INTRODUCTION

β-Adrenergic receptor antagonists (β-blockers) are medications used in the treatment of various cardiovascular, neurologic, endocrine, ophthalmologic, and psychiatric disorders. Among all the exposures to cardiovascular agents, β-blocker exposures were the leading cause of poison center calls and ranked among the top three in this class as a cause of severe toxicity and mortality.¹

PHARMACOLOGY

The β-adrenergic receptors are membrane glycoproteins present as three subtypes in various tissues (Table 194-1). These receptors play a critical role in cardiovascular physiology by modulating cardiac activity and vascular tone.
TABLE 194-1

Location and Activity of β-Adrenergic Receptors

<table>
<thead>
<tr>
<th>β-Receptor Type</th>
<th>Location</th>
<th>Agonism</th>
<th>Antagonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>β₁</td>
<td>Myocardium&lt;br&gt; Kidney&lt;br&gt; Eye</td>
<td>Increases inotropy&lt;br&gt; Increases chronotropy&lt;br&gt; Stimulates renin release&lt;br&gt; Stimulates aqueous humor production</td>
<td>Decreases inotropy&lt;br&gt; Decreases chronotropy&lt;br&gt; Inhibits renin release&lt;br&gt; Inhibits aqueous humor production</td>
</tr>
<tr>
<td>β₂</td>
<td>Bronchial smooth muscle&lt;br&gt; Visceral smooth muscle&lt;br&gt; Skeletal muscle&lt;br&gt; Liver&lt;br&gt; Vascular</td>
<td>Causes bronchodilation&lt;br&gt; Relaxes uterus&lt;br&gt; Causes ileus&lt;br&gt; Increases force of contraction&lt;br&gt; Stimulates glycogenolysis&lt;br&gt; Stimulates glycogenolysis and gluconeogenesis&lt;br&gt; Vasodilation</td>
<td>Causes bronchospasm&lt;br&gt; —&lt;br&gt; —&lt;br&gt; Inhibits glycogenolysis and gluconeogenesis&lt;br&gt; Minimal vasoconstriction</td>
</tr>
<tr>
<td>β₃</td>
<td>Adipose tissue&lt;br&gt; Skeletal muscle</td>
<td>Stimulates lipolysis&lt;br&gt; Stimulates thermogenesis</td>
<td>Inhibits lipolysis&lt;br&gt; Inhibits thermogenesis</td>
</tr>
</tbody>
</table>

During times of stress (i.e., catecholamine release), β-adrenergic receptor stimulation increases myocardial and vascular smooth muscle cell activity through a sequence of intracellular events (Figure 194-1).²,³

**FIGURE 194-1.** Cardiac myocyte β₁-receptor and calcium signaling. Following myocyte depolarization, extracellular calcium (Ca²⁺) enters the cell via the L-type or voltage-gated calcium channel (L-VDCC) and binds to the ryanodine receptor (RyR) in the sarcoplasmic reticulum, causing an efflux of sequestered Ca²⁺ out of the sarcoplasmic reticulum into the cytosol. Free Ca²⁺ binds to troponin that allows the myosin and actin interaction, resulting in contraction of the cardiac myocyte. Binding of a β-agonist to the β₁-adrenergic receptor (B₁) on the cell surface activates the Gs protein. The Gs protein then activates adenylate cyclase (AC), which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). The increased cAMP activates protein kinase A (PKA). Activated PKA serves as further stimulus for the L-VDCC opening. Glucagon independently activates adenylate cyclase. cAMP is metabolized by phosphodiesterase (PDE) into inactive adenosine 5’-monophosphate (5’AMP).
The β-receptor is coupled to a stimulatory G\textsubscript{s} protein. This G\textsubscript{s} protein stimulates adenylate cyclase, which in turn catalyzes the formation of cyclic adenosine monophosphate, the so-called intracellular second messenger. Increased cyclic adenosine monophosphate ultimately phosphorylates the L-type calcium channel, which leads to channel opening and calcium entry into the cell. Extracellular calcium is then coupled to the ryanodine receptor to carry the calcium current to the sarcoplasmic reticulum, which then releases its stored calcium. This process is termed calcium-induced calcium release. Stored calcium becomes available to participate in mechanical contraction via the actin and myosin complex. Like the cardiac myocyte, the vascular smooth muscle uses L-type calcium channels to regulate intracellular calcium and subsequently coordinate vascular tone. To prevent overdrive of the cell, phosphodiesterase breaks down cyclic adenosine monophosphate to adenosine 5'-monophosphate, thus removing the stimulus for calcium channel opening, and the contractile process ceases.

