β -adrenoceptor agonists, its effects may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol or dobutamine.

Peripheral Artery Disorders

Metoprolol may aggravate the symptoms of peripheral arterial circulatory disorders, mainly due to its blood pressure lowering effect.

Phaeochromocytoma

Where a β -blocker is prescribed for a patient known to be suffering from a phaeochromocytoma, an α -blocker should be given concomitantly.

Reaction Time

β -blockers may adversely affect the patient's reaction time. Patients should be advised to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with BETALOC has been determined.

Usage in Pregnancy

Metoprolol crosses the placental barrier. Since BETALOC has not been studied in human pregnancy, the drug should not be given to pregnant women. The use of any drug in patients of child-bearing potential requires that the anticipated benefit be weighed against the possible hazards.

Nursing Mothers

Metoprolol is excreted in breast milk in very small quantities. Caution should be exercised when BETALOC is administered to a nursing woman.

Usage in Children

The safety and efficacy of BETALOC in children has not been established.

Usage in the Elderly

Caution is indicated when using BETALOC in elderly patients. An excessively pronounced decrease in blood pressure or pulse rate may cause the blood supply to vital organs to fall to inadequate levels.

Drug Interactions

Antihypertensives

BETALOC dosage should be adjusted according to the individual requirements of the patient especially when used concomitantly with other antihypertensive agents (see DOSAGE AND ADMINISTRATION).

MAO Inhibitors and Adrenergic Neuron Blockers

Patients receiving MAO inhibitors or catecholamine-depleting drugs (such as reserpine or guanethidine) should be closely monitored because the added β -adrenergic-blocking action of BETALOC may produce an excessive reduction of sympathetic activity. BETALOC should

not be combined with other β -blockers. Similarly, patients taking Selective Serotonin Reuptake Inhibitors (SSRI's), such as paroxetine, fluoxetine, and sertraline, in combination with BETALOC, should be aware that the plasma concentration of metoprolol may be raised. This occurs as metoprolol is metabolised via cytochrome P450 2D6, which is inhibited by SSRI's.

Calcium Entry Blockers

As with other β -blockers, BETALOC should not be given to patients receiving calcium antagonists of the verapamil type. However, in exceptional cases, when in the opinion of the physician concomitant use is considered essential, such use should be instituted gradually in a hospital setting under careful supervision. Negative inotropic, dromotropic, and chronotropic effects may occur when BETALOC is given together with calcium antagonists. Verapamil and diltiazem may reduce the clearance of metoprolol.

Antiarrhythmic Agents

β -blockers may enhance the negative inotropic and negative dromotropic effect of antiarrhythmic agents such as quinidine and amiodarone. Coadministration of these and other antiarrhythmics (e.g. propafenone) may raise plasma levels of metoprolol.

Digitalis Glycosides

Digitalis glycosides, in association with β -blockers, may increase atrioventricular conduction time and may induce bradycardia.

Clonidine Withdrawal Syndrome

The hypertensive crisis which may follow the withdrawal of clonidine may be accentuated in the presence of β -blockade. It has been proposed that withdrawal of the β -blocker several days before the clonidine may reduce the danger of rebound effects.

Oral Anti-Diabetics

The dosage of oral anti-diabetics may have to be readjusted in patients receiving β -blockers (see PRECAUTIONS).

Indomethacin

Concurrent treatment with indomethacin may decrease the antihypertensive effect of β -blockers.

Cytochrome P450 Inducers and Inhibitors

Metoprolol is a metabolic substrate for the cytochrome P450 isoenzyme CYP2D6. Drugs that act as enzyme-inducing and enzyme-inhibiting substances may exert an influence on the plasma level of metoprolol. Plasma levels of metoprolol may be raised by co-administration

of compounds metabolised by CYP2D6, such as antihistamines, histamine-2-receptor antagonists (e.g. cimetidine, ranitidine), antidepressants, antipsychotics and COX-2-inhibitors. The plasma concentration of metoprolol is lowered by rifampicin and may be raised by alcohol and hydralazine.

