INTRODUCTION

Background: Beta-adrenergic antagonist (ie, beta-blocker) overdose is increasingly common. Besides being used primarily for their cardiovascular effects to treat hypertension and postmyocardial infarction, beta-blockers are used to treat migraine headaches, essential tremors, thyrotoxicosis, glaucoma, anxiety, and various other disorders. As a result of their expanded use, the incidence of overdose with these agents has also increased.

Beta-blocker overdose manifests with signs and symptoms of sympathetic beta-adrenergic receptor blockade and seizures associated with some types of beta-blockers. An understanding of the involved beta-blocker's unique actions is critical for evaluation and treatment of the patient with beta-blocker overdose.

Pathophysiology: In general, blockade of beta-receptors results in decreased production of intracellular cyclic adenosine monophosphate (cAMP) with a resultant blunting of multiple metabolic and cardiovascular effects of circulating catecholamines. Beta 1-receptors increase the force and rate of myocardial contraction and atrioventricular (AV) node conduction velocity. Beta-blockers, therefore, reduce heart rate, blood pressure, myocardial contractility, and myocardial oxygen consumption. Beta 2-receptor blockade inhibits relaxation of smooth muscle in blood vessels, bronchi, and the gastrointestinal and genitourinary tract. In addition, Beta 2-blockade inhibits glycogenolysis and gluconeogenesis.

Other than the direct effects of the beta-adrenoreceptor blockade, toxicity may result from other mechanisms including sodium and calcium channel blockade, a centrally mediated cardiac depression, and alteration of cardiac myocyte energy metabolism.

Pharmacology

Beta-blockers are a numerous and comprise a heterogeneous drug family with toxicologic characteristics that vary between classes. An understanding of the different characteristics of each class is helpful for understanding the various
clinical presentations and for guiding therapy.

Nonselective beta-blockers

Propranolol was the first beta-blocker with widespread use; much of the clinical and overdose experience that exists with beta-blockers was provided by case reports and clinical studies of this drug. Propranolol is a nonselective beta-blocker, demonstrating equal affinity for both beta 1- and beta 2-receptors.

Other nonselective beta-blockers include nadolol, timolol, and pindolol. Nonselective beta-blockers exert a wider variety of extracardiac manifestations.

Intrinsic sympathomimetic activity

Some beta-blockers, such as pindolol and acebutolol, also have beta-agonist properties. While their agonist property is weaker than that of catecholamines, they are capable of stimulating beta-receptors, especially when catecholamine levels are low. These agents are said to have intrinsic sympathomimetic activity; this agonist property is protective in overdoses.

Membrane stabilizing effects

Beta-blockers, such as propranolol, labetalol, and pindolol, can have membrane stabilizing effects (eg, quinidinelike effects, Vaughan-Williams class I antiarrhythmic effects). This property, usually not evident with therapeutic doses, may significantly contribute to toxicity by prolonging QRS duration and impairing cardiac conduction. Seizures are more commonly observed in the drugs with quinidinelike membrane stabilizing effects.

Lipid solubility

Lipid solubility is higher in agents such as propranolol and lower in agents such as atenolol and nadolol. It may influence the degree of central nervous system (CNS) effects and utility of hemodialysis or hemoperfusion. High lipid solubility leads to a larger volume of distribution with the drug penetrating into the CNS. Metabolism is primarily hepatic in these drugs. Among the beta-blockers metabolized by the liver, propranolol has active metabolites (4-OH propranolol) that prolong its biological life so that it can exceed its normal plasma life (2-5 h). Conversely, hydrophilic beta-blockers are less widely distributed and are eliminated primarily by the kidneys in unchanged form and may be more easily removed by extracorporeal techniques, such as hemoperfusion.

Case reports have documented charcoal hemoperfusion to rapidly lower plasma drug levels, with a parallel improvement in clinical condition after metoprolol (a hydrophilic beta-blocker) overdose.

QT interval prolongation

The electrophysiologic effects of sotalol deserve special consideration. Unlike other beta-blockers, sotalol has antiarrhythmic properties consistent with the Vaughan-Williams class III agents, which may lengthen the QT interval duration. Reports exist of prolonged QT interval, multifocal premature ventricular contractions (PVCs), bigeminy, ventricular tachycardia, ventricular fibrillation, and torsade de pointes. Toxicity with sotalol has been reported to result in ventricular dysrhythmias for as long as 2 days postingestion because of persistent QT prolongation.

Frequency:

- **In the US:** The most recent data from the American Association of Poison Control Centers (AAPCC) for 1999 report more than 9500 exposures and 26 deaths. This represents a 6% annual increase in total reported cases since 1988.

- **Internationally:** Propranolol is the most toxic beta-blocker and the most frequently used in suicide attempts worldwide.