The β-blockers modulate the activity of myocyte and vascular smooth muscle contraction by decreasing calcium entry into the cell.\textsuperscript{2,3} Therapeutically, β-blockade lessens the work performed by the diseased or
injured myocardium and lowers elevated blood pressure. On the other hand, excessive β-blockade may lead to profound pump failure, with bradycardia, decreased contractility, and hypotension.\textsuperscript{2}

The pharmacologic properties of various β-blockers influence their spectrum of action, adverse drug reactions, and toxicity (\textit{Table 194-2}).\textsuperscript{4,5} These properties include receptor selectivity, sodium channel blockade (also known as \textit{membrane-stabilizing activity}), lipid solubility, protein binding, and partial agonist activity (also known as \textit{intrinsic sympathomimetic activity}). For example, highly lipid-soluble agents, such as propranolol, readily cross the blood–brain barrier and achieve high concentrations in brain tissue.\textsuperscript{2,3} This may contribute to the more severe CNS manifestations of mental status depression, seizures, and coma seen after an overdose of such agents.\textsuperscript{2,3} Several β-blockers inhibit myocardial sodium channels, similar to quinidine and cyclic antidepressants, rendering these drugs potentially more cardiodepressant following overdose.\textsuperscript{3} However, in massive overdoses, all β-blockers can be severely cardiodepressive.\textsuperscript{6}
TABLE 194-2

β-Blocker Pharmacologic Profiles

<table>
<thead>
<tr>
<th>Agent</th>
<th>β₁ Selectivity</th>
<th>Lipophilicity</th>
<th>Partial Agonism</th>
<th>Protein Binding (%)</th>
<th>Sodium Channel Blockade</th>
<th>Half-Life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>+</td>
<td>Moderate</td>
<td>+</td>
<td>25</td>
<td>+</td>
<td>3–4</td>
</tr>
<tr>
<td>Atenolol</td>
<td>+</td>
<td>Weak</td>
<td>0</td>
<td>6–16</td>
<td>0</td>
<td>6–9</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>+</td>
<td>High</td>
<td>0</td>
<td>55</td>
<td>±</td>
<td>14–22</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>++</td>
<td>Moderate</td>
<td>0</td>
<td>30–40</td>
<td>0</td>
<td>9–12</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>0</td>
<td>Moderate</td>
<td>0</td>
<td>&gt;95</td>
<td>±</td>
<td>7–10</td>
</tr>
<tr>
<td>Esmolol</td>
<td>+</td>
<td>Weak</td>
<td>0</td>
<td>55</td>
<td>±</td>
<td>9 min</td>
</tr>
<tr>
<td>Labetalol</td>
<td>+</td>
<td>Weak</td>
<td>0</td>
<td>50</td>
<td>±</td>
<td>3–4</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>++</td>
<td>Moderate</td>
<td>0</td>
<td>12</td>
<td>±</td>
<td>3–4</td>
</tr>
<tr>
<td>Nadolol</td>
<td>0</td>
<td>Weak</td>
<td>0</td>
<td>30</td>
<td>0</td>
<td>12–24</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>+++</td>
<td>Moderate</td>
<td>0</td>
<td>98</td>
<td>0</td>
<td>8–27</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>0</td>
<td>Moderate</td>
<td>++</td>
<td>80</td>
<td>+</td>
<td>1–2</td>
</tr>
<tr>
<td>Pindolol</td>
<td>0</td>
<td>High</td>
<td>++</td>
<td>40–60</td>
<td>±</td>
<td>3–4</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>0</td>
<td>High</td>
<td>+</td>
<td>80–98</td>
<td>0</td>
<td>5–20</td>
</tr>
<tr>
<td>Propranolol</td>
<td>0</td>
<td>High</td>
<td>0</td>
<td>&gt;90</td>
<td>++</td>
<td>3–4</td>
</tr>
<tr>
<td>Sotalol</td>
<td>0</td>
<td>Weak</td>
<td>0</td>
<td>Minimal</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Timolol</td>
<td>0</td>
<td>High</td>
<td>±</td>
<td>10–60</td>
<td>0</td>
<td>4–5</td>
</tr>
</tbody>
</table>

*Abbreviations:* + = some activity; ++ = strong activity; ± = possible activity; 0 = no activity.
Although $\beta_1$ cardioselective medications have less risk of unwanted $\beta_2$ effects, such as bronchospasm, selectivity is often lost following large overdoses. $^3$ Several $\beta$-blockers like pindolol have partial agonist activity, causing weak stimulation of the $\beta$-receptor, with a lessor tendency for bradycardia during therapeutic use. $^4$ Some $\beta$-blockers, such as labetalol and carvedilol, are also antagonists at $\alpha_1$-adrenergic receptors, which can result in exaggerated hypotension during therapeutic use. Sotalol is unique among $\beta$-blockers in its ability to block potassium channels important for repolarization, as do other class III antiarrhythmic drugs.$^{2,3,4}$

In addition to having cardiopulmonary effects, $\beta$-blockers also alter metabolism in the liver, skeletal muscle, and adipose tissue. Under normal conditions, the heart uses free fatty acids as its primary energy source, but during times of stress, it switches to using carbohydrates to maintain metabolism. Inhibition of glycogenolysis and gluconeogenesis reduces the availability of carbohydrates for use by metabolically active cells. Although hypoglycemia can occur as a consequence of $\beta$-blocker toxicity, it is actually uncommon.$^2$ In the presence of adequate glucose stores, euglycemia and hyperglycemia are more common than hypoglycemia.

