

PRODUCT MONOGRAPH

**^{Pr}DOBUTAMINE INJECTION USP
(as Dobutamine Hydrochloride)**

Sterile Solution

12.5 mg/mL

Sympathomimetic

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

Date of Revision:
February 11, 2019

Submission Control No: 220995

**^{Pr}Dobutamine Injection USP
(as Dobutamine Hydrochloride)**

Sterile Solution

12.5 mg/mL

Sympathomimetic

ACTION AND CLINICAL PHARMACOLOGY

Dobutamine Injection USP (dobutamine hydrochloride) is a direct-acting inotropic agent whose primary activity results from stimulation of the β receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. The direct stimulation of the β_1 -receptors of the heart results in increased myocardial contractility and stroke volume, resulting in increased cardiac output. Unlike dopamine, dobutamine does not cause the release of endogenous norepinephrine.

In both animal and human studies, dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol. In patients with depressed cardiac function, both dobutamine and isoproterenol increase the cardiac output to a similar degree. In the case of dobutamine, this increase is usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. In contrast, isoproterenol increases the cardiac index primarily by increasing the heart rate while stroke volume changes little or declines.

Systemic vascular resistance is usually decreased (afterload reduction) with administration of dobutamine; however, systolic blood pressure and pulse pressure may remain unchanged or be increased because of increased cardiac output.

Unlike dopamine, dobutamine does not appear to affect dopaminergic receptors and causes no renal vasodilation; however, renal blood flow and urine output may increase because of increased cardiac output.

Following intravenous administration, the onset of action of dobutamine is within 1 to 2 minutes; however, as much as 10 minutes may be required to obtain the peak effect of a particular infusion rate. The duration of action is very short (a few minutes) and the effects of the drug generally cease shortly after discontinuance of the infusion.

INDICATIONS AND CLINICAL USES

Dobutamine Injection USP (dobutamine hydrochloride) is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

Most clinical experience with dobutamine is short-term - not more than 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 output returned toward baseline values in others.

CONTRAINDICATIONS

Dobutamine Injection USP (dobutamine hydrochloride) is contraindicated in patients with mechanical obstruction affecting left ventricular filling or outflow, especially in the case of obstructive cardiomyopathy, aortic stenosis or constrictive pericarditis, in patients with pheochromocytoma, in patients with idiopathic hypertrophic subaortic stenosis and in patients who have shown previous manifestations of hypersensitivity to dobutamine or to sulfites. Dobutamine must not be used for detection of myocardial ischemia and of viable myocardium in case of recent (within the last 30 days) myocardial infarction (see **Cardiac Rupture - WARNINGS**).

WARNINGS

Cardiac Rupture

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 detection of myocardial ischemia and of viable myocardium with dobutamine. 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 dyskinctic and thinned inferior wall. Patients considered at risk of cardiac rupture during dobutamine testing should therefore be carefully evaluated prior to testing.

Increase in Heart Rate or Blood Pressure

Dobutamine Injection USP (dobutamine hydrochloride) 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 50-mm Hg or greater increase in systolic pressure. Patients with pre-existing hypertension appear to have an increased risk of developing an exaggerated pressor response. Usually, reduction of dosage promptly reverses these effects.

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, but intervention may be required and reversibility may not be immediate.

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

Ectopic Activity

Dobutamine may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia. Dobutamine Injection USP should not be used in the presence of uncorrected tachycardia or ventricular fibrillation.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with Dobutamine Injection USP. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response(See **Increase in Heart Rate or Blood Pressure - WARNINGS**).

Hypersensitivity

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

Dobutamine Injection USP contains sodium metabisulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

General

During the administration of Dobutamine Injection USP (dobutamine hydrochloride), as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of dobutamine.

Caution should be exercised in order to prevent infiltration at the injection site.

Bolus administration of dobutamine should be avoided.

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

Animal studies indicate that the inotropic effects of dobutamine on the heart are antagonized by concurrent administration of beta-blockers. Consequently, dobutamine may be ineffective or may have a slight vasoconstricting effect in patients who have recently received beta blockers(See Drug Interactions).