Mortality/Morbidity: Between 1985 and 1995, a total of 52,156 exposures were reported to the AAPCC, 164 of which were fatal. In 59% of cases, cardiopulmonary arrest did not develop until patients were under observation by health care personnel.

- Beta-blocker type: Beta-blockers that are lipid soluble and have marked antiarrhythmic (ie, quinidinelike effects) are more lethal (eg, propranolol, sotalol, oxprenolol). Between 1985 and 1995, 71% of fatalities reported to the AAPCC were caused by propranolol, despite being responsible for 44% of exposures.

- Co-ingestions and state of health: The prognosis is significantly worse if existing cardiac pathology or co-ingestion of psychotropic or cardioactive drugs is present, even if the amount of beta-blocker is relatively small. The single most important factor associated with the development of cardiovascular morbidity in beta-blocker ingestion is history of a cardioactive co-ingestant, primarily calcium channel blockers, cyclic antidepressants, and neuroleptics. In the absence of such co-ingestion, exposure to a beta-blocker with membrane stabilizing activity is associated with an increased risk of cardiovascular morbidity.
Sex: According to the AAPCC, young women were associated with 63% of reported fatalities caused by beta-blockers between 1985 and 1995.

Age: Of fatalities reported to the AAPCC between 1985 and 1995, 92% were associated with individuals younger than 50 years. Twenty-seven percent of all cases (9500) reported to the AAPCC in 1999 were associated with children younger than 6 years.

History:
- Ascertaining the amount and specific type of beta-blocker used as well as the time of the overdose may be important for determining prognosis and therapy.
- Information regarding the patient's underlying medical condition and the presence or absence of co-ingestions is critical.
- Angina may worsen in patients after withdrawal from chronic beta-blocker therapy.

Physical: Consider beta-blocker overdose in the differential diagnosis of a comatose patient if clinical findings of bradycardia, hypotension, decreased body temperature, and hypoglycemia are present and no definite history of drug overdose exists.
- Myocardial conduction delays with decreased contractility typify the acute beta-blocker ingestion.
- Cardiac output falls may occur, with resulting hypotension from bradycardia and negative inotropy. Hypotension, in turn, jeopardizes myocardial perfusion, creating a downward spiral of events.
- Oliguric renal failure occurred in a 19-year-old woman who developed moderate hypotension (70/50) lasting approximately 3 hours after labetalol overdose; this was postulated to have occurred secondary to alpha-blocking effects on renal vasculature.
- Beta-blocking compounds that are not sustained-release formulations are all rapidly absorbed from the gastrointestinal tract.
  - The first critical signs of overdose can appear 20 minutes postingestion but are more commonly observed within 1-2 hours.
  - A retrospective review of English medical literature from 1963-1993 reveals that the onset of symptoms in all cases occurred within 6 hours. Only one case involving a sustained release preparation was included in this review. A recent prospective study of 280 beta-blocker exposures reported to two regional poison centers also found that all patients who developed symptoms did so within 6 hours of ingestion.
- While the half-life of these compounds is usually short (2-12 h), half-lives in the overdose patient may be prolonged because of a depressed cardiac output reducing blood flow to the liver and kidneys or because of the formation of active metabolites.
- Saturation kinetics prolong elimination at high plasma concentrations, and delayed absorption from long-acting preparation can significantly increase the apparent elimination half-life. Prolonged effects (>72 h) after massive overdoses are not uncommon.
- Asymptomatic intoxication occurs mainly in healthy persons with tolerance to these drugs who ingest beta-blockers lacking membrane stabilizing effects or having a partial agonist effect (eg, pindolol). Individual sensitivity to beta-blockade may be significant in some patients who have tolerated therapeutic doses of up to 4 g of propranolol daily and deliberate overdose of both practolol and propanolol without serious adverse effects.
- Conversely, circulatory collapse may occur in patients with preexisting cardiac failure when sympathetic drive is inhibited by even a small dose of a particular beta-blocker.
- Intermediate toxicity results in a moderate drop in blood pressure (systolic BP >80 mm Hg) and/or bradycardia (heart rate <60 BPM).
- Bradycardia with associated hypotension and shock (systolic BP <80 mm Hg, HR <60 BPM) defines severe beta-blocker toxicity. Patients with severe toxicity often manifest extracardiac manifestations of intoxication.
  - Bradycardia, by itself, is not necessarily helpful as a warning sign because slowing of the heart rate and damping of tachycardia in response to stress is observed with therapeutic levels.
  - While case reports have documented hypotension in the absence of bradycardia, blood pressure usually does not fall before the onset of bradycardia.
  - Acute dilated cardiomyopathy was reported in a 16-year-old adolescent boy who ingested 3200 mg propranolol in a suicide attempt. Echocardiography revealed a dilated left ventricle with poor contraction.
Bradycardia may be isolated or accompanied by mild conduction disturbances affecting the entire cardiac conduction system from the sinus node to the intraventricular Purkinje system.

