

DOBUTAMINE USE IN CARDIAC PATIENTS

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ABSTRACT

Dobutamine is a direct-acting agent whose primary activity results from stimulation of the β_1 -adrenoceptors of the heart, increasing contractility and cardiac output. Since it does not act on dopamine receptors to induce the release of norepinephrine (another α agonist), dobutamine is less prone to induce hypertension than is dopamine. Dobutamine is a sympathomimetic drug used in the treatment of heart failure and cardiogenic shock. Its primary mechanism is direct stimulation of β_1 receptors of the sympathetic nervous system. Dobutamine is used to treat acute but potentially reversible heart failure, such as which occurs during cardiac surgery or in cases of septic or cardiogenic shock, on the basis of its positive inotropic action. Most clinical experience with dobutamine is short-term-not more than several hours in duration. Dobutamine hydrochloride is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in patients who have shown previous manifestations of hypersensitivity to dobutamine injection. Primary side effects include those commonly seen for β_1 active sympathomimetics, such as hypertension, angina, arrhythmia, and tachycardia. Used with caution in atrial fibrillation as it has the effect of increasing the atrioventricular (AV) conduction. 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.

KEYWORDS: Dobutamine, hypertension, angina, arrhythmia, and tachycardia.

INTRODUCTION

Dobutamine is a sympathomimetic drug used in the treatment of heart failure and cardiogenic shock. Its primary mechanism is direct stimulation of β_1 receptors of the sympathetic nervous system. Dobutamine was developed in the 1970s by Drs. Ronald Tuttle and Jack Mills at Eli Lilly and Company, as a structural analogue of isoprenaline.^[1]

Clinical Uses

Dobutamine injection 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.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with dobutamine hydrochloride.^[2,3,4,5]

Dobutamine is used to treat acute but potentially reversible heart failure, such as which occurs

during cardiac surgery or in cases of septic or cardiogenic shock, on the basis of its positive inotropic action.^[2] Dobutamine can be used in cases of congestive heart failure to increase cardiac output. It is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of patients with cardiac decompensation due to depressed contractility, which could be the result of either organic heart disease or cardiac surgical procedures. It is not useful in ischemic heart disease because it increases heart rate and thus increases myocardial oxygen demand.^[6-10]

Clinical Pharmacology

Dobutamine is a direct-acting inotropic agent whose primary activity results from stimulation of the β_1 receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It does not cause the release of endogenous norepinephrine, as does dopamine. In animal 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.

Facilitation of atrioventricular conduction has been observed in humanelectrophysiologic studies and in patients with atrial fibrillation. Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed.

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.