Dobutamine like other β_2 -agonists, can produce a slight reduction in serum potassium concentration, rarely to hypokalemic levels. Accordingly, consideration should be given to monitoring serum potassium concentrations during dobutamine therapy.

After Dilution

Excess parenteral administration of potassium-free solutions may result in significant hypokalemia. The intravenous administration of these solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema.

Solutions containing dextrose should be used with caution in patients with known subclinical or overt diabetes mellitus.

Use in patients with special conditions

Dobutamine Injection USP should be used with caution in patients with hyperthyroidism, in patients receiving inhalation anaesthetic agents such as cyclopropane or halothane and in patients taking concomitantly other sympathomimetic amines, guanethidine or rauwolfia alkaloids(See **Drug Interactions**).

Usage Following Acute Myocardial Infarction

Particular care is required when administering dobutamine to patients with acute myocardial infarction, as any significant increase in heart rate or excessive increases in arterial pressure that occur may intensify ischaemia and cause angina pain and ST segment elevation.

Use in Pregnancy

Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to dobutamine. However, the drug has not been administered to pregnant women and therefore, should be used only when the expected benefits clearly outweigh the potential risks to the fetus. It is not known if dobutamine crosses the placenta.

Use in Nursing Mothers

It is not known if dobutamine is distributed into milk. If a mother requires dobutamine treatment, breastfeeding should be discontinued for the duration of the treatment.

Use in Labour and Delivery

The effect of dobutamine on labour and delivery is unknown.

Use in Children

The safety and effectiveness of dobutamine for use in children have not been established.

Drug Interactions

There was no evidence of drug interactions in clinical studies in which dobutamine was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, nitroglycerin, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid and acetaminophen.

As with other sympathomimetic agents, caution is advised when Dobutamine Injection USP is used concurrently with either β -adrenergic blocking agents or general anesthetics.

- ***β -Adrenergic Blocking Agents*** - In animals, the cardiac effects of dobutamine are antagonized by β -adrenergic blocking agents such as propranolol and metoprolol resulting in predominance of α -adrenergic effects and increased peripheral resistance.
- ***General Anesthetics*** - Ventricular arrhythmias have been reported in animals receiving usual doses of dobutamine during halothane or cyclopropane anesthesia; therefore, caution should be used when administering dobutamine to patients receiving general anesthetics.

Preliminary studies 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.

Dobutamine is metabolized by catechol-o-methyltransferase (COMT), pharmacokinetic drug interactions between COMT inhibitors such as entacapone may enhance dobutamine activity. Frequent dose titration to the lowest effective dose of dobutamine is recommended when coadministered with COMT inhibitors including entacapone.

ADVERSE REACTIONS

- Cardiovascular:** The most common adverse reactions relate to the effect of dobutamine on the cardiovascular system. A 10 to 20 mm Hg increase in systolic blood pressure and an increase in heart rate of 5 to 15 beats/minute have been noted in most patients. Approximately 5% of patients have had increased premature ventricular beats during infusions. These effects are usually dose-related. Other post-market adverse effects included eosinophilic myocarditis, ventricular tachycardia, arteriospasm coronary, stress cardiomyopathy, arrhythmia. Fatal or nonfatal; myocardial rupture, ventricular fibrillation, and ventricular dysfunction.
- Hypotension:** Precipitous decreases in blood pressure have occasionally been described in association with dobutamine therapy. Decreasing the dose or discontinuing the infusion usually results in rapid return of blood pressure to baseline values. In rare cases, intervention may be required but the effect on pressure may not be readily reversible.
- Investigations:** Electrocardiogram ST segment elevation.
- Less common:** The following adverse effects have been reported in 1% to 3% of patients: nausea, anginal pain, nonspecific chest pain, palpitations, headache and shortness of breath. Isolated cases of thrombocytopenia have been reported.
- Miscellaneous:** Phlebitis has been occasionally reported. Pruritus, and local inflammatory changes may occur following inadvertent infiltration. Isolated cases of cutaneous necrosis have been reported.