Severe bradycardia (30 BPM) developed after use of betaxolol ophthalmic drops in an 80-year-old man with a history of sick sinus syndrome who also was taking digoxin.

Tachycardia, while unusual, has been reported with practolol, pindolol and sotalol.

A depressed level of consciousness and seizures may occur as a result of cellular hypoxia from poor cardiac output, a direct CNS effect caused by sodium channel blocking, or even hypoglycemia. The lipid-soluble agents have increased distribution into the brain and these agents are associated with severe CNS toxicity. Lipid soluble beta-blockers, such as propranolol, frequently present with seizures after an overdose.

Seizures are generalized and may be multiple but are usually brief, lasting seconds to minutes. Seizures occasionally have been reported after therapeutic use of esmolol and with over-dose of alprenolol, metoprolol, and oxprenolol. Seizures are far more common after propranolol overdose.

Coma may be prolonged, depending on the half-life of the agent involved and the coexisting morbidity. Severe memory impairment developed in an 81-year-old woman taking propranolol 20 mg three times per day. Effects were associated with an elevated propranolol blood level (163 mcg/L) and resolved after discontinuation of the drug.

Bronchospasm is a rare complication of beta-blocker therapy or overdose, except in patients who already have bronchospastic disease. Sudden fatality has been reported in 4 patients with asthma after therapeutic doses of beta-blockers were administered. Pulmonary edema had been reported to occur as a result of cardiac failure. Respiratory arrest also has been described with beta-blocker intoxication, especially with propranolol, and is thought to be secondary to a central drug effect.

Hypoglycemia is relatively uncommon but described in unstable diabetics and children. Beta-blocking drugs may cause hypoglycemia by inhibiting glycogenolysis. Reports exist of patients responding to glucose with normal blood glucose measurements. Some, therefore, recommend administering a bolus of 50% glucose to any patient with CNS depression. Severe hyperkalemia is not a usual finding but has been reported particularly with co-ingestion of potassium chloride.

Causes:

- Beta-blocker toxicity in children usually results from exposure to an adult's unattended medications.
- Beta-blocker toxicity in adults usually results from a suicide attempt or an accidental over dosage of therapeutic medication.

**Differentials**

- Congestive Heart Failure and Pulmonary Edema
- Epidural Hematoma
- Epidural and Subdural Infections
- Hyperkalemia
- Meningitis
- Pediatrics, Hypoglycemia
- Pediatrics, Meningitis and Encephalitis
- Pediatrics, Sudden Infant Death Syndrome
- Plant Poisoning, Glycosides - Cardiac
- Shock, Cardiogenic
- Shock, Hemorrhagic
- Shock, Hypovolemic
- Shock, Septic
- Torsade de Pointes
- Toxicity, Antidepressant
- Toxicity, Calcium Channel Blocker
- Toxicity, Carbamazepine
- Toxicity, Carbon Monoxide
- Toxicity, Cocaine
Lab Studies:
- Blood glucose
  - Beta-blockers may be associated with hypoglycemia, especially in diabetics and children.
  - Blood glucose determination is particularly important when mental status is altered.
- Serum electrolytes
  - Determine serum electrolyte levels to detect for possible hyperkalemia. A 20-year-old man developed bradycardia, hypotension, coma, and metabolic acidosis after overdose with acetaminophen (25 g) and propranolol (2 g). He became severely hyperkalemic (serum potassium 10 mmol/L with wide QRS complexes and asystolic arrest) after receiving 45 mmol potassium intravenously over 1 hour.
  - Hypokalemia may contribute to cardiac arrhythmias.
  - Acidosis from poor cardiac perfusion may be manifested by low serum bicarbonate.
  - Co-ingestions or concomitant medical conditions also may alter all other serum electrolytes that should be monitored closely, especially in patients with seizures or altered mental status.
- Measure cardiac enzymes to rule out myocardial infarction in any hemodynamically unstable patient.
- No studies have been performed to correlate serum levels of beta-blockers with outcome of beta-blocker overdose.
- Arterial blood gases (ABGs) may be helpful for managing metabolic acidosis from seizures or cardiogenic shock or rare cases of severe bronchospasm, respiratory acidosis, or hypoxia.

Imaging Studies:
- Chest x-rays may show evidence of pulmonary edema.

Other Tests:
- Electrocardiogram
  - ECG results may indicate progressively severe sinus bradycardia, increased PR intervals, loss of atrial activity, atrioventricular junctional rhythm, widening of the QRS complex, atrioventricular block, idioventricular rhythm, and asystole.
  - A prolonged QT interval has been observed after sotalol overdose.
  - Ventricular fibrillation and ventricular tachycardia are uncommon because of the antiarrhythmic effects of most beta-blockers.
  - Asystole is rare, except in cases of apnea.