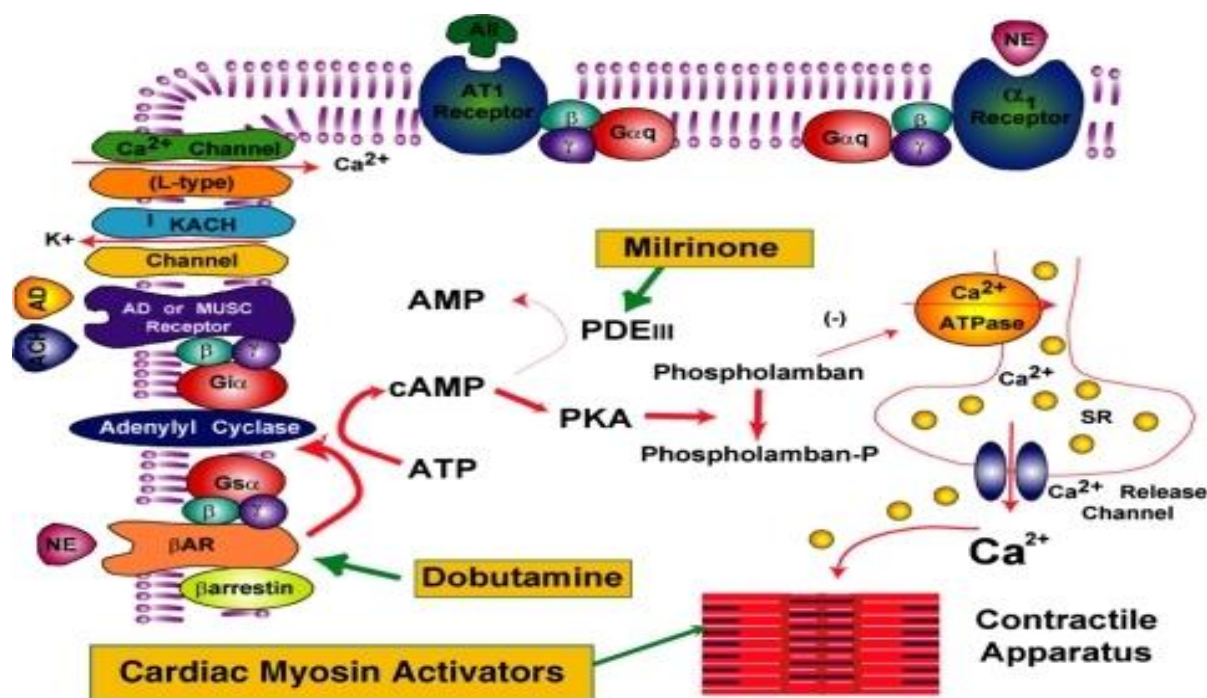
The onset of action of dobutamine is within 1 to 2 minutes; however, as much as 10 minutes may be required to obtain the peak effect of a particular infusion rate. The plasma half-life of dobutamine in humans is 2 minutes. The principal routes of metabolism are methylation of the catechol and conjugation. 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.^[10-15]

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.

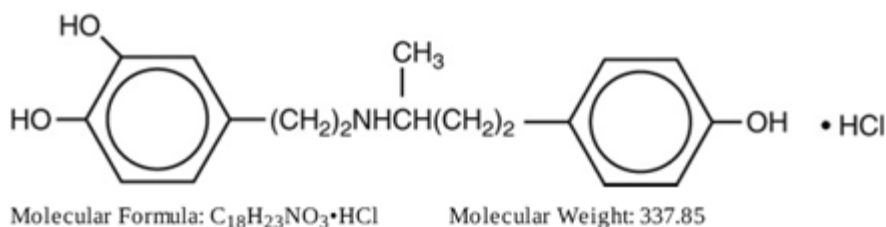
Dobutamine is a direct-acting agent whose primary activity results from stimulation of the β_1 -adrenoceptors of the heart, increasing contractility and cardiac output. Since it does not act on dopamine receptors to induce the release of norepinephrine (another α_1 agonist), dobutamine is less prone to induce hypertension than is dopamine.

Dobutamine is predominantly a β_1 -adrenergic agonist, with weak β_2 activity, and α_1 selective activity, although it is used clinically in cases of cardiogenic shock for its β_1 inotropic effect in increasing heart contractility and cardiac output. Dobutamine is administered as a racemic mixture consisting of both (+) and (-) isomers; the (+) isomer is a potent β_1 agonist and α_1 antagonist, while the (-) isomer is an α_1 agonist.^[4] The administration of the racemate results in the overall β_1 agonism responsible for its activity. (+)-Dobutamine also has mild β_2 agonist activity, which makes it useful as a vasodilator.^[5]



Drug Description

Dobutamine Injection, USP is 1,2-benzenediol,4-[2-[[3-(4-hydro-xyphenyl)-1-methylpropyl]amino]ethyl]-hydrochloride, (\pm). It is a synthetic catecholamine.



The clinical formulation is supplied in a sterile form for intravenous use only. Each mL contains: Dobutamine hydrochloride, equivalent to 12.5 mg (41.5 μ mol) dobutamine; 0.24 mg sodium metabisulfite (added during manufacture), and water for injection. pH adjusted between 2.5 to 5.5 with hydrochloric acid and/or sodium hydroxide. Dobutamine is oxygen sensitive.^[11-20]

Dosage and Administration

The drug is also commonly used in the hospital setting as a pharmacologic stress testing agent to identify coronary artery disease.