Administration of dobutamine, like other catecholamines, can produce a mild reduction in serum potassium concentration rarely to hypokalemia levels (see **PRECAUTIONS**).

Longer-Term Safety:

Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

A recent report has been published describing an accidental overdose of dobutamine. The patient received an intravenous infusion of dobutamine at a rate of more than 130 mcg/kg/min for 30 minutes (3 x the recommended maximum dose). The patient experienced anxiety, tachycardia, tachypnea, raised systolic blood pressure, vomiting, palpitations, chest pain, dyspnoea, and paraesthesia as well as urinary incontinence, an effect not previously associated with dobutamine. Effects subsided over two hours.

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 β -receptor stimulation. The symptoms of toxicity may include anorexia, nausea, vomiting, tremor, anxiety, tachycardia, 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 ischemia, and ventricular fibrillation. Hypotension may result from vasodilation.

Treatment - In case of overdosage, as evidenced by excessive blood pressure alteration or tachycardia, reduce the rate of administration or temporarily discontinue dobutamine therapy until the patient's condition stabilizes. Because the duration of action of dobutamine is short ($T_{1/2} = 2$ to 3 minutes) no additional measures are usually necessary.

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

DOSAGE AND ADMINISTRATION

Dobutamine Injection USP (dobutamine hydrochloride) IS A POTENT DRUG; IT IS NOT FOR DIRECT INJECTION AND MUST BE DILUTED EXACTLY AS DIRECTED BEFORE ADMINISTRATION TO PATIENTS AS AN INTRAVENOUS INFUSION (see INSTRUCTIONS FOR USE).

Note: Do not add Dobutamine Injection USP to 5% Sodium Bicarbonate Injection or any other strong alkaline solution.

Administration

At the time of administration, Dobutamine Injection USP must be further diluted in an intravenous container to at least 50 mL with a compatible intravenous solution. It is recommended that a precision

volume control intravenous set be used when administering dobutamine by continuous intravenous infusion. Intravenous solutions should be used within 24 hours.

The rate of administration and the duration of therapy should be carefully adjusted according to the patient's response as indicated by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Solutions containing Dobutamine Injection USP may exhibit a pink colour that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency within the 24 hours after being reconstituted.

Dosage

The dosage of dobutamine hydrochloride is expressed in terms of dobutamine.

Recommended Dosage: The rate of infusion needed to increase cardiac output usually ranged from 2.5 to 10 mcg/kg/min (see Table 1). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Table 1			
Rates of Infusion for Concentrations of 250, 500 and 1,000 mg/L			
Drug Delivery Rate (mcg/kg/min)	INFUSION DELIVERY RATE		
	250 mg/L* (mL/kg/min)	500 mg/L** (mL/kg/min)	1,000 mg/L*** (mL/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

* 250 mg/L of admixture (add one 20 mL vial of 12.5 mg/mL of Dobutamine Injection USP to obtain a final admixture volume of 1 L).
 ** 500 mg/L or 250 mg/500 mL of admixture (add one 20 mL vial of 12.5 mg/mL of Dobutamine Injection USP to obtain a final admixture volume of 500 mL).
 *** 1000 mg/L or 250 mg/250 mL of admixture (add one 20 mL vial of 12.5 mg/mL of Dobutamine Injection USP to obtain a final admixture volume of 250 mL).

The final volume administered should be determined by the fluid requirements of the patient.

Instructions for Use

Parenteral Products - Dilution

Dobutamine Injection USP (dobutamine hydrochloride) must be further diluted in an intravenous container to at least 50 mL with one of the following intravenous solutions:

- 0.9% Sodium Chloride Injection, USP
- 5% or 10% Dextrose Injection, USP
- 3.3% Dextrose and 0.3% Sodium Chloride Injection
- 5% Dextrose and 0.9% Sodium Chloride Injection, USP
- Lactated Ringer's Injection

Intravenous solutions should be used within 24 hours of preparation. Dobutamine admixture with Lactated Ringer's Injection should be used immediately.

