PRODUCT INFORMATION
DOBUTAMINE SANDOZ® 250mg/20mL (as hydrochloride)
CONCENTRATED INJECTION

NAME OF THE MEDICINE

Active.  Dobutamine hydrochloride

Inactive.  Sodium metabisulfite, water for injections, hydrochloric acid and/or sodium hydroxide to adjust pH

DESCRIPTION

Chemical name:  (+/-)-4-[2-[[3- (para-hydroxyphenyl)-1-methylpropyl]amino]ethyl]-pyrocatechol hydrochloride

Molecular formula:  C_{18}H_{23}NO_{3}HCl

Molecular Weight:  337.84

CAS  49745-95-1

PHARMACOLOGY

Dobutamine 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 adrenoreceptor 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, dobutamine 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.

Dobutamine is typically less chronotropic than other inotropic catecholamines, like dopamine and isoprenaline. Significant tachycardia, however, may occur with increasing doses of dobutamine, particularly above 10 microgram/kg/minute.

Mean arterial pressure in patients with heart failure usually is not changed significantly by dobutamine 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 normotenive at the time, seem more susceptible to sustaining a pressor response.

Dobutamine 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, dobutamine 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 dobutamine in human electrophysiological studies in normal subjects and in patients with atrial fibrillation.

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

- level of wall tension required to generate intraventricular pressure during systole;
- changes in afterload, generally proportional to changes in systolic blood pressure; and
- changes in heart rate.

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, dobutamine 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, and indirect evidence of unimpeded aerobic metabolism, may be reduced during
administration of dobutamine. 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 dobutamine, 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 dobutamine for 24 hours, as compared to similar patients who did not receive dobutamine. In this study, dobutamine was titrated so that heart rate did not increase by more than 10% of baseline values or to a maximum of 120 beats/minute, whichever was less; and blood pressure did not exceed 130mmHg. In animals, administration of dobutamine 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 dobutamine 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 dobutamine, is related to their chronotropic effect rather than to the positive inotropism. When dobutamine 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.

Dobutamine has been used in combination with dopamine. In general, the combination does not increase cardiac output more than does an equivalent dose of dobutamine alone. Whereas systemic blood pressure typically does not change significantly with dobutamine alone, this can be expected to increase with the addition of dopamine. Similarly, whereas dobutamine 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 microgram/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 dobutamine 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 dobutamine in humans is 2.4L/minute/m², the volume of distribution is about 20% of bodyweight, and plasma elimination half-life is less than three 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-O-methyl dobutamine. The 3-O-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 baseline values. Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

INDICATIONS

Adults who require short-term treatment of cardiac failure secondary to acute myocardial infarction, or cardiac surgery.

CONTRAINDICATIONS

Idiopathic hypertrophic subaortic stenosis. Previous manifestations of hypersensitivity to dobutamine or any of the excipients.

PRECAUTIONS

During the administration of dobutamine, 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 dobutamine.

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

Because positive inotropic therapy can be associated with increases in intrapulmonary shunting, attention to arterial blood gases during treatment with dobutamine is recommended.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with dobutamine.

The potency of dobutamine may be decreased if the patient is given beta-adrenergic receptor antagonists. In such a case, the unopposed alpha-agonist effects of dobutamine 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.

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

Dobutamine, like other beta_2-agonists, can produce a mild reduction in serum potassium concentration, rarely to hypokalaemic levels. Accordingly, consideration should be given to monitoring serum potassium.
Increase in heart rate or blood pressure

Dobutamine may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10% of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5% have had a 50mmHg 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.

Increased atrioventricular conduction

Because dobutamine facilitates atrioventricular conduction, patients with atrial flutter or fibrillation may develop rapid ventricular responses.

Ectopic activity

Dobutamine may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia or fibrillation.

Hypersensitivity

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

Dobutamine Sandoz contains sodium metabisulfite, which may cause allergic type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people.

Anaesthetics

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

Use 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 dobutamine following acute myocardial infarction are limited but suggest that dobutamine 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 dobutamine should be titrated to prevent an excessive increase in heart rate and systolic blood pressure.