Do not add dobutamine injection to 5% Sodium Bicarbonate Injection or to any other strongly alkaline solution. Because of potential physical incompatibilities, it is recommended that 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.

Preparation And Stability

At the time of administration, dobutamine injection must be further diluted in an IV container. Dilute 20 mL of dobutamine in at least 50 mL of diluent and dilute 40 mL of dobutamine in at least 100 mL of diluent. Use one of the following intravenous solutions as a diluent: Dextrose Injection 5%, Dextrose 5% and Sodium Chloride 0.45% Injection, Dextrose 5% and Sodium Chloride 0.9% Injection, Dextrose Injection 10%, Isolyte M with 5% Dextrose Injection, Lactated Ringer's Injection, 5% Dextrose in Lactated Ringer's Injection, Normosol -M in D5-W, 20% Osmitrol in Water for Injection, Sodium Chloride Injection 0.9%, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Recommended Dosage

The rate of infusion needed to increase cardiac output usually ranged from 2.5 to 15 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Dobutamine Injection Rates of Infusion for Concentrations of 250, 500, and 1,000 mcg/mL.

Drug Delivery Rate (MCG/KG/MIN)	Infusion Delivery Rate		
	250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1,000 mcg/ml‡ (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 mcg/mL of diluents
† 500 mcg/mL or 250 mg/500 mL of diluents
‡ 1,000 mcg/mL or 250 mg/250 mL of diluents

Rates of infusion in mL/h for Dobutamine Injection concentrations of 500 mcg/mL, 1000 mcg/mL, and 2000 mcg/mL are given in Table 2.

Table 2: Dobutamine Injection Infusion Rate (mL/h) for 500 mcg/mL concentration.

Dobutamine Injection Infusion Rate (MI/H) For 500 Mcg/MI Concentration									
Drug Delivery Rate (Mcg/Kg/Min)	Patient Body Weight (Kg)								
	30	40	50	60	70	80	90	100	110
2.5	9	12	15	18	21	24	27	30	33
5	18	24	30	36	42	48	54	60	66
7.5	27	36	45	54	63	72	81	90	99
10	36	48	60	72	84	96	108	120	132
12.5	45	60	75	90	105	120	135	150	165
15	54	72	90	108	126	144	162	180	198



Dobutamine injection infusion rate (ml/h) for 1,000 mcg/ml concentration									
Drug Delivery Rate (mcg/kg/min)	Patient Body Weight (Kg)								
	30	40	50	60	70	80	90	100	110
2.5	4.5	6	7.5	9	10.5	12	13.5	15	16.5
5	9	12	15	18	21	24	27	30	33
7.5	13.5	18	22.5	27	31.5	36	40.5	45	49.5
10	18	24	30	36	42	48	54	60	66
12.5	22.5	30	37.5	45	52.5	60	67.5	75	82.5
15	27	36	45	54	63	72	81	90	99

Dobutamine injection infusion rate(ml/h) for 2,000 mcg/ml concentration									
Drug Delivery Rate (mcg/kg/min)	Patient Body Weight (KG)								
	30	40	50	60	70	80	90	100	110
2.5	2	3	4	4.5	5	6	7	7.5	8
5	4.5	6	7.5	9	10.5	12	13.5	15	16.5
7.5	7	9	11	13.5	16	18	20	22.5	25
10	9	12	15	18	21	24	27	30	33
12.5	11	15	19	22.5	26	30	34	37.5	41
15	13.5	18	22.5	27	31.5	36	40.5	45	49.5

The rate of administration and the duration of therapy should be adjusted according to the patient's response as determined 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.^[21-25]

Concentrations of up to 5,000 mcg/mL have been administered to humans (250 mg/50 mL). The final volume administered should be determined by the fluid requirements of the patient.