Lidocaine

Metoprolol may reduce the clearance of lidocaine.

Inhalation Anesthetics

In patients receiving β -blocker therapy, inhalation anesthetics enhance the cardiodepressant effect.

ADVERSE REACTIONS

The most common adverse events reported are exertional tiredness, gastrointestinal disorders and disturbances of sleep patterns. The most serious adverse events reported are congestive heart failure, bronchospasm and hypotension.

Reported adverse events according to organ systems are:

Cardiovascular

- Congestive heart failure (see WARNINGS)
- Secondary effects of decreased cardiac output which include:
 - syncope, vertigo, lightheadedness and postural hypotension
- Severe bradycardia
- Lengthening of PR interval
- Second and third degree A-V block
- Sinus arrest
- Cardiac arrhythmias
- Palpitations
- Chest pains
- Edema
- Cold extremities
- Claudication
- Gangrene in patients with pre-existing severe peripheral circulatory disorders
- Hot flushes
- Cardiogenic shock in patients with acute myocardial infarction*

In a placebo controlled study in patients with acute myocardial infarction, the incidences of the following cardiovascular reactions were:

| | Metoprolol | Placebo |
|---|-------------------|----------------|
| Hypotension (systolic BP < 90 mmHg) | 27.4% | 23.2% |
| Bradycardia (heart rate < 40 beats/min) | 15.9% | 6.7% |
| Second- or Third-Degree Heart Block | 4.7% | 4.7% |
| First-Degree Heart Block (PR ≥ 0.26 sec) | 5.3% | 1.9% |
| Heart Failure | 27.5% | 29.6% |

*Excess frequency of 0.4% compared with placebo in a study of 46000 patients with acute myocardial infarction where the frequency of cardiogenic shock was 2.3% in the metoprolol group and 1.9% in the placebo group in the subset of patients with low shock risk index. The shock risk index was based on the absolute risk of shock in each individual patient derived from age, sex, time delay, Killip class, blood pressure, heart rate, ECG abnormality, and prior history of hypertension. The patient group with low shock risk index corresponds to the patients in which metoprolol is recommended for use in acute myocardial infarction.

Central Nervous System

- Headache
- Dizziness
- Mental depression
- Lightheadedness
- Concentration impaired
- Anxiety
- Weakness
- Fatigue
- Sedation
- Somnolence or insomnia
- Vivid dreams/nightmares
- Vertigo
- Paresthesia
- Hallucination
- Nervousness
- Impotence/sexual dysfunction
- Amnesia/memory impairment
- Confusion

Gastrointestinal

- Diarrhea
- Constipation
- Flatulence
- Heartburn

Nausea and vomiting
Abdominal pain
Dryness of mouth
Hepatitis

Respiratory

Shortness of breath
Wheezing
Bronchospasm
Status asthmaticus
Rhinitis

Allergic/Dermatological (see WARNINGS)

Skin rash (exanthema, urticaria psoriasiform and dystrophic skin lesion, aggravated psoriasis)
Sweating
Pruritus
Photosensitivity

Eye, Ear, Nose and Throat (EENT)

Blurred vision and non-specific visual disturbances
Dry and/or itching eyes
Conjunctivitis
Tinnitus
Hearing difficulties in doses exceeding those recommended
Taste disturbances

Miscellaneous

Muscle cramps
Exertional tiredness
Weight gain
Loss of hair
Arthritis
Peyronie's disease
Arthralgia

Clinical Laboratory

The following laboratory parameters have been rarely elevated: transaminases, BUN, alkaline phosphatase and bilirubin. Isolated cases of thrombocytopenia and leukopenia have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

The most common signs to be expected with overdosage of a β -adrenoceptor blocking agent are hypotension, bradycardia, congestive heart failure, bronchospasm and hypoglycemia. Atrioventricular block, cardiogenic shock and cardiac arrest may develop. In addition, impairment of consciousness (or even coma), nausea, vomiting and cyanosis may occur.