Compatibility

Dobutamine Injection USP is incompatible with alkaline solutions, and it should not be mixed with 5% Sodium Bicarbonate Injection or any other alkaline solution. Because of potential physical incompatibilities, it is recommended that dobutamine not be mixed with other drugs in the same solution. Dobutamine Injection USP should not be used in conjunction with other agents or diluents containing ethanol.

Dobutamine solutions without added electrolytes (in dilution vehicle) should not be administered simultaneously with blood through the same infusion set because of the possibility that pseudoagglutination of red cells may occur.

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

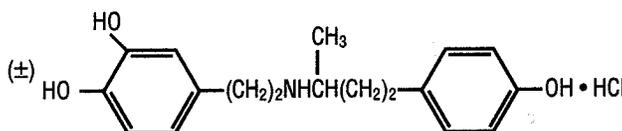
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Dobutamine Hydrochloride

Chemical Name: (±)-4-[2-[[3-(p-hydroxyphenyl)-1-methylpropyl]amino]ethyl]-pyrocatechol hydrochloride.

Structural Formula:



Molecular Formula: C₁₈H₂₃NO₃.HCl

Molecular Weight: 337.85

Description:

Dobutamine is a synthetic sympathomimetic drug which is structurally related to dopamine. Dobutamine hydrochloride occurs as a white to off-white crystalline powder, which is sparingly soluble in water and in alcohol. Dobutamine has a pK_a of 9.4.

Composition:

Dobutamine Injection USP is a clear, practically colorless sterile, nonpyrogenic solution of dobutamine hydrochloride in Water for Injection. Each mL contains 12.5 mg dobutamine (as hydrochloride), 0.20 mg sodium metabisulfite (as antioxidant). Headspace is nitrogen gassed. May contain hydrochloric acid and/or sodium hydroxide to adjust the pH. pH is 3.3 (2.5 to 5.5).

Stability and Storage Recommendations:

Store vials between 15°C to 25°C.

AVAILABILITY OF DOSAGE FORMS

Dobutamine Injection USP is supplied in single dose Fliptop vials as follows:

- 12.5 mg/mL dobutamine in 20 mL (250 mg/20 mL), List L898.

This presentation MUST BE DILUTED PRIOR TO INTRAVENOUS USE.

PHARMACOLOGY

Human

Three male volunteers received 2 mcg/kg/min of dobutamine via intravenous infusion for 15 minutes. During the infusion period plasma concentrations reached 15 to 24 mcg/mL, and upon cessation of infusion the plasma levels fell to 0 to 2 mcg/mL within 10 to 15 minutes ($t_{1/2} = 2$ minutes). Limited urinary studies indicated that dobutamine was rapidly metabolized to 3-OH-methyl dobutamine conjugate and dobutamine conjugate, which were mainly excreted over 2 hours and essentially completely excreted in 6 hours.

The pharmacokinetics of dobutamine were investigated in 7 patients with severe cardiac failure. Dobutamine was administered by a constant intravenous infusion at rates of 2.5, 5.0, 7.5 and 10.0 mcg/kg/min. Steady-state plasma levels increased in proportion to the infusion rate, indicating that there was no saturation of the disposition processes.

The disappearance $t_{1/2}$ of dobutamine was calculated to be 2.37 ± 0.7 min with a distribution volume of 0.202 ± 0.084 L/kg and a total body clearance of 2.35 ± 1.01 (SD) L/min/M².

Animal

Studies in dogs given intravenous infusions of C¹⁴ - dobutamine (25 mcg/kg/min for 30 minutes) indicated peak plasma levels of unchanged drug at 8 to 10 min and upon cessation of the infusion the unchanged drug disappeared rapidly from plasma with a $t_{1/2}$ of 1 to 2 minutes. The dobutamine appeared to be redistributed into tissues, to be metabolized, and to reenter the circulation mainly as 3-hydroxy-methyl dobutamine glucuronide. The plasma $t_{1/2}$ of the metabolites was determined to be 1.9 hours. Over a period of 48 hours, 87% of the administered radioactive dose was excreted in urine (67%) and feces (20%). Almost all of the metabolites found in urine were in the form of glucuronide conjugates (i.e., approx. 82% and 7% of urinary excretion products were 3-hydroxy-methyl dobutamine glucuronide and dobutamine glucuronide, respectively).