Prehospital Care:
- Follow standard protocols for bradycardia, hypotension, and seizures. Cardiac monitoring, oxygen administration, and good intravenous access are essential.
- Activated charcoal
  - For patients with recent ingestion, paramedics may administer activated charcoal if regional protocols permit.
  - If protocols do not permit paramedics to administer activated charcoal, transport rapidly to a nearby hospital.
  - Ipecac syrup is contraindicated because of the potential for rapid loss of consciousness and pulmonary aspiration of intestinal contents.

Emergency Department Care: The goal of therapy in beta-blocker toxicity is to restore perfusion to critical organ systems by increasing cardiac output. This may be accomplished by improving myocardial contractility, increasing heart rate, or both.
- Crystalloid: If hypotensive, administer 10-20 mL/kg of isotonic intravenous fluids and place the patient in Trendelenburg position. If the patient is unresponsive to these measures, administer pharmacologic therapies as discussed in the following section.
- Gastric decontamination: Gastric lavage is preferred over emesis because of the rapid absorption and occasionally precipitous onset of toxicity that may place the patient at risk for aspiration. Gastric lavage may be beneficial if the patient presents to the ED within 1-2 hours of ingestion. Volunteer studies have indicated that multiple dose activated charcoal (MDAC) may be useful in reducing bioavailability of nadolol, probably by removal of the drug through the...
enterohepatic circulation. Single dose activated charcoal should be administered routinely upon presentation to the ED. Some recommend that gastric lavage be undertaken after pretreatment with atropine to avoid the potential for increased vagal tone.

- Enhanced elimination: Hemodialysis may be useful in severe cases of atenolol overdoses because atenolol is less than 5% protein bound and 40-50% is excreted unchanged in urine. Nadolol, sotalol, and atenolol (low lipid solubility, low protein binding) reportedly are removed by hemodialysis. Acebutolol is dialyzable. Propranolol, metoprolol, and timolol are not removed by hemodialysis. Consider hemodialysis or hemoperfusion only when treatment with glucagon and other pharmacotherapy fails.

- Cardiac pacing/cardiopulmonary resuscitation: Cardiac pacing may be effective in increasing the rate of myocardial contraction. Electrical capture is not always successful and, if capture does occur, blood pressure is not always restored.
  - Reserve cardiac pacing for patients unresponsive to pharmacological therapy or for those with torsade de pointes unresponsive to magnesium. Multiple case reports describe complete neurological recovery, even with profound hypotension, if a cardiac rhythm can be sustained.
  - Resuscitation should, therefore, be aggressive and prolonged. Some have postulated the possibility of a protective effect on the CNS from the membrane stabilizing effects of drugs such as propranolol.

- Extracorporeal circulation/intra-aortic balloon pump: As noted above, aggressive therapy to support persistent hypotension has achieved excellent results in case reports.
  - In one case report, the application of extracorporeal circulation for 6 hours (after failure with pacing), catecholamines, and glucagon resulted in full neurologic recovery following massive propranolol ingestion.
  - In this case, the authors postulate that application of the intra-aortic balloon pump allowed vasopressors, which contributed to the serious rhythm disturbances, to be tapered off. It also may have allowed increased clearance of the drug.

Consultations:
- Regional poison control center and/or medical toxicologist
- Critical care for the intensive care management of multiple cardiac vasopressors and invasive monitoring
- Cardiology for management of cardiogenic shock and, possibly, cardiac pacing
- Nephrology, in rare instances where hemodialysis or hemoperfusion may be considered

Case series and animal models have evaluated the effects of different pharmacotherapies. However, no prospective controlled trials document the superiority of one pharmacologic therapy over another. Commonly used agents include atropine, catecholamines, glucagon, and inamrinone (formerly amrinone).

Drug Category: **Cardiovascular agents** - Used for symptomatic bradycardia and/or hypotension. Catecholamines are considered a primary treatment for more severe cases of beta-blocker poisoning.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Atropine (Atropair) - Enhances sinus node automaticity by blocking the effects of acetylcholine at the AV node, decreasing refractory time and speeding conduction through the AV node.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>Hypotension: 0.5-1 mg IV with repeated doses at 5 min intervals until desired response Cardiac arrest: 1 mg IV repeated at 3-5 min intervals; minimal dose: 0.5 mg IV Maximal dose: 0.04 mg/kg IV or 3 mg IV is fully vagolytic</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Hypotension: 0.02 mg/kg IV; minimum dose 0.1 mg IV Cardiac arrest: Maximum single dose of 0.5 mg for children and 1 mg for adolescents; may repeat dose once; not to exceed 1 mg for children and 2 mg for adolescents</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Documented hypersensitivity; thyrotoxicosis; narrow-angle glaucoma; tachycardia</td>
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<tr>
<td><strong>Interactions</strong></td>
<td>Coadministration with other anticholinergics have additive effects; pharmacologic effects of atenolol and digoxin may increase; antipsychotic effects of phenothiazines may decrease; tricyclic antidepressants with anticholinergic activity may increase effects</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>Avoid in Down syndrome or children with brain damage to prevent hyperreactive response; avoid in coronary heart disease, tachycardia, congestive heart failure, cardiac arrhythmias, and hypertension; caution in peritonitis, ulcerative colitis, hepatic disease, and hiatal hernia with reflux esophagitis; in prostatic hypertrophy, prostatism can have dysuria and may require catheterization</td>
</tr>
</tbody>
</table>