Concomitant ingestion of alcohol, antihypertensives, quinidine, or barbiturates aggravate the signs and symptoms.

The first manifestations of overdosage set in 20 minutes to 2 hours after drug administration.

Treatment

If an overdose occurs, in all cases therapy with BETALOC (metoprolol tartrate) should be discontinued and the patient hospitalized and observed closely. To prevent absorption of any drug still present in the gastrointestinal tract, gastric lavage or activated charcoal should be used. In addition, if required, the following therapeutic measures are suggested:

Bradycardia and Hypotension

Initially 1-2 mg of atropine sulfate should be given intravenously and/or a cardiac pacemaker should be used. If a satisfactory effect is not achieved, norepinephrine or dopamine may be administered after preceding treatment with atropine (see PRECAUTIONS concerning the use of epinephrine in β -blocked patients). Treatment with glucagon or administration of calcium ions may also be considered.

Congestive Heart Failure

Conventional therapy.

Bronchospasm

Bronchospasm can usually be reversed by bronchodilators such as β_2 -agonists.

Hypoglycemia

Intravenous glucose.

It should be remembered that BETALOC is a competitive antagonist of isoproterenol and hence, large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of BETALOC. However, the complications of excess isoproterenol, e.g. hypotension and tachycardia, should not be overlooked.

DOSAGE AND ADMINISTRATION

Hypertension

BETALOC (metoprolol tartrate) is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic, but may be used alone (see INDICATIONS).

The dose must always be adjusted to the individual requirements of the patient, in accordance with the following guidelines.

BETALOC treatment should be initiated with doses of 50 mg b.i.d. If an adequate response is not seen after one week, dosage should be increased to 100 mg b.i.d. In some cases the daily dosage may need to be increased by further 100 mg increments at intervals of not less than two weeks up to a maximum of 200 mg b.i.d., which should not be exceeded. The usual maintenance dose is within the range of 100-200 mg daily.

When BETALOC is combined with another antihypertensive agent which is already being administered, BETALOC should be added initially at a dose of 50 mg b.i.d. After one or two weeks the daily dosage may be increased if required, in increments of 100 mg, at intervals of not less than two weeks, until adequate blood pressure control is obtained.

Angina Pectoris

The recommended dosage range for BETALOC in angina pectoris is 100-400 mg per day in divided doses.

Treatment should be initiated with 50 mg b.i.d. for the first week.

If response is not adequate, the daily dosage should be increased by 100 mg for the next week. The usual maintenance dose is 200 mg/day.

The need for further increases should be closely monitored at weekly intervals and the dosage increased in 100 mg increments to a maximum of 400 mg/day in two or three divided doses.

A BETALOC dose of 400 mg/day should not be exceeded.

Slow-Release BETALOC DURULES

BETALOC DURULES (200 mg slow release tablets) are intended only for maintenance dosing in those patients requiring doses of 100-400 mg per day. Treatment must always be initiated and individual titration of dosage carried out using the regular tablets. Dosing with half or whole DURULES may be preferred for maintenance because of the convenience of once daily administration. One half BETALOC DURULES will provide 100 mg slow release metoprolol. The following maintenance doses may now be accommodated: 100 mg = ½ DURULES, 200 mg = 1 DURULES, 300 mg = 1½ DURULES, 400 mg = 2 DURULES.

Whole tablets may sometimes seem to appear in the stool; these will only be the matrices which have remained intact after the active substance has been leached out.