Biliary excretion also accounted for a significant portion of the eliminated drug. In dogs with cannulated bile ducts that were given C¹⁴-dobutamine (5mcg/kg/min) for 4 hours, approximately 30 to 35% of the administered dose was excreted in the bile.

Studies in rats with cannulated bile ducts, receiving single intravenous injection of C¹⁴-dobutamine (0.5 mg/kg) resulted in 18.7% of the dose being excreted in urine and 80% being excreted in the bile in 24 hours.

These results indicated that the major route of excretion of dobutamine and/or metabolites in rats was via biliary excretion (80% of administered radioactivity over 24 hours).

Tissue distribution studies performed in dogs and rats revealed no unusual localization of radioactivity except for organs of excretion and metabolism (liver, kidney and intestines).

Alteration of synaptic concentrations of catecholamines with either reserpine or tricyclic antidepressants does not alter the actions of dobutamine in animals, which indicates that the actions of dobutamine are not dependent on presynaptic mechanisms.

Although the positive inotropic activity of dobutamine is attributed to the selective stimulation of myocardial β_1 -adrenoceptors, recent animal studies suggest that this activity results from a combination of α -stimulant activity on myocardial α_1 -receptors, a property residing in the (-)-enantiomer, with β_1 stimulation by the (+)-enantiomer.

Hemodynamic Effects

In isolated cat papillary muscle, dobutamine and isoproterenol in concentrations of 1×10^{-8} to 1×10^{-4} M produced similar increases in contractile tension (0.5 ± 0.1 to 7.5 ± 1.0 mm). However, for a given increase in tension, the incidence of automatic beating was less for dobutamine than for isoproterenol, i.e., dobutamine had less effect on heart rate.

In anesthetized dogs, the doses of dobutamine required to increase contractile force by 50% and 100% were 3.1 ± 1 and 10.3 ± 3 mcg/kg intravenous, respectively. These doses increased heart rate by 13 ± 3 and 30 ± 3 bpm. In contrast, doses of isoproterenol that increased tension by 50% and 100% increased heart rate by 33 ± 3 and 64 ± 4 bpm, respectively. Thus, at doses causing similar inotropic effects, dobutamine had less effect on heart rate.

In dogs administered intravenous dobutamine or dopamine infusion at incremental doses (range: 5 to 160 mcg/kg/min) both drugs produced dose-related increases in cardiac output; however, with dopamine the dose-response curve reached a plateau at doses greater than 40 mcg/kg/min. Dobutamine, in contrast to dopamine, decreased systemic vascular resistance without significant changes in mean arterial pressure or pulmonary vascular resistance.

Several studies in dogs indicate that the positive inotropic and chronotropic effects of dobutamine were due to a direct effect on beta receptors; (1) pretreatment with desmethylinipramine did not alter the inotropic effects of dobutamine (4 to 32 mcg/kg) or isoproterenol (0.03 to 0.5 mcg/kg) whereas effects of tyramine (32 to 512 mcg/kg) and dopamine (8 to 64 mcg/kg) were reduced; (2) in reserpine-pretreated animals, intravenous infusions of 2 to 20 mcg/kg/min of dobutamine produced increases in contractile force and heart rate whereas tyramine did not; and (3) pretreatment with propranolol blocked the inotropic and chronotropic effects of dobutamine (4 to 32 mcg/kg).

In dogs, the doses of dobutamine that increased contractile force by 50% and 100% (i.e., 3 ± 1 and 10 ± 3 mcg/kg) increased blood pressure by 20 ± 2 and 30 ± 3 mmHg. Similar doses of norepinephrine increased pressure by 22 ± 2 and 47 ± 4 mmHg, and similar doses of dopamine increased pressure by 27 ± 3 and 44 ± 3 mmHg. The magnitude of the change seen with dobutamine and the slight increment in effect between the two doses suggests that (1) enhanced cardiac output is in part responsible for the effect, and (2) that part of the effect is due to alpha-receptor stimulation.