**Drug Name**

Epinephrine- Agents with combined alpha- and beta-selective properties may be necessary to maintain blood pressure. A beta-agonist may competitively antagonize the effect of the beta-blocker. The amount of beta-agonist required might be several orders of magnitude above those recommended in standard ACLS protocols.

| **Adult Dose** | 1 mcg/min IV; titrate to effect |
| **Pediatric Dose** | 0.1 mcg/kg/min; titrate to effect |

**Contraindications**

Documented hypersensitivity; tachyarrhythmias, tachycardia, heart block caused by digitalis intoxication, ventricular arrhythmias which require inotropic therapy, angina pectoris; uncorrected hypovolemia

| **Interactions** | Guanethidine may increase effect of direct-acting vasopressors, possibly resulting in severe hypertension; TCAs may potentiate pressor response of direct-acting vasopressors; phenytoin, alpha- and beta-adrenergic blockers, general anesthesia, and MAOIs increase and prolong effects of epinephrine |
| **Pregnancy** | C - Safety for use during pregnancy has not been established. |

| **Precautions** | By increasing myocardial oxygen requirements while decreasing effective coronary perfusion, may have a deleterious effect on the injured or failing heart; in some patients, presumably with organic disease of the AV node and its branches, may paradoxically worsen heart blocks or precipitate Adams-Stokes attacks; caution in coronary artery disease, coronary insufficiency, diabetes, or hyperthyroidism and sensitivity to sympathomimetic amines; if heart rate >110 BPM, may be advisable to decrease infusion rate or temporarily discontinue infusion |

Toxicity, Beta-blocker from Emergency Medicine / Toxicology
### Drug Name

Dopamine- Agents with combined alpha- and beta-selective properties may be necessary to maintain blood pressure. A beta-agonist may competitively antagonize the effect of the beta-blocker. The amount of beta-agonist required might be several orders of magnitude above those recommended in standard ACLS protocols. In a canine model, the doses of isoproterenol and dopamine had to be increased 15 and 5 times, respectively, in order to effect similar hemodynamic changes that occurred before beta-blockade with 1 mg/kg propranolol.

### Adult Dose

Begin at 2-5 mcg/kg/min IV progressing in 5-10 mcg/kg/min increments prn

### Pediatric Dose

Administer as in adults

### Contraindications

Documented hypersensitivity; tachyarrhythmias, tachycardia, heart block caused by digitalis intoxication, ventricular arrhythmias which require inotropic therapy, angina pectoris; uncorrected hypovolemia

### Interactions

Guanethidine may increase effect of direct-acting vasopressors, possibly resulting in severe hypertension; TCAs may potentiate pressor response of direct-acting vasopressors; phenytoin, alpha- and beta-adrenergic blockers, general anesthesia, and MAOIs increase and prolong effects of dopamine

### Pregnancy

C - Safety for use during pregnancy has not been established.

### Precautions

By increasing myocardial oxygen requirements while decreasing effective coronary perfusion, may have a deleterious effect on the injured or failing heart; in some patients, presumably with organic disease of the AV node and its branches, may paradoxically worsen heart blocks or precipitate Adams-Stokes attacks; caution in coronary artery disease, coronary insufficiency, diabetes, or hyperthyroidism and sensitivity to sympathomimetic amines; if heart rate >110 BPM, may be advisable to decrease infusion rate or temporarily discontinue infusion

### Drug Name

Isoproterenol- Agents with combined alpha- and beta-selective properties may be necessary to maintain blood pressure. A beta-agonist may competitively antagonize the effect of the beta-blocker. The amount of beta-agonist required might be several orders of magnitude above those recommended in standard ACLS protocols. In a canine model, the doses of isoproterenol and dopamine had to be increased 15 and 5 times, respectively, in order to effect similar hemodynamic changes that occurred before beta-blockade with 1 mg/kg propranolol.

