PRODUCT INFORMATION

DOBUTREX
(dobutamine hydrochloride)

DESCRIPTION

DOBUTREX (dobutamine hydrochloride) is (±)-4-[2-[[3-(p-hydroxyphenyl)-1-methylpropyl]amino]ethyl]-pyrocatechol hydrochloride.

Molecular Formula: C_{18}H_{23}NO_{3}HCl        Molecular Weight: 337.84

PHARMACOLOGY

Pharmacodynamics

DOBUTREX is a synthetic catecholamine prepared as a 50:50 racemic mix of levo- and dextro-enantiomers. Animal studies have demonstrated that the levo-stereoisomer is a partial alpha-1 agonist with modest beta-2 activity. The dextro-stereoisomer is a beta-1 and beta-2 agonist with alpha-1 blocking activity. These functional adrenoceptor profiles are consistent with dobutamine's well-described potent inotropic activity and typically mild vasodilatory action. The exact role each enantiomer plays in dobutamine's observed clinical effects, however, is unknown. It produces comparatively mild chronotropic, hypertensive and arrhythmogenic effects.

In contrast with dopamine, it does not release noradrenaline and its actions are not dependent on noradrenaline stores in the heart. In animal studies, dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoprenaline.

Pretreatment of dogs with reserpine or desmethyl imipramine does not alter the actions of dobutamine. This provides strong experimental evidence that the drug is a direct agonist.

In patients with heart failure, DOBUTREX increases stroke volume and cardiac output and decreases pulmonary artery wedge pressure and total systemic and pulmonary vascular resistances. Occasionally, minimal vasoconstriction has been observed. The increased stroke
volume and decreased pulmonary artery wedge pressure are consistent with a shift in the ventricular function curve upward and to the left.

DOBUTREX is typically less chronotropic than other inotropic catecholamines, like dopamine and isoproterenol. Significant tachycardia, however, may occur with increasing doses of DOBUTREX, particularly above 10 μg/kg/min.

Mean arterial pressure in patients with heart failure usually is not changed significantly by DOBUTREX because the effect of the increase in cardiac output is balanced by the concomitant decrease in peripheral vascular resistance. Both increments and decrements in arterial blood pressure have been reported. Patients with pre-existing arterial hypertension, even those who are normotensive at the time, seem more susceptible to sustaining a pressor response.

DOBUTREX does not appear to act at dopamine receptors; thus it does not selectively dilate renal or splanchnic vessels. In patients with congestive heart failure from cardiomyopathy DOBUTREX may improve renal blood flow, glomerular filtration rate, urine flow, and sodium excretion by increasing cardiac output and by nonselective vasodilatation.

Facilitation of atrioventricular conduction has been observed during administration of DOBUTREX in human electrophysiologic studies in normal subjects and in patients with atrial fibrillation.

Like all positive inotropic agents, DOBUTREX increases myocardial oxygen consumption. DOBUTREX also increases coronary blood flow and myocardial oxygen supply. The changes in oxygen demand are dependent on several factors, including the following:

(a) level of wall tension required to generate intraventricular pressure during systole;
(b) changes in afterload, generally proportional to changes in systolic blood pressure;
(c) changes in heart rate. ¹, ²

When the use of a positive inotropic agent in a patient with a failing, dilated heart results in a decrease in ventricular diameter, oxygen demand need not increase, provided afterload and heart rate do not increase markedly. In general, DOBUTREX does not cause an imbalance between oxygen consumption and supply in either animals or humans with heart disease. The arteriovenous extraction ratio of lactic acid, an indirect evidence of unimpeded aerobic metabolism, may be reduced during administration of DOBUTREX. In some instances net myocardial lactate extraction has become negative. Net lactate production has been reported in a few patients; this has usually occurred in patients with severe coronary artery disease especially when heart rate and/or arterial blood pressure have increased excessively during infusion of DOBUTREX, or in patients who respond poorly to the drug.

Myocardial infarct size and the incidence and severity of ventricular arrhythmias were not increased in patients with acute myocardial infarction who were treated with DOBUTREX for 24 hours, as compared to similar patients who did not receive DOBUTREX. In this study, DOBUTREX was titrated so that (1) heart rate did not increase by more than 10% of baseline values or to a maximum of 120 beats/minute, whichever was less, and (2) blood pressure did
not exceed 130 mmHg. In animals, administration of DOBUTREX shortly after the ligation of coronary arteries reduces infarct size, when compared to controls receiving saline solution or dopamine. In other animals with experimental infarction who were given DOBUTREX at doses that increased both heart rate and myocardial contractility, there were electrocardiographic signs of increased ischaemia. Recent studies in animals suggest that functional deterioration and possible enlargement of experimental myocardial lesions during the administration of positive inotropic drugs including DOBUTREX is related to their chronotropic effect rather than to the positive inotropism. When DOBUTREX was infused in dogs at doses that produced significant inotropic effect with a minimal increase in heart rate, there was no evidence of enhanced myocardial damage.

