Dobutamine Injection USP

DESCRIPTION

Dobutamine Injection USP is (1S,2S,4S)-4-[2-[(3-Hydroxyphenyl)-(1-methylpropyl)amino]ethyl]-pyrocatechol hydrochloride. It is a synthetic catecholamine.

Molecular Formula: C_{19}H_{23}NO_{3}•HCl

Molecular Weight: 337.84

The drug is supplied in a sterile form for intravenous use only. Each mL contains: dobutamine hydrochloride, equivalent to 12.5 mg (41.5 µmol) dobutamine; sodium bisulfite 0.28 mg (added during manufacture), and water for injection, q.s. Hydrochloric acid and/or sodium hydroxide may have been added during manufacture to adjust the pH (2.5 to 5.5).

CLINICAL PHARMACOLOGY

Dobutamine is a direct-acting inotropic agent whose primary activity results from stimulation of the β receptors of the heart while producing comparatively mild chronicotropic, hypotensive, 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 human electrophysiologic 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.

Alteration of sympathetic 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.

The effective infusion rate of dobutamine varies widely from patient to patient, and titration is always necessary (see DOSAGE AND ADMINISTRATION). At least in pediatric patients, dobutamine-induced increases in cardiac output and systemic pressure are generally seen, in any given patient, at lower infusion rates than those that cause substantial tachycardia (see PRECAUTIONS. Pediatric Use).

INDICATIONS AND USAGE

Dobutamine is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac manifestations of hypersensitivity to dobutamine.

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

3. 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 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 results in increased infarct size.

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

Drug Interactions—Animal studies indicate that dobutamine may be ineffective if the patient has recently received a β-blocking drug. In such a case, the peripheral vascular resistance may increase.

Preparations—Atropine, propranolol, and other drugs that have the 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 mcg/kg), and in rabbits at doses up to twice 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 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 is administered to a nursing woman. If a mother requires dobutamine treatment, breastfeeding should be discontinued for the duration of the treatment.

PEDIATRIC USE—Dobutamine has been shown to increase cardiac output and systemic pressure in pediatric patients of every age group.

In premature neonates, however, dobutamine is less effective than dopamine in raising systemic blood pressure without causing undue tachycardia, and dobutamine has not been shown to provide any added benefit when given to such infants already receiving optimal infusions of dopamine.

Geriatric Use—Of the 1893 patients in clinical studies who were treated with dobutamine, 930 (49.1%) were 65 and older. No overall differences in safety or effectiveness were observed between these and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosage range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy.

ADVERSE REACTIONS

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 (see WARNINGS regarding exaggerated chronotropic and pressor effects). 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, may produce a mild reduction in serum potassium concentration, rarely to hypokalemic levels (see PRECAUTIONS).
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 is usually due to excessive cardiac \( \beta \)-receptor stimulation. The duration of action of dobutamine is generally short \( (T_{1/2}= 2 \text{ minutes}) \) because it is rapidly metabolized by catechol-0-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.

**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). To manage overdoses, 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 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. Hypotension 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, unpalatable 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 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, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of dobutamine.

DOSEAGE AND ADMINISTRATION

Note—Do not add dobutamine to 5% Sodium Bicarbonate Injection or to any other strongly alkaline solution. Because of potential physical incompatibilities, it is recommended that dobutamine not be mixed with other drugs in the same solution. Dobutamine 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 must be further diluted in an IV container to at least a 50 mL solution using one of the following intravenous solutions as a diluent: 5% Dextrose Injection, 5% Dextrose and 0.45% Sodium Chloride Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, 10% Dextrose Injection, Isolyte® M with 5% Dextrose Injection, Lactated Ringer’s Injection, 5% Dextrose in Lactated Ringer’s Injection, Normosol®-M in DS-W, 20% Osmoltril® in Water for Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Recommended Dosage—Infusion of dobutamine should be started at a low rate (0.5 to 1 mcg/kg/min) and titrated at intervals of a few minutes, guided by the patient's response, including systemic blood pressure, urine flow, frequency of ectopic activity, heart rate, and (whenever possible) measurements of cardiac output, central venous pressure, and/or pulmonary capillary wedge pressure. In reported trials, the optimal infusion rates have varied from patient to patient, usually 2 to 20 mcg/kg/min but sometimes slightly outside of this range. On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect. Rates of infusion (mL/h) for dobutamine concentrations of 500 mcg/mL, 1000 mcg/mL, and 2000 mcg/mL necessary to attain various delivery rates of dobutamine (mcg/kg/min) for patients of different weights are given in Table 1.

<table>
<thead>
<tr>
<th>Drug Delivery Rate (mcg/kg/min)</th>
<th>Patient Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>1.5</td>
<td>0.4</td>
</tr>
<tr>
<td>2</td>
<td>0.6</td>
</tr>
<tr>
<td>2.5</td>
<td>0.7</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
</tr>
<tr>
<td>7.5</td>
<td>1.1</td>
</tr>
<tr>
<td>10</td>
<td>1.2</td>
</tr>
<tr>
<td>15</td>
<td>1.5</td>
</tr>
<tr>
<td>17.5</td>
<td>1.9</td>
</tr>
<tr>
<td>20</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Table 1: Dosetamine Injection USP

Infusion Rate (mL/h) for 500 mcg/mL concentration

Infusion Rate (mL/h) for 1000 mcg/mL concentration

Table 2: Dobutamine Injection USP

Infusion Rate (mL/h) for 2000 mcg/mL concentration

<table>
<thead>
<tr>
<th>Drug Delivery Rate (mcg/kg/min)</th>
<th>Patient Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>0.07</td>
</tr>
<tr>
<td>1.5</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>2.5</td>
<td>0.25</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>7.5</td>
<td>1.1</td>
</tr>
<tr>
<td>10</td>
<td>1.2</td>
</tr>
<tr>
<td>15</td>
<td>1.5</td>
</tr>
<tr>
<td>17.5</td>
<td>1.9</td>
</tr>
<tr>
<td>20</td>
<td>2.2</td>
</tr>
</tbody>
</table>

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.

HOW SUPPLIED

D Dobutamine Injection USP, 20 mL single dose vial contains dobutamine hydrochloride, equivalent to 250 mg dobutamine per 20 mL; ten vials per carton. NDC 55390-560-90.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Manufactured for:
Bedford Laboratories™,
Bedford, OH 44146

March 2013 DBP06