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 predischarge examination in patients hospitalised with recent (within 4 to 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.

Carcinogenicity / mutagenicity / impairment of fertility

Studies to evaluate the carcinogenic or mutagenic potential of dobutamine, or its potential to affect fertility, have not been conducted.

Use in pregnancy (Category B2)

Reproduction studies performed in rats (15mg/kg intravenously) and rabbits (30mg/kg intravenously) 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 lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised. If a mother requires treatment with dobutamine, breastfeeding should be discontinued for the duration of the treatment.

Use in children

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

Interactions with other medicines

There was no evidence of drug interactions in clinical studies in which dobutamine 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 glyceryl trinitrate results in a lower pulmonary wedge pressure than when dobutamine is used alone and a higher cardiac output than when glyceryl trinitrate is used alone.

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

ADVERSE EFFECTS

Many of the adverse effects of dobutamine 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 20mmHg increase in systolic blood pressure and an increase in heart rate of 5 to 15 beats/minute have been noted in most patients. (See PRECAUTIONS regarding exaggerated chronotropic and pressor effects). Approximately 5% 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% 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 dobutamine, 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**

**Recommended dosage.** The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 microgram/kg/minute (see Table 1). On rare occasions, infusion rates up to 40 microgram/kg/minute 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.

### Table 1
Rates of infusion for concentrations of 250, 500 and 1000μg/mL

<table>
<thead>
<tr>
<th>Drug delivery rate (μg/kg/min)</th>
<th>Infusion delivery rate</th>
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<tbody>
<tr>
<td></td>
<td>250μg/mL* (mL/kg/min)</td>
</tr>
<tr>
<td>2.5</td>
<td>0.01</td>
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<tr>
<td>5.0</td>
<td>0.02</td>
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<tr>
<td>7.5</td>
<td>0.03</td>
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<td>12.5</td>
<td>0.05</td>
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<tr>
<td>15.0</td>
<td>0.06</td>
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* 250mg/L of diluent  
** 500mg/L or 250mg/500mL of diluent  
*** 1000mg/L or 250mg/250mL 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 5,000 microgram/mL have been administered to humans (250mg/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.

### Reconstitution and stability

Dobutamine Sandoz solution must be diluted at the time of administration to at least 50mL in an intravenous container with one of the following solutions. Glucose 5% injection, glucose 5% and sodium chloride 0.45% injection, glucose 5% and sodium chloride 0.9% injection, glucose 10% injection, lactated Ringer's injection, Normosol-M in D5W, Osmiotrol 20% in water for injection, sodium chloride 0.9% injection, or sodium lactate injection.

**Note.** Do not add Dobutamine Sandoz to sodium bicarbonate injection 5% or to any other strongly alkaline solution. Because of potential physical incompatibilities, it is recommended dobutamine hydrochloride not be mixed with other drugs in the same solution. Dobutamine hydrochloride should not be used in conjunction with other agents or diluents containing both sodium bisulfite and ethanol.

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 24 hours.
Parenteral drug products which are hazy, discoloured or contain visible particulate matter should be discarded. Solutions containing Dobutamine Sandoz 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.

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

**Administration**

Because of its short half-life, Dobutamine Sandoz 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 ten 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.

**OVERDOSAGE**

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

**Symptoms**

Toxicity from dobutamine hydrochloride is usually due to excessive cardiac beta-receptor stimulation. The duration of action of dobutamine hydrochloride is generally short (t½ = two minutes) because it is rapidly metabolised by catechol-ortho-methyltransferase. The symptoms of toxicity may include anorexia, nausea, vomiting, tremor, anxiety, palpitations, headache, shortness of breath, and anginal and non-specific 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 vasodilatation. 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 the 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 Poison Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Dobutamine Sandoz 250mg/20mL Concentrated Injection, 20mL: 1’s.

Concentrated Injection: Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 07/01/2003

Date of most recent amendment: 10/02/2016