### Adult Dose

2-4 mcg/min; titrate to effect

### Pediatric Dose

0.1 mcg/kg/min; titrate to effect
<table>
<thead>
<tr>
<th><strong>Contraindications</strong></th>
<th>Documented hypersensitivity; tachyarrhythmias, tachycardia, heart block caused by digitalis intoxication, ventricular arrhythmias which require inotropic therapy, angina pectoris; uncorrected hypovolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interactions</strong></td>
<td>Guanethidine may increase effect of direct-acting vasopressors, possibly resulting in severe hypertension; TCAs may potentiate pressor response of direct-acting vasopressors</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>C - Safety for use during pregnancy has not been established.</td>
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<tr>
<td><strong>Precautions</strong></td>
<td>By increasing myocardial oxygen requirements while decreasing effective coronary perfusion, may have a deleterious effect on the injured or failing heart; in some patients, presumably with organic disease of the AV node and its branches, may paradoxically worsen heart blocks or precipitate Adams-Stokes attacks; caution in coronary artery disease, coronary insufficiency, diabetes, or hyperthyroidism and sensitivity to sympathomimetic amines; if heart rate &gt;110 BPM, may be advisable to decrease infusion rate or temporarily discontinue infusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Drug Name</strong></th>
<th>Glucagon- Considered DOC by many. Stimulates production of cAMP through nonadrenergic pathways. Result is enhanced myocardial contractility, heart rate, and AV conduction. An upper dose limit has not been established.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult Dose</strong></td>
<td>3-10 mg IV bolus followed by 2-5 mg/h infusion</td>
</tr>
<tr>
<td><strong>Pediatric Dose</strong></td>
<td>150 mcg/kg IV over 1 min; followed 2-5 mg/h infusion</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Documented hypersensitivity; pheochromocytoma</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>May enhance effects of anticoagulants (although onset may be delayed); monitor prothrombin activity and for signs of bleeding in patients receiving anticoagulants; adjust dose accordingly</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>B - Usually safe but benefits must outweigh the risks.</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>Monitor blood glucose levels in hypoglycemic patients until they are asymptomatic; effective in treating hypoglycemia only if sufficient liver glycogen is present; because liver glycogen availability is necessary to treat hypoglycemic patients, glucagon has virtually no effects on patients with starvation, adrenal insufficiency, or chronic hypoglycemia; nausea may cause increased vagal tone; avoid phenol toxicity by diluting in D5W</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Drug Name</strong></th>
<th>Inamrinone - formerly amrinone (Inocor)- Produces vasodilation and increases inotropic state. More likely to cause tachycardia than dobutamine. May exacerbate myocardial ischemia. Case reports describe as effective when other agents fail.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult Dose</strong></td>
<td>0.75 mg/kg IV initial, followed by 5-10 mcg/kg/min maintenance infusion; additionally, 0.75 mg/kg may be given 30 min after therapy begins; not to exceed 10 mg/kg/d</td>
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<tr>
<td>Drug Name</td>
<td>Calcium chloride</td>
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<tr>
<td>Pediatric Dose</td>
<td>Not established  Suggested dosing: 0.75 mg/kg IV initial, followed by 10 mcg/kg/min maintenance infusion; infants may require larger doses</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; uncorrected hypovolemia</td>
</tr>
<tr>
<td>Interactions</td>
<td>Coadministration with diuretics may result in hypovolemia and decrease in filling pressure; cardiac glycosides have additive effects on inamrinone; admixing with furosemide or dextrose may cause precipitation</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Discontinue therapy if symptoms of liver toxicity develop; correct hypokalemia before giving therapy</td>
</tr>
<tr>
<td>Drug Name</td>
<td></td>
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<tr>
<td>Adult Dose</td>
<td>100-1000 mg slow IV push of 10% solution</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>25-50 mg/kg diluted to 10 mg/mL for IV infusion over several min</td>
</tr>
<tr>
<td>Interactions</td>
<td>Concurrent use with nifedipine may cause hypotension and neuromuscular blockade; may increase neuromuscular blockade observed with aminoglycosides and potentiate neuromuscular blockade produced by tubocurarine, vecuronium, and succinylcholine; may increase CNS effects and toxicity of CNS depressants, betamethasone, and cardiototoxicity of ritodrine</td>
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<tr>
<td>Pregnancy</td>
<td>A - Safe in pregnancy</td>
</tr>
<tr>
<td>Precautions</td>
<td>May alter cardiac conduction leading to heart block in digitalized patients; monitor respiratory rate, deep tendon reflex, and renal function when electrolyte is administered parenterally; caution when administering magnesium dose because may produce significant hypertension or asystole; in overdose, calcium gluconate, 10-20 mL IV of 10% solution, can be given as antidote for clinically significant hypermagnesemia</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Insulin (Novolin, Humulin)- High dose insulin therapy with euglycemia was associated with significant improvement in survival, compared with high-dose infusions of epinephrine and glucagon in an anesthetized canine model as well as case series of human overdose. This intriguing therapy is still highly investigational but should be considered when other therapies are failing. Dextrose infusion of 10-75 g/h may be required. Consult a toxicologist if this regimen is considered.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>Not established Suggested dosing: 0.5-1 U/kg/h with frequent boluses of dextrose</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; hypoglycemia; inability to closely monitor serum glucose concentrations</td>
</tr>
<tr>
<td>Interactions</td>
<td>Medications that may decrease hypoglycemic effects of insulin include acetazolamide, AIDS antivirals, asparaginase, phenytoin, nicotine isoniazid, diltiazem, diuretics, corticosteroids, thiazide diuretics, thyroid estrogens, ethacrynic acid, calcitonin, oral contraceptives, diazoxide, dobutamine phenothiazines, cyclophosphamide, dextrothyroxine, lithium carbonate, epinephrine, morphine sulfate, and niacin; medications that may increase hypoglycemic effects of insulin include calcium, ACE inhibitors, alcohol, tetracyclines, beta-blockers, lithium carbonate, anabolic steroids, pyridoxine, salicylates, MAOIs, mebendazole, sulfonamides, phenylbutazone, chloroquine, clofibrate, fenfluramine, guanethidine, octreotide, pentamidine, and sulfinpyrazone</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>B - Usually safe but benefits must outweigh the risks.</td>
</tr>
</tbody>
</table>
Precautions