Clinically relevant pharmacokinetic characteristics include drug formulation (regular or extended release), rate of drug absorption, protein binding, lipid solubility, elimination mostly by hepatic metabolism, and volume of distribution. These properties determine onset of symptoms, duration of symptoms, target organ toxicity, and potential treatment modalities.

**CLINICAL FEATURES**

Toxicity due to $\beta$-blockers can produce a spectrum of clinical symptoms (**Table 194-3**).$^{2,3,7}$ The timing of symptom appearance depends upon the formulation. Absorption of regular-release $\beta$-blockers occurs rapidly, often with peak effects within 1 to 4 hours. However, delays of up to 6 hours following acute ingestion have occurred.$^8$ Experience is limited regarding onset of symptoms with poisoning following an ingestion of sustained-release $\beta$-blocker formulations, but based on other sustained-release cardiac drugs, it is assumed that symptoms may be delayed $>6$ hours after ingestion.$^{2,3}$ Co-ingestants that alter gut function, such as opioids and anticholinergics, may affect absorption of $\beta$-blockers and subsequent onset of symptoms.$^2$
Common Findings with β-Blocker Toxicity

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>Asystole</td>
</tr>
<tr>
<td>Conduction delays and blocks (first-degree atroventricular block)</td>
<td>Decreased contractility</td>
</tr>
<tr>
<td>Ventricular dysrhythmias (sotalol)</td>
<td>CNS</td>
</tr>
<tr>
<td>Asystole</td>
<td>Depressed mental status</td>
</tr>
<tr>
<td>Conduction delays and blocks (first-degree atroventricular block)</td>
<td>Coma</td>
</tr>
<tr>
<td>Ventricular dysrhythmias (sotalol)</td>
<td>Psychosis</td>
</tr>
<tr>
<td>Asystole</td>
<td>Seizures</td>
</tr>
<tr>
<td>Conduction delays and blocks (first-degree atroventricular block)</td>
<td>Respiratory arrest</td>
</tr>
<tr>
<td>Ventricular dysrhythmias (sotalol)</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>Asystole</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>Conduction delays and blocks (first-degree atroventricular block)</td>
<td>Electrolytes</td>
</tr>
<tr>
<td>Ventricular dysrhythmias (sotalol)</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Asystole</td>
<td>Hyperkalemia</td>
</tr>
</tbody>
</table>

The primary organ system affected by β-blocker toxicity is the cardiovascular system, and the hallmark of severe toxicity is bradycardia and shock.²,³,⁷,⁹ Bradycardia due to sinus node suppression or conduction abnormalities occurs in virtually all significant β-blocker intoxications, although ingestion of β-blockers with partial agonist activity may initially present with hypertension and tachycardia.⁹ The β-blockers with sodium channel antagonism can worsen conduction abnormalities, causing a wide-complex bradycardia (especially when the QRS interval is >100 milliseconds).⁹

The cardiotoxic profile of sotalol is different from that of other β-blockers due to its ability to block potassium channels and prolong the QT interval.³ Thus, sotalol is more often associated with ventricular dysrhythmias, including premature ventricular contractions, bigeminy, ventricular tachycardia, ventricular fibrillation, and torsades de pointes.³

β-Blockers also affect the CNS and pulmonary system. Neurologic manifestations include depressed mental status, coma, and seizures.² These symptoms most likely occur as a result of a combination of hypoxia due to
poor perfusion, sodium channel antagonism, and direct neuronal toxicity. More lipophilic β-blockers, such as propranolol, cause greater neurologic toxicity than the less lipophilic agents. Seizures are generally brief, and status epilepticus is rare. Nonselective β-blockers may antagonize the β₂-receptor in bronchial smooth muscle causing bronchospasm. Similarly, in large ingestions of cardioselective β-blockers, the β₁ selectivity may be lost.