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

BRAND	FORM.	PILL IMAGE
dobutamine	250mg/20mL (12.5 mg/mL) solution	
dobutamine	250mg/20mL (12.5 mg/mL) solution	

Side Effects

Increased Heart Rate, Blood Pressure, And Ventricular Ectopic Activity

A 10- to 20-mm 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 dose related.

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, nonspecific chest pain, palpitations, and shortness of breath.

Isolated cases of thrombocytopenia have been reported. Administration of dobutamine, like other catecholamines, can produce a mild reduction in serum potassium concentration, rarely to hypokalemic levels.

Longer-Term Safety

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

Warnings

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 50 mm Hg or greater increase in systolic pressure. Usually, reduction of dosage promptly reverses these effects. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

Ectopic Activity

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

Hypersensitivity

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

Dobutamine injection contains sodium metabisulfite, a sulfite 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, 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 hydrochloride.

Hypovolemia should be corrected with suitable volume expanders before treatment with dobutamine is instituted. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction

Clinical experience with dobutamine injection following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent that increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Laboratory Tests

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

Carcinogenesis, Mutagenesis, Impairment Of Fertility

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

Pregnancy

Teratogenic Effects.

Pregnancy Category B - Reproduction studies performed in rats at doses up to the normal human dose (10 mcg/kg/min for 24 h, total daily dose of 14.4 mg/kg) and in rabbits at doses up to 2 times the normal human dose have revealed no evidence of harm to the fetus due to dobutamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor And Delivery

The effect of dobutamine injection on labor and delivery is unknown.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dobutamine hydrochloride is administered to a nursing woman. If a mother requires dobutamine treatment, breast-feeding should be discontinued for the duration of the treatment.

Pediatric Use

The safety and effectiveness of dobutamine injection for use in pediatric patients have not been studied. This monograph has been modified to include the generic and brand name in many instances.

Overdose

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 β -receptor stimulation. The duration of action of dobutamine hydrochloride is generally short ($T_{1/2} = 2$ minutes) because it is rapidly metabolized 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 ischemia, and ventricular fibrillation. Hypotension may result from vasodilation.^[26-28]

Treatment

To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians' Desk Reference (PDR). 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 lidocaine. 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. If the product is ingested, unpredictable absorption may occur from the mouth and the gastrointestinal tract. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis of 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, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of dobutamine hydrochloride.^[29-35]

Contraindications

Dobutamine hydrochloride is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in

patients who have shown previous manifestations of hypersensitivity to dobutamine injection.

This monograph has been modified to include the generic and brand name in many instances.

Adverse Effects

Primary side effects include those commonly seen for β_1 active sympathomimetics, such as hypertension, angina, arrhythmia, and tachycardia. Used with caution in atrial fibrillation as it has the effect of increasing the atrioventricular (AV) conduction.^[3]

The most dangerous side effect of dobutamine is increased risk of arrhythmia, including fatal arrhythmias. Cardiovascular: Ventricular arrhythmia, atrial fibrillation (at very high doses), ectopic beats, tachycardia, anginal pain, palpitation, cardiac conduction abnormalities, widened QRS complex, bradycardia, hypotension, hypertension, vasoconstriction

Respiratory: Dyspnea

Gastrointestinal: Nausea, vomiting

Metabolic/nutritional: Azotemia

Central nervous system: Headache, anxiety

Endocrine: Piloerection

Ocular: Increased intraocular pressure; dilated pupils

Gangrene of extremities has occurred when high doses were administered for prolonged periods or in patients with occlusive vascular disease receiving low doses of dopamine hydrochloride.^[36-40]

CONCLUSION

Dobutamine features prominently in the evaluation and management of valvular heart disease by helping to assess the effects of mitral and aortic stenoses, as well as a specific use in differentiating true severe valvular aortic stenosis from pseudostenosis that may occur in the setting of left ventricular systolic dysfunction. Dobutamine is generally well tolerated, and its side effects and contraindications generally relate to consequences of excess inotropic and/or chronotropic stimulation of the heart.

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