The latter mechanism was indicated from studies in reserpinized animals in which the pressor effect of dobutamine was not antagonized, and from studies in which phenoxybenzamine blocked the pressor effect of dobutamine.

Coronary blood flow and myocardial oxygen consumption are usually increased because of increased myocardial contractility.

Dobutamine reduces elevated ventricular filling pressure (preload reduction) and facilitates atrioventricular (AV) node conduction.

The plasma $t_{1/2}$ of dobutamine in humans is 2 minutes. Dobutamine is metabolized in the liver and other tissues by catechol-o-methyltransferase to an inactive compound, 3-O-methyl dobutamine and by conjugation with glucuronic acid.

The conjugates of dobutamine and 3-O methyldobutamine are excreted mainly in urine and to a lesser extent in feces.

TOXICOLOGY

Acute Toxicity

The results of acute toxicity studies of dobutamine are presented in Table 2.

Table 2 LD₅₀ of Dobutamine				
Species	Sex	Maturity	Route	LD₅₀ (mg/kg ± SE)
Mouse	M/F	Mature	intravenous	64.8 ± 2.9/73.2 ± 3.7
Rat	M/F	Mature	intravenous	84.1 ± 4.5/93.9 ± 2.9
Rat	M/F	Weanling (21 days)	intravenous	92.1 ± 5.6/94.3 ± 5.8
Rat	M/F	Newborn (48 hrs)	intravenous	68.7 ± 2.5
Rat	M/F	Newborn (24 hrs)	intravenous	71.5 ± 5.1

Toxic signs included prostration (indicative of circulatory collapse) hypoactivity, dyspnea, tremors, ptosis, cyanosis and salivation. Death occurred within 6 hours, usually within minutes. The acute toxicity of dobutamine in newborn rats was only slightly greater than in weanlings or adults.

Other Studies

Cats

Cats (1M & 1F) received daily increasing intravenous injections (over 2 min) of dobutamine at 5, 10, 20 and 40 mg/kg on 4 successive days. The changes that were observed included peripheral vasodilation and a strengthened pulse rate but no prominent tachycardia (all doses), sedation (10 and 20 mg/kg), mydriasis (20 and 40 mg/kg) and ataxia and vomiting (40 mg/kg). All changes were of short duration (less than 1 hour). No deaths occurred.

Dogs

Two Beagles (2M) were continuously infused intravenous dobutamine at 20 mcg/kg/min (approx. 30 mg/kg/day) for 2 days. The drug was fairly well tolerated; the main effects noted were slight to moderate tachycardia in both animals, marked changes in EKG patterns, vasodilation and vomiting. No deaths occurred.

Subacute Toxicity

Rats

Rats (10/sex/group) received intravenous injections (over approx. 4 min) of 0, 2, 5 and 10 mg/kg/day of dobutamine, and 0.25 mg/kg/day of isoproterenol, for 15 days. A slight increase in relative heart weight occurred in the high dose dobutamine group and in the isoproterenol group. Notable pathology was confined to the heart and included very slight to slight focal degeneration and chronic peri-epicarditis.

Dogs

Beagles (2/sex/group) received intravenous injections (over approx. 1 min) of acetate buffer, or dobutamine at 1.5, 3 and 6 mg/kg/day for 14 days. The main signs of toxicity which occurred at every dose of dobutamine included vomiting, excitation and occasional myoclonic jerking, increased respiration, peripheral vasodilation, increased strength of the heart beat and tachycardia.

All these changes lasted for less than 15 minutes. One dog in the high dose group (6 mg/kg) showed changes in EKG with some arrhythmia which lasted for 48 hours.

Beagles (1/sex/group) received continuous intravenous infusions of 25, 50 or 100 mcg/kg/min of dobutamine for 14 days. No deaths occurred. Changes seen at both mid and high dose infusions included salivation and vomiting (on 1st day), vasodilation, tremors, anorexia and slight weight loss. Additional changes which occurred at the high dose infusion only included lethargy, marked respiratory depression, elevated serum alkaline phosphatase and creatine phosphokinase levels and reduced serum potassium (these latter 3 changes occurred at 24 hours and were normal by 72 hours).