DOBUTREX has been used in combination with dopamine. In general, the combination does not increase cardiac output more than does an equivalent dose of DOBUTREX alone. Whereas systemic blood pressure typically does not change significantly with DOBUTREX alone, this can be expected to increase with the addition of dopamine. Similarly, whereas DOBUTREX tends to increase renal blood flow in patients with heart failure in proportion to improvement in cardiac output, the addition of dopamine in doses up to 5 μg/kg/minute will exert a further enhancement of renal blood flow. Finally, ventricular filling pressure which can increase with dopamine therapy alone, tends either not to change or to decrease when DOBUTREX is given concomitantly. Avoiding such increases in ventricular filling pressure may be beneficial to the patient at risk of pulmonary congestion and oedema.

**Pharmacokinetics**

The onset of action is within one to two minutes; however, as much as ten minutes may be required to obtain the peak effect of a particular infusion rate. Steady state plasma concentrations are linearly related to infusion rates.

Plasma clearance of DOBUTREX in humans is 2.4 L/min/m², the volume of distribution is about 20% of body weight, and plasma elimination half-time is less than 3 minutes. The principle routes of disposition include methylation followed by conjugation. Metabolites are eliminated by renal and biliary mechanisms. In human urine the major excretion products are the conjugates of dobutamine and 3-0-methyl dobutamine. The 3-0-methyl derivative of dobutamine is inactive.

Most clinical experience with dobutamine is short-term, up to several hours in duration. In the limited number of patients who were studied for 24, 48, and 72 hours, a persistent increase in cardiac output occurred in some, whereas the output of others returned toward base-line values. Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

**INDICATIONS**

DOBUTREX is indicated in adults who require short-term treatment of cardiac failure secondary to acute myocardial infarction, or cardiac surgery.
CONTRAINDICATIONS

DOBUTREX is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in patients who have shown previous manifestations of hypersensitivity to DOBUTREX.

WARNINGS

1. **Increase in Heart Rate or Blood Pressure.**
DOBUTREX may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50 mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Patients with pre-existing hypertension are more likely to develop an exaggerated pressor response.

2. **Increased Atrioventricular Conduction.**
Because DOBUTREX facilitates atrioventricular conduction, patients with atrial flutter or fibrillation may develop rapid ventricular responses.

3. **Ectopic Activity.**
DOBUTREX may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia or fibrillation.

4. **Hypersensitivity**
Reactions suggestive of hypersensitivity associated with the administration of DOBUTREX, including skin rash, fever, eosinophilia, and bronchospasm, have been reported occasionally.

5. **Anaesthetics.**
The myocardium may be sensitised to the effect of dobutamine by cyclopropane or halogenated hydrocarbon anaesthetics, and these should be avoided.

PRECAUTIONS

1. During the administration of DOBUTREX, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary artery wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of DOBUTREX.

2. Hypovolaemia should be corrected with suitable volume expanders before treatment with DOBUTREX is instituted.

3. Because positive inotropic therapy can be associated with increases in intra-pulmonary shunting, attention to arterial blood gases during treatment with DOBUTREX is recommended.
4. In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with DOBUTREX.

5. The potency of DOBUTREX may be decreased if the patient is given beta-adrenergic receptor antagonists. In such a case, the unopposed alpha-agonist effects of DOBUTREX may become apparent, including peripheral vasoconstriction and hypertension. Conversely, alpha-adrenergic blockade may make the beta-1 and beta-2 effects apparent, resulting in tachycardia and vasodilatation.

6. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

7. Dobutamine, like other B₂-agonists, can produce a mild reduction in serum potassium concentration, rarely to hypokalaemic levels. Accordingly, consideration should be given to monitoring serum potassium.

8. **Usage for Heart Failure Complicating an Acute Myocardial Infarction**—Although the treatment of heart failure and the reduction in cardiac diameter will decrease myocardial oxygen consumption, there is still concern that the use of any positive inotropic agent may increase myocardial oxygen demand and the size of an infarction by intensifying ischaemia. Pertinent clinical data with DOBUTREX following acute myocardial infarction are limited but suggest that DOBUTREX does not have an adverse effect on the myocardium when used in doses that do not cause excessive increments in heart rate or arterial pressure. The dose of DOBUTREX should be titrated to prevent an excessive increase in heart rate and systolic blood pressure.