Myocardial Infarction

In addition to the usual contraindications:

| ONLY PATIENTS WITH SUSPECTED ACUTE MYOCARDIAL INFARCTION WHO MEET THE FOLLOWING CRITERIA ARE SUITABLE FOR THERAPY AS DESCRIBED BELOW: | |
|--|-----------------------|
| Systolic blood pressure | ≥ 100 mmHg |
| Heart rate* | ≥ 45 beats per minute |
| PR interval | < 0.24 seconds |
| Rales* | < 10 cm |
| Adequate peripheral circulation | |

* Extreme caution should be exercised when giving intravenous metoprolol to patients with heart rates between 45 and 60 and/or pulmonary rales less than 10 cm. Therapy should be discontinued in patients if the heart rate drops below 45 or the systolic blood pressure drops below 100 mmHg.

Early Treatment

During the early phase of definite or suspected acute myocardial infarction, treatment with BETALOC can be initiated as soon as possible after the patient's arrival in the hospital. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized.

Treatment in this early phase should begin with the intravenous administration of three bolus injections of 5 mg of BETALOC each. The injections should be given at approximately 2 minute intervals. During the intravenous administration of BETALOC, blood pressure, heart rate, and electrocardiogram should be carefully monitored. If any of the injections are associated with adverse cardiovascular effects, intravenous administration should be stopped immediately and the patient should be observed carefully and appropriate therapy instituted.

In patients who tolerate the full intravenous dose (15 mg), BETALOC tablets, 50 mg every 6 hours should be initiated 15 minutes after the last intravenous dose and continued for 48 hours. Thereafter, patients should receive a maintenance dosage of 100 mg twice daily (see Late Treatment below).

Patients who appear not to tolerate the full intravenous dose should be started on either 25 mg or 50 mg every 6 hours (depending on the degree of intolerance) 15 minutes after the last intravenous dose or as soon as their clinical condition allows. In patients with severe intolerance, treatment with BETALOC should be discontinued (see WARNINGS).

Late Treatment (for proven myocardial infarction patients only)

Patients with contraindications to treatment during the early phase of myocardial infarction, patients who appear not to tolerate the full early treatment, and patients in whom the physician wishes to delay therapy for any other reason should be started on BETALOC tablets, 100 mg twice daily, as soon as their clinical condition allows. Treatment can begin within 3 to 10 days of the acute event. Therapy should be continued for at least 3 months. Although the efficacy

of treatment with BETALOC beyond 6 months has not been conclusively established, data from studies with other β -blockers suggest that the treatment should be continued for 1 to 3 years.

Impaired Liver Function

Dose adjustment is normally not needed in patients suffering from liver cirrhosis because metoprolol has low protein binding (5-10%). When there are signs of serious impairment of liver function (e.g., shunt-operated patients) a dose reduction should be considered.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

PHARMACEUTICAL INFORMATION

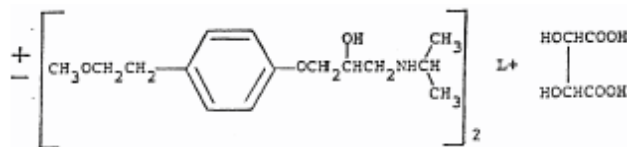
Drug Substance

Molecular Formula: $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$

Molecular Weight: 684.82

Chemical Name: 2-propanol, 1-[4-(2-methoxyethyl) phenoxy]-3-[(1-methylethyl)amino]-, (\pm)-, [*R*-(*R**, *R**)]-2,3-dihydroxybutanedioate (2:1) (salt).

Structural Formula:



Description: Colorless, odorless, crystalline powder with a bitter taste.

Solubility: Very soluble in water at 20°C.

pH: 6.7 (2% water solution)

Composition

| | 50 mg tablet | 100 mg tablet | 200 mg DURULES | 1 mg/mL 5 mL ampoule |
|---------------------|--------------|---------------|----------------|----------------------|
| Active Ingredients: | | | | |
| metoprolol tartrate | 50 mg | 100 mg | 200 mg | 5 mg |

| | 50 mg tablet | 100 mg tablet | 200 mg DURULES | 1 mg/mL 5 mL ampoule |
|----------------------------|---|---------------|---|----------------------|
| Non-Medicinal Ingredients: | Lactose Microcrystalline cellulose Sodium starch glycolate Colloidal silica Polyvinyl pyrrolidone Magnesium stearate | | Aluminum silicate Paraffin Magnesium stearate Ethylcellulose Hydroxypropyl methylcellulose Polyethylene glycol Titanium dioxide | Sodium chloride |

Stability and Storage Recommendations

Store at 15 to 30°C. BETALOC 1 mg/mL in a 5 mL ampoule should be protected from light.