Investigational; hyperthyroidism may increase renal clearance of insulin and may need more insulin to treat hyperkalemia; hypothyroidism may delay insulin turnover, requiring less insulin to treat hyperkalemia; monitor glucose carefully; dose adjustments of insulin may be necessary in patients diagnosed with renal and hepatic dysfunction.

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**Drug Category:** *Benzodiazepines*  - Prevent seizure recurrence and terminate clinical and electrical seizure activity.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Lorazepam (Ativan)- Benzodiazepines are considered the treatment of choice for beta-blocker induced seizures. Of the benzodiazepines, lorazepam has the longest anticonvulsant activity (4-6 h) and is preferred. By increasing the action of GABA, which is a major inhibitory neurotransmitter in the brain, may depress all levels of CNS, including limbic and reticular formation. Important to monitor patient's blood pressure after administering dose. Adjust prn.</td>
<td></td>
</tr>
</tbody>
</table>

| **Contraindications** | Documented hypersensitivity; preexisting CNS depression; hypotension; narrow-angle glaucoma |
| **Interactions**     | Toxicity of benzodiazepines in CNS increases when used concurrently with alcohol, phenothiazines, barbiturates, and MAOIs |
| **Pregnancy**        | D - Unsafe in pregnancy |
| **Precautions**      | Caution in renal or hepatic impairment, myasthenia gravis, organic brain syndrome, Parkinson disease, shock, respiratory depression, or glaucoma |

| **Adult Dose** | 0.05-0.10 mg/kg IV over 2 min |
| **Pediatric Dose** | 0.03-0.05 mg/kg IV, not to exceed 4 mg/dose |

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<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Diazepam (Valium)- Depresses all levels of CNS (eg, limbic and reticular formation), possibly by increasing activity of GABA. Is second line therapy for seizures.</th>
</tr>
</thead>
</table>

| **Contraindications** | Documented hypersensitivity; narrow-angle glaucoma; hypotension |
| **Interactions**     | Increases toxicity of benzodiazepines in CNS with coadministration of phenothiazines, barbiturates, alcohols, and MAOIs |
| **Pregnancy**        | D - Unsafe in pregnancy |
| **Precautions**      | Caution with other CNS depressants, low albumin levels, hepatic disease (may increase toxicity), shock, respiratory depression, or glaucoma |

| **Adult Dose** | 0.10 mg/kg IV over 2 min; may repeat q5-10min |
| **Pediatric Dose** | 0.2-0.5 mg/kg/dose over 2 min; may repeat q5-15min |

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<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Phenobarbital (Barbita, Luminal)- May be necessary to control status epilepticus.</th>
</tr>
</thead>
</table>

| **Adult Dose** | 15-20 mg/kg IV over 20 min |
| **Pediatric Dose** | 10-20 mg/kg IV; not to exceed 1 mg/kg/min |
### Contraindications
- Documented hypersensitivity; severe respiratory disease; marked impairment of liver function; hypotension; nephritic patients

### Interactions
- May decrease effects of chloramphenicol, digitoxin, corticosteroids, carbamazepine, theophylline, verapamil, metronidazole, and anticoagulants (patients stabilized on anticoagulants may require dosage adjustments if added to or withdrawn from their regimen); coadministration with alcohol may produce additive CNS effects and death; chloramphenicol, valproic acid, and MAOIs may increase phenobarbital toxicity; rifampin may decrease phenobarbital effects; induction of microsomal enzymes may result in decreased effects of oral contraceptives in women (must use additional contraceptive methods to prevent unwanted pregnancy); menstrual irregularities also may occur

### Pregnancy
- D - Unsafe in pregnancy

### Precautions
- In prolonged therapy, evaluate hematopoietic, renal, hepatic, and other organ systems; caution in fever, hyperthyroidism, diabetes mellitus, and severe anemia because adverse reactions can occur; caution in myasthenia gravis and myxedema

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**Drug Category:** GI decontaminant - Used to minimize the absorption of ingested compound.