9. **Cardiac Rupture as a Complication of Myocardial Infarction** – Cardiac rupture is a potential complication of myocardial infarction. The risk of cardiac rupture (septal and free wall) may be influenced by a variety of factors including site of, and time, since, infarct. There have been very rare, fatal reports of acute cardiac rupture during dobutamine stress testing. These events have occurred during pre-discharge examination in patients hospitalised with recent (within 4-12 days) myocardial infarction. In the reported cases of free wall rupture, resting echocardiogram showed a dyskinetic and thinned inferior wall. Patients considered at risk of cardiac rupture during dobutamine testing should therefore be carefully evaluated.

**USE IN PREGNANCY** -- Pregnancy Category B2

Reproduction studies performed in rats (15 mg/kg,IV) and rabbits (30 mg/kg,IV) have revealed no evidence of impaired fertility, harm to the foetus, or teratogenic effects due to dobutamine hydrochloride. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, dobutamine hydrochloride should not be used during pregnancy unless the potential benefits outweigh the potential risks to the foetus.
USE IN CHILDREN

Safety and efficacy for use in children have not been studied.

INTERACTIONS WITH OTHER DRUGS

There was no evidence of drug interactions in clinical studies in which DOBUTREX was administered concurrently (but by separate routes or methods of administration) with other drugs, including digitalis preparations, frusemide, spironolactone, lignocaine, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and paracetamol.

Preliminary studies in heart failure patients indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Studies on limited numbers of patients with heart failure demonstrate that the combination of dobutamine and nitroglycerin results in a lower pulmonary wedge pressure than when dobutamine is used alone and a higher cardiac output than when nitroglycerin is used alone.

Beta-adrenergic receptor antagonists, alpha-adrenergic receptor antagonists, cyclopropane or halogenated hydrocarbon anaesthetics (see WARNINGS and PRECAUTIONS).

ADVERSE REACTIONS

Many of the adverse effects of DOBUTREX are a quantitative extension of the pharmacological actions. The following adverse effects have been reported.

Increased Heart Rate, Blood Pressure and Ventricular Ectopic Activity--A 10 to 20 mm Hg increase in systolic blood pressure and an increase in heart rate of 5 to 15 beats per minute have been noted in most patients (see WARNINGS regarding exaggerated chronotropic and pressor effects). Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related and their occurrence may require that the dose be reduced.

Hypotension--Precipitous decreases in blood pressure have occasionally been described in association with dobutamine therapy. Decreasing the dose or discontinuing the infusion typically results in rapid return of blood pressure to baseline values. In rare cases, however, intervention may be required and reversibility may not be immediate.

Reactions at Sites of Intravenous Infusion--Phlebitis has occasionally been reported. Local inflammatory changes have been described following inadvertent infiltration. Isolated cases of cutaneous necrosis (destruction of skin tissue) have been reported.
Miscellaneous Uncommon Effects--The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, non-specific chest pain, palpitations, shortness of breath, skin rash, fever, eosinophilia and bronchospasm. Isolated cases of thrombocytopenia have been reported.

Administration of DOBUTREX, like other catecholamines, can produce a mild reduction in serum potassium concentrations, rarely to hypokalaemic levels (see PRECAUTIONS).

There have been rare reports of fatal cardiac rupture during dobutamine stress testing.

**DOSAGE AND ADMINISTRATION**

Do not add DOBUTREX to 5% Sodium Bicarbonate Injection or any other strongly alkaline solutions. Because there are numerous physical incompatibilities, DOBUTREX should not be mixed with other drugs in the same solution. Saline solutions should not be used to reconstitute DOBUTREX, because chloride ions may interfere with the initial dissolution through a common ion effect with DOBUTREX.

DOBUTREX should not be used in conjunction with other agents or diluents containing both sodium bisulphite and ethanol.

**Reconstitution and Stability of DOBUTREX 250 mg.**

DOBUTREX may be reconstituted with Sterile Water for Injection or 5% Glucose Injection. To reconstitute, add 10 mL of diluent to the vial. If the material is not completely dissolved, add an additional 10 mL of diluent.

Reconstituted DOBUTREX must be further diluted to at least 50 mL at the time of administration in 5% Glucose Injection, Lactated Ringer's Injection or Sodium Lactate Injection. I.V. solutions should be used within 24 hours of reconstitution.

Although the chemical and physical stability of reconstituted / further diluted solutions of Dobutamine Hydrochloride has been demonstrated for 48 hours under refrigeration (2-8°C) or for 6 hours at room temperature (below 25°C) it is recommended that, in order to reduce microbiological contamination hazards, the reconstituted / further diluted solution should be prepared immediately prior to use and infusion commenced as soon as practicable after preparation of the mixture. The further diluted infusion solution should be used within 24 hours of reconstitution and any residue discarded. Storage of Dobutrex Solution and its reconstituted solution should be at 2-8°C.