AVAILABILITY OF DOSAGE FORMS

Tablet

50 mg: A compressed, white, biconvex circular tablet, scored and engraved $\frac{A}{BB}$

100 mg: A compressed, white, biconvex circular tablet, scored and engraved $\frac{A}{ME}$

DURULES

200 mg: A white, biconvex rod-shaped film-coated tablet scored and engraved $\frac{A}{MD}$

Ampoule

5 mL:1 mg/mL. An aqueous injectable solution also containing 45 mg (9 mg/mL) of sodium chloride

PHARMACOLOGY

Effect on the Cardiovascular System

Metoprolol produced dose-dependent reductions in heart rate and contractile force responses to sympathetic nerve stimulation in the anesthetized cat. The ED₅₀ value for blockade of the chronotropic response to nerve stimulation was approximately 7 times less than that for isoproterenol stimulation. Metoprolol reduced the heart rate in conscious dogs at rest and during exercise. With the exception of PR interval prolongation, ECG complexes were not changed.

In anesthetized cats, intravenous doses up to 2.0 mg/kg did not significantly influence the pressor response to intravenous epinephrine.

In anesthetized cats, intravenously-administered metoprolol antagonized the hind limb vasodilating response to intra-arterial isoproterenol in much higher doses (ED₅₀ 5 mg/kg) than required to block the increase in chronotropic response (ED₅₀ 0.4 mg/kg) or increase in contractile force (ED₅₀ 0.2 mg/kg).

In 5 healthy volunteers, intravenously-administered 10 mg doses of metoprolol reduced exercise-induced tachycardia by 13% and systolic blood pressure during exercise by 13%. The decrease in mean blood pressure after epinephrine was abolished by metoprolol, whereas the increase in systolic blood pressure was reduced by 50%; vascular resistance in the forearm was unchanged after metoprolol.

In healthy volunteers, intravenous metoprolol 0.15 mg/kg significantly lowered cardiac output by 1.3 litre/min at rest, and 3.6 litre/min during exercise. The mean decreases in heart rate were 9 and 16 beats/min during rest and exercise, respectively. Right atrial pressure was significantly increased during rest and exercise. Oxygen consumption was not significantly influenced by drug administration. Significant increases in the calculated arteriovenous oxygen differences were observed (6 and 20 mL/litre at rest and during exercise, respectively).

Studies in reserpinized cats showed that metoprolol was devoid of β -receptor stimulating (intrinsic) activity. In cumulative doses up to 0.85 mg/kg, the drug did not significantly influence heart rate or contractile force.

A single oral dose of 40 mg of metoprolol administered to 17 anginal patients 90 minutes before testing, increased total work performed from 5994 to 8462 k.p.m. (40%). Times to onset of pain and appearance of ST depression were similarly increased from 11.8-16.9 min and 9.9-13.9 min respectively.

Effects on Pulmonary Function

The effects on specific airways resistance (SR_{aw}) of single oral doses of 100 mg of metoprolol were assessed in 6 healthy volunteers and in 12 patients with bronchial asthma. No bronchodilator was used. Metoprolol did not have a significant effect on SR_{aw} in the normal subjects, but in the asthmatic patients, SR_{aw} was significantly increased. Similar findings were observed with an 80 mg dose of propranolol.

In a controlled study, 17 patients with bronchial asthma received concomitantly a bronchodilator (terbutaline) with 50 mg or 100 mg b.i.d. of metoprolol. The FEV_{1.0} values fell only in the high dose group, indicating some β_2 -blocking effect.