#### Drug Name
Activated charcoal (Liqui-Char)- Although most useful if used within 4 h of ingestion, repeated doses may be used, especially with ingestions of sustained released agents. Limited outcome studies exist, especially when activated charcoal is used more than 1 h postingestion. No data exist to suggest a benefit of multiple dose activated charcoal with beta-blockers, even sustained release preparations. May repeat the dose q4h at 0.5 g/kg (alternate use of cathartic; monitor for active bowel sounds).

#### Adult Dose
- 1 g/kg PO (first dose usually with cathartic), up to 50-100 g

#### Pediatric Dose
- 1-2 g/kg PO (<2 y: omit cathartic), up to 15-30 g

#### Contraindications
- Documented hypersensitivity; poisoning or overdosage of mineral acids and alkalies; unprotected airway with absent gag reflex

#### Interactions
- May inactivate ipecac syrup if used concomitantly; effectiveness of other medications decreases with coadministration; do not mix with sherbet, milk, or ice cream (decreases absorptive properties)

#### Pregnancy
- C - Safety for use during pregnancy has not been established.

#### Precautions
- Monitor for active bowel sounds before readministration to minimize risk of charcoal ileus; not very effective in poisonings of ethanol, methanol, and iron salts; induce emesis before administering activated charcoal; after emesis with ipecac, patient may not tolerate activated charcoal for 1-2 h; can administer in early stages of gastric lavage; without sorbitol, gastric lavage returns are black
**FOLLOW-UP**

**Further Inpatient Care:**
- Noninvasive monitoring techniques
  - Simple methods of monitoring include repeat physical examinations, serial electrocardiograms, and continuous measurement of urinary output with a Foley catheter.
  - End points of therapy may include a heart rate more than 60 beats per minute, blood pressure of greater than 90 mm Hg systolic, and evidence of good organ perfusion (improved mentation or urine output).
- Invasive monitoring techniques
  - The best monitoring methods for patients with severe toxicity are early insertion of an arterial catheter to accurately monitor changes in systolic blood pressure and the placement of a Swan-Ganz catheter.
  - This monitors the pulmonary capillary wedge pressure (PCWP) in patients with pulmonary edema or questionable volume status.

**Further Outpatient Care:**
- Patients who present initially without symptoms can be safely discharged to psychiatric care, if indicated, after an observation period of 8-10 h, as long as they remain asymptomatic with normal vital signs and electrocardiogram. Increased caution is necessary if sustained release products are ingested or child poisoning is involved. In these cases, admission to the hospital for 24 h is recommended.
- Patients who present with signs and symptoms of beta-blocker toxicity may be discharged to psychiatric care, if indicated, after all symptoms have resolved and they have been observed for a period of 8-10 h.
- To avoid recurrent complications, adjust dosages or change medications for patients who have experienced adverse drug reactions due to combination therapy with calcium channel blockers or impaired metabolism caused by renal or hepatic dysfunction.

**Transfer:**
- Because of the potential for rapid deterioration, only asymptomatic patients who have been observed for a period of 8-10 h should be considered stable for transfer.
- If intensive care monitoring or therapy is not available, transfer the unstable patient to the closest facility with the necessary capabilities for care, including a medical toxicologist.

**Deterrence/Prevention:**
- The use of childproof containers has significantly decreased the number of accidental ingestion by children.

**Complications:**
- Complications may result from cardiovascular collapse and prolonged hospitalization and/or intensive care stays.

**Prognosis:**
- The prognosis mainly depends on the initial response to therapy 6-12 h postingestion because drug levels are likely to have peaked at this time.
- Underlying cardiac or pulmonary disease places the patient at increased risk for poor outcome.

**MISCELLANEOUS**

**Medical/Legal Pitfalls:**
- Failure to recognize beta-blocker toxicity as a cause of bradycardia and hypotension without a history of intentional overdose
- Failure to administer activated charcoal because of missed diagnosis of beta-blocker intoxication
- Administering ipecac syrup before the onset of sedation and seizures
- Failure to adequately monitor a patient on multiple cardiac vasopressors (eg, use of Swan-Ganz catheter and/or arterial blood pressure monitoring)
- Medically clearing a patient with beta-blocker toxicity before an 8- to 10-hour observation period
- Failure to administer large enough doses of antidotes, including catecholamines, glucagon, calcium, and potentially insulin.


NOTE:

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