Beagles (2M & 2F) received a constant intravenous infusion of dobutamine in stepwise increasing doses up to 300 mcg/kg/min over a period of 4 days. The effects seen included salivation at 20 to 40 mcg/kg/min (i.e., at total dose of approx. 1.8 to 6.0 mg/kg over 3 to 5 hours), peripheral vasodilation at 40 mcg/kg/min or more (i.e., total dose of approx. 6.0 mg/kg over 5 hours), tachycardia and ECG changes at 75 mcg/kg/min or more (i.e., total doses of approx. 61.5 mg/kg over 23 hours) and hypoactivity and lethargy at 125 mcg/kg/min (i.e., total dose of approx. 108 mg/kg over 31 hours). No deaths occurred.

REPRODUCTION AND TERATOLOGY

Reproduction Studies

Pregnant rats (N=25/dose) received single intravenous injections of dobutamine at 5, 10 and 15 mg/kg/day on gestation days 6 to 15. Pregnant rabbits (N=18/dose) received an intravenous infusion (given into veins of ears or hindlimbs over 30 minutes) of 30 mg/kg/day on gestation days 6 to 18.

In rats, receiving the highest dose, the effects seen in the dams included: 1) 2 unexplained deaths; 2) flaccidity or ataxia with tremors; 3) reduced average no. of implantation sites (i.e. 9.0 vs. 10.4 controls). Consequently, the mean no. of live fetuses/pregnant dam was reduced (i.e. 8.5 vs. 9.9 in controls) and the implantation index (ratio of no. implantations/no. corpora lutea) was depressed (i.e., 0.76 vs. 0.87 in controls). In the fetuses, minor skeletal variations were seen but were not considered to be treatment-related.

In rabbits the effects seen at 30 mg/kg/day in the dams included 1) a slight increase in resorption index, i.e., in the proportion of implanted conceptuses that resulted in resorption (0.24 vs. 0.18 in controls), and 2) the implantation index was slightly reduced (0.90 vs. 0.95 in controls). In the fetuses, minor skeletal variations were seen but were not considered to be treatment-related.

REFERENCES

1. **Abdul-Rasool IH, Chamberlain JH, Swan PC, Ward DS.** Cardiorespiratory and metabolic effects of dopamine and dobutamine infusions in dogs. *Crit Care Med.* 1987;15(11):1044-50.
2. **Akhtar N, Mikulic E, Cohn JN, Chaudhry MH.** Hemodynamic effect of dobutamine in patients with severe heart failure. *Amer J Cardiol* 1975;36:202-205.
3. **Beregovich J, Bianchi C, D'Angelo R, Diaz R, Rubley S.** Hemodynamic effects of a new inotropic agent (dobutamine) in chronic cardiac failure. *Br. Heart J.* 1975;Vol 37:629-634.
4. **Berkowitz C, Croke R, Jacobs W, Loeb H, Gunnar R.** Comparative responses to dobutamine and nitroprusside in patients. *Amer J. Cardiol.* 1977;39(2):297-
5. **Bianchi C, Diaz R, Gonzales C, Bergovich J.** Effects of Dobutamine on Atrioventricular Conduction. *Am Heart J.* 1975;90:474-78.
6. **Erlemeier HH, Kupper W, Bleifeld W.** Intermittent infusion of dobutamine in the therapy of severe congestive heart failure--long-term effects and lack of tolerance. *Cardiovasc Drugs Ther.* 1992;6(4):391-98.
7. **Goldenberg IF, et al.** Effect of dobutamine on plasma potassium in congestive heart failure secondary to idiopathic or ischemic cardiomyopathy. *Am J Cardiol.* 1989;63:843-846.
8. **Jewitt D, Jennings K, Jackson PG.** Efficacy of new inotropic drugs in clinical coronary heart failure. *Am J Med* 1978;65:197-202.
9. **Jewitt D, Mitchell A, Birkhead J, Dollery C.** Clinical cardiovascular pharmacology of dobutamine: a selective inotropic catecholamine. *Lancet.* 1974;Vol 2:363-367.
10. **Kates RE, Leier CV.** Dobutamine pharmacokinetics in severe heart failure. *Clin. Pharmacol. Ther.* 1978;Vol 24:537-541.
11. **Kenakin TP, Johnson SF.** The importance of the alpha-adrenoceptor agonist activity of dobutamine and its relevance to inotropic selectivity. *J Pharmacol Exp Ther* 1981;216:210-219.
12. **Kersting F, Follath F, Moulds F, Mucklow J, McCloy R, Sheares J, Dollery C.** A comparison of cardiovascular effects of dobutamine and isoprenaline after open-heart surgery. *Brit Heart J.* 1976;38:622.
13. **Leier CV, Webel J, Bush CA.** The cardiovascular effects of the continuous infusion of dobutamine in patients with severe cardiac failure. *Circulation* 1977;56(3):468-472.
14. **Leier CV, Unverth DV, Kates RE.** Relationship between plasma dobutamine concentrations and cardiovascular responses in cardiac failure. *The Am J Med* 1979;238-242.