Other Effects

Metoprolol showed a negligible local anesthetic effect on the isolated sciatic nerve of the frog and in the intracutaneous wheal test in guinea pigs. The cardiostimulant effects of ouabain, glucagon and theophylline were not affected by doses of 2-3 mg/kg in the anesthetized cat.

The same dosage of metoprolol was found to be devoid of anticholinergic, ganglionic blocking, antihistaminic and alpha-receptor blocking properties in cats.

Metoprolol inhibited the increase in plasma renin activity induced by furosemide.

The effects of metoprolol on isoproterenol-stimulated metabolic effects showed inhibition of the increase in liberation of glycerol, glucose, insulin and free fatty acids.

TOXICOLOGY

Acute Toxicity

| Species | Sex | Route | Solutions | LD50 (mg/kg) |
|---------|--------|-------|-----------|--------------|
| mouse | male | i.v. | 1% | 69.4 ± 5.1 |
| mouse | female | i.v. | 1% | 79.9 ± 4.5 |
| mouse | male | p.o. | 23% | 2460 ± 210 |
| mouse | female | p.o. | 25% | 2300 ± 200 |
| rat | male | i.v. | 5% | 71.9 ± 4.1 |
| rat | female | i.v. | 5% | 74.3 ± 4.4 |
| rat | male | p.o. | 50% | 4670 ± 1210 |
| rat | female | p.o. | 50% | 3470 ± 580 |

The toxic symptoms in rats included: sedation, piloerection, ataxia, irritation, spasm and lacrimation. Rats were unconscious before death, which occurred within 5-10 min after intravenous injection and 6-20 h after oral administration.

In mice the most pronounced symptoms were: sedation, hypersensitivity, irritation, spasms and ptosis. Convulsions were seen before death, which occurred within 5 minutes after intravenous injection.

No symptoms of toxicity were detectable 24 h after administration in surviving animals.

Subacute Toxicity

Subacute Toxicity in Animals

| Species | Strain | Sex | | No. of Groups | No. of Animals/ Group | Dose mg/kg/day | Route | Duration of Study | Toxic Effects |
|---------|----------------|-----|----|---------------|--------------------------|---|-------|----------------------|--|
| | | M | F | | | | | | |
| Rats | Sprague-Dawley | 40 | 40 | 4 | 10 M 10 F | Saline, 10,50,100 mg/kg/day (after 14 days, high dose incr. to 200 mg/kg/day). | p.o. | 5 weeks | Slight incr in hematocrit & slight decr in blood sugar in high dose females. |
| Dogs | Beagle | 1 | 1 | 1 | 1M 1F | 40 mg/kg x 3 days, incr by 20 mg/kg/day to 140 mg/kg x 6 days to 160 mg/kg/day. | p.o. | 3 weeks | Disturbance of balance; incr abdominal muscular tone, mydriasis, hyperemia in visible mucous membranes. One dog died at dose level of 140 mg/kg/day. |
| Dogs | Beagle | 1 | 2 | 2 | 1 M | 80 mg/kg b.i.d./one day; 2 days later, single dose of 100 mg/kg | p.o. | 3 days | Disturbance of balance; vomiting, prostration, dyspnea, loss of consciousness, death. |
| | | | | | 2 F | 20 mg/kg/b.i.d., incr every 5 days by 20 mg/kg/b.i.d. up to 120 mg/kg/b.i.d. | p.o. | 4 weeks | Vomiting; incr salivation, tremor, ataxia, one dog died at highest dose. |
| Dogs | Beagle | 4 | 4 | 4 | 1M 1F | 0,5,20,40 mg/kg/day | p.o. | 4 weeks | None |
| Dogs | Beagle | 3 | 3 | 3 | 1 M 1 F | Saline, 0.5, 5 mg/kg/day | i.v. | 2 weeks | Prolonged PR interval in ECG. |
| Dogs | Beagle | 2 | 2 | 2 | 1 M 1 F | Saline, 5 mg/kg/day | i.v. | 2 weeks | Prolonged PR interval in ECG. |