**Warning:** Reconstituted and/or further diluted solutions which are hazy, discoloured or contain visible particulate matter should be discarded. Solutions containing DOBUTREX may exhibit a pink colour that, if present, will increase with time. This colour change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.
Administration--Because of its short half-life, DOBUTREX must be administered as a continuous intravenous infusion. This is most reliably accomplished using a mechanical infusion pump or controller. Following the initiation of a constant rate infusion, or upon changing the rate, a steady-state dobutamine plasma concentration is achieved within approximately 10 minutes. Thus, loading doses or bolus injections are not necessary and are not recommended.

Reactions at sites of intravenous infusion - phlebitis has occasionally been reported. Local inflammatory changes have been described following inadvertent infiltration.

Recommended Dosage--The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 μg/kg/min (see table). On rare occasions, infusion rates up to 40 μg/kg/min have been required to obtain the desired effect. However, the possibility of intensifying myocardial ischaemia should be borne in mind and the lowest effective dose infused.

Rates of Infusion for Concentrations of 250, 500, and 1000 microgram/mL

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<th>Drug Delivery Rate (μg/kg/min)</th>
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<tr>
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<td>250 μg/mL *</td>
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<td>(mL/kg/min)</td>
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* 250 mg per litre of diluent
+ 500 mg per litre or 250 mg per 500 mL of diluent
± 1000 mg per litre or 250 mg per 250 mL of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by the following clinical indicators: haemodynamic parameters such as heart rate and rhythm, arterial pressure, and, whenever possible, cardiac output and measurements of ventricular filling pressures (central venous, pulmonary artery wedge, and left atrial), and signs of pulmonary congestion and organ perfusion (urine flow, skin temperature, and mental status).

Concentrations up to 5000 μg/mL have been administered to humans (250 mg/50mL). The final volume administered should be determined by the fluid requirements of the patient. Rather than abruptly discontinuing therapy with dobutamine hydrochloride, it is often advisable to decrease the dosage gradually.
OVERDOSAGE

Overdoses of dobutamine have been reported rarely. The following is provided to serve as a guide if such an overdose is encountered.

Signs and Symptoms--Toxicity from dobutamine hydrochloride is usually due to excessive cardiac-receptor stimulation. The duration of action of dobutamine hydrochloride is generally short ($T_{1/2} = 2$ minutes) because it is rapidly metabolised by catechol-O-methyltransferase. The symptoms of toxicity may include anorexia, nausea, vomiting, tremor, anxiety, palpitations, headache, shortness of breath, and anginal and nonspecific chest pain. The positive inotropic and chronotropic effects of dobutamine on the myocardium may cause hypertension, tachyarrhythmias, myocardial ischaemia and ventricular fibrillation. Hypotension may result from vasodilation. If the product is ingested, unpredictable absorption may occur from the mouth and the gastrointestinal tract.

Treatment--In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient. The initial actions to be taken in a dobutamine hydrochloride overdose are discontinuing administration, establishing an airway, and ensuring oxygenation and ventilation. Resuscitative measures should be initiated promptly. Severe ventricular tachyarrhythmias may be successfully treated with propranolol or lignocaine. Hypertension usually responds to a reduction in dose or discontinuation of therapy.

Protect the patient's airway and support ventilation and perfusion. If needed, meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, haemodialysis, or charcoal haemoperfusion have not been established as beneficial for an overdose of dobutamine hydrochloride.

Contact the Poisons Information Centre on 131126 for management of overdose.

STORAGE

Store below 25 degrees Celsius. For storage conditions after reconstitution, see “DOSAGE AND ADMINISTRATION”.

PRESENTATION

DOBUTREX 250 mg powder for injection vial is a white to off-white, sterile, lyophilised powder for intravenous use only. It requires reconstitution and then further dilution before
use. Each vial contains 250 mg dobutamine (as dobutamine hydrochloride), 250 mg mannitol and water for injections q.s. Hydrochloric acid is used during manufacture to adjust the pH. The pH of the reconstituted solution is between 2.5 and 5.5. Packs of 1 vial.

**POISON SCHEDULE**

S4

**SPONSOR**

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos Street
St Leonards, NSW 2065
Australia

**REFERENCES**


**DATE OF TGA APPROVAL**

Approved by the Therapeutic Goods Administration: 8 November 1995
Safety Related-Change: 15th December 2003
Date of most recent amendment: 19 February 2010.