15. **Liang CS, Sherman LG, Doherty JU, Wellington K, Lee VW, Hood WB, Jr.** Sustained improvement of cardiac function in patients with congestive heart failure after short-term infusion of dobutamine. *Circulation*. 1984;69(1):113-9.
16. **Loeb HS, Khan M, Klodnycky ML, Sinno MZ, Towne WD, Gunnar RM.** Hemodynamic effects of dobutamine in man. *Circ Shock*. 1975;2:29-35.
17. **Loeb HS, Khan M, Saudye A, Gunnar RM.** Acute hemodynamic effects of dobutamine and isoproterenol in patients with low output cardiac failure. *Circ Shock*. 1976;3:55.
18. **Loeb HS, Bredakis J, Gunnar RM.** Superiority of dobutamine over dopamine for augmentation of cardiac output in patients with chronic low output cardiac failure. *Circ*. 1977;55(2):375-381.
19. **Meyer SL, Curry GC, Donsky MS, Parkey RW, Willerson JT.** Influence of dobutamine on hemodynamics and coronary blood flow in patients with and without coronary artery disease. *Am. J. Cardiol*. 1976;Vol 38:103-108.
20. **Paulman PM, Cantral K, Meade JG, Vettel K, Loperena R, Odrezin M.** Dobutamine overdose. *JAMA* 1990;264:2386-2387.
21. **Robie NW, Goldberg LI.** Comparative systemic and regional hemodynamic effects of dopamine and dobutamine. *Amer Heart J* 1975;90(3)340-345.
22. **Ruffolo RR Jr.** The mechanism of action of dobutamine. *Ann Intern Med*. 1984;100:313-314.
23. **Sakamoto T, Yamada T.** Hemodynamic effects of dobutamine in patients following open heart surgery. *Circulation*. 1977;Vol.55:525-533.
24. **Sonnenblick EH, Frishman WH, LeJemtel TH.** Dobutamine: A new synthetic cardioactive sympathetic amine. *N Engl J Medicine* 1979;300(1):17-22.
25. **Steen PA, Tinker JH, Pluth JR, Barnhorst DA, Tarhan S.** Efficacy of dopamine, dobutamine and epinephrine during emergency from cardiopulmonary bypass in man. *Circulation* 1978;57(2):378-384.
26. **Summary of Basis of Approval of Dobutrex** (dobutamine hydrochloride, Eli Lilly) IND-8504 and NDA-820).
27. **Tinker JH, Tarhan S, White RD, Pluth JR, Barnhorst DA.** Dobutamine for inotropic support during emergency from cardiopulmonary bypass. *J Anesthesiology*. 1976;Vol 44:281-286.
28. **Unverferth DV, Magorien RD, Altshuld R, Kolibash AJ, Lewis RP, Leier CV.** The hemodynamic and metabolic advantages gained by a three-day infusion of dobutamine in patients with congestive cardiomyopathy. *Am Heart J* 1983;106:29-34.

Last revision: February 11, 2019

Pfizer Canada ULC
Kirkland, Québec H9J 2M5