Chronic Toxicity

Chronic Toxicity in Animals

| Species | Strain | Sex | | No. of Groups | No. of Animals/ Group | Dose mg/kg/day | Route | Duration of Study | Toxic Effects |
|---------|----------------|-----|----|-------------------------|------------------------------|---|-------|-------------------|--|
| | | M | F | | | | | | |
| Rats | Sprague-Dawley | 60 | 60 | 4 | 15 M 15 F | Saline, 10,100,200 mg/kg/day. High dose increased to 200 mg/kg/day after 13 weeks. | p.o. | 6 M | None |
| Dogs | Beagle | 11 | 11 | Cont. 1 Active 3 | 2 M 2 F 3 M 3 F | 0,5,20,40 mg/kg/b.i.d. After 7 W, high dose incr to 50 mg/kg/b.i.d.; after 3 M, intermediate dose increased to 30 mg/b.i.d. and high dose to 80 mg/b.i.d. | p.o. | 6 M | Bradycardia, incr. PR interval and QT interval in ECG. |
| Dogs | Beagle | 24 | 24 | Cont. 1 Active 3 | 6 M 6 F 6 M 6 F | 0, 10, 60 mg/kg/day. High level dogs rec'd 120 mg/day on day 1, 60 mg/kg on days 3 to 8, 90 mg/kg/day on days 9 to 22 and 105 mg/kg/day for balance. | p.o. | 1 Y | 2 high dosed dogs died on Day 1, otherwise, none. |

Teratology and Reproduction Studies

Rat (Sprague-Dawley Strain)

Doses of 10, 50 and 200 mg/kg were administered orally to groups of 20 pregnant rats on days 6-15 of gestation. Treatment with metoprolol did not adversely affect any of the parameters studied.

Rabbit (New Zealand White Strain)

Doses of 5, 12.5 and 25 mg/kg were administered orally to groups of 20 pregnant rabbits on days 6-18 of gestation. Parameters studied were not significantly affected, although litter size was lower and fetal loss higher in the high dose group. The incidence of fetal abnormality was unaffected by treatment.

Rat (Sprague-Dawley Strain)

Doses of 10, 50 and 200 mg/kg were administered orally to groups of 50 rats from day 15 of gestation through lactation to 21 days post partum. Parameters studied in litter and parent animals were not adversely affected.

Rat (Charles River CD Strain)

Doses of 50 and 500 mg/kg were administered orally to groups of 10 male and 20 female rats. Males were treated for 63 days prior to mating and during the mating period. The females were treated for 14 days prior to mating, during mating and throughout the gestation and lactation periods to 21 days post partum, with an interim sacrifice at day 13 of gestation. The only significant finding in this study was a slight reduction of intrauterine growth in rats at 50 and 500 mg/kg/day and a higher frequency of stillbirths in the high dose group.

Carcinogenicity Studies

Metoprolol was administered to 3 groups of 60 male and 60 female Charles River Sprague-Dawley rats at dietary levels of 50, 200 and 800 mg/kg per day for 78 weeks. A fourth group received 2-AAF (positive control) and the fifth was the negative control group. The incidence of nodules and masses observed at necropsy were comparable between the treated and control groups. The only histopathological changes noted were an increased incidence of impaction of pulmonary alveoli by septal cells in all the treated animals and an increase in biliary hyperplasia in the high and intermediate metoprolol-treated groups. The strain of rats was susceptible to the known carcinogen 2-AAF; a statistically higher incidence of neoplasms, primarily hepatomas, was present.

A similar study in Swiss albino mice at doses of 75, 150 and 750 mg/kg/day for 78 weeks showed that the tumors were distributed with equal frequency in the treated and control groups. The strain was susceptible to the known carcinogen.

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