**DIAGNOSIS**

The diagnosis of β-blocker toxicity is primarily made on clinical grounds, including patient history, physical examination findings, and results of basic diagnostic testing. Patients commonly present with a history of intentional overdose or therapeutic misadventure. The diagnosis may be more challenging in the case of polypharmacy "heart or blood pressure medication" overdose or with suspected chronic drug toxicity in the patient on multiple cardiovascular drugs. Exposure to other drugs and toxins can present with bradycardia and hypotension, but useful features can help differentiate toxicity from these agents from that due to β-blockers (Table 194-4).
TABLE 194-4

Toxicologic Causes of Bradycardia and Hypotension

<table>
<thead>
<tr>
<th>Cause</th>
<th>Differentiating Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td>Elevated lactate level and hyperglycemia</td>
</tr>
<tr>
<td>Naturally occurring cardiac glycosides (oleander, foxglove, lily of</td>
<td>Ventricular ectopy</td>
</tr>
<tr>
<td>the valley, rhododendron, and toad-derived bufotoxin)</td>
<td>May cross-react with digoxin immunoassay</td>
</tr>
<tr>
<td>Class IC antiarrhythmic drugs (propafenone)</td>
<td>Wide-complex bradycardia</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Opioid-like manifestations: coma, miosis, decreased respirations</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Profound metabolic acidosis and elevated lactate level</td>
</tr>
<tr>
<td>Digoxin (acute)</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>Elevated level on digoxin immunoassay</td>
</tr>
<tr>
<td>Organophosphates</td>
<td>Muscarinic toxidrome</td>
</tr>
</tbody>
</table>

Laboratory testing is recommended to assess renal function, glucose level, oxygenation, and acid-base status. Although specific β-blocker drug levels might be of value for later confirmation of an ingestion, these levels are not helpful initially because they do not correlate with the degree of toxicity and are generally not available in a timely fashion to affect acute management.\(^2,3,7\) False-positive amphetamine results can be seen on urine drug screens from labetalol, because one of its metabolites is structurally similar to amphetamine and methamphetamine.\(^10\) Cardiac function is evaluated with a 12-lead ECG, rhythm monitor, and bedside cardiac US.\(^11\) A drug-induced Brugada pattern may be observed in an overdose of propranolol, a β-blocker that also affects cardiac sodium channels.\(^12\)

TREATMENT

GENERAL MANAGEMENT
Evaluate patients with suspected β-blocker overdose in a critical-care area of the ED with appropriate monitoring because these patients may experience abrupt cardiovascular collapse or neurologic depression. If orotracheal intubation is needed, the drugs used to sedate and paralyze may worsen hypotension in the face of an already depressed myocardium.²,³,⁷

GI DECONTAMINATION

Although there is little evidence to support routine GI decontamination following overdose of most substances, ingestion of a significant quantity of β-blockers with the risk of severe toxicity is a circumstance in which decontamination should be considered.¹³ Activated charcoal may be of benefit if it can be given within 1 hour after ingestion and the patient is able to maintain the airway.¹⁴,¹⁵ There may be an additional window of opportunity for activated charcoal therapy following ingestion of sustained-release β-blockers. Ipecac syrup and cathartic agents are not recommended.¹⁶ Gastric lavage is not recommended.¹³ Whole-bowel irrigation may be beneficial after a large ingestion of an extended-release product.¹⁷

PHARMACOLOGIC TREATMENT

Specific pharmacologic therapies are directed at restoring perfusion to critical organ systems by improving myocardial contractility, increasing heart rate, or both.²,³,⁷ This is done through fluid resuscitation and administration of glucagon, adrenergic agonists, high-dose insulin, calcium, and phosphodiesterase inhibitors (Figure 194-2). Individual pharmacologic therapies have variable effectiveness and are often used simultaneously.⁷ Aggressive measures such as hemodialysis, hemoperfusion, cardiac pacing, placement of intra-aortic balloon pumps, and extracorporeal circulatory support have also been used when patients are refractory to pharmacologic therapy.¹⁸

FIGURE 194-2.
Management strategies in β-blocker toxicity. Cardiac function is evaluated using ECG, cardiac US, and/or central hemodynamic monitoring. For wide QRS interval, consider sodium bicarbonate therapy. For impaired myocardial contractility, consider glucagon, high-dose insulin, adrenergic agents, and calcium therapy. For decreased systemic vascular resistance, consider vasopressors, such as norepinephrine, epinephrine, dopamine, and phenylephrine. For bradycardia, consider glucagon, adrenergic agents, and cardiac pacing. (See text for details.) SVR = systemic vascular resistance.
GLUCAGON

**Glucagon is a first-line agent in the treatment of acute β-blocker–induced bradycardia and hypotension.**

Glucagon, produced in the pancreatic α-cells from proglucagon, independently activates myocardial adenylate cyclase, bypassing the impaired β-receptor ([Figure 194-1](#)). Effects from an IV bolus of glucagon are seen within 1 to 2 minutes, reach a peak in 5 to 7 minutes, and have a duration of action of 10 to 15 minutes. Due to the short duration of effect, a continuous infusion is often necessary after bolus administration. The bolus dose of glucagon is 3 to 10 milligrams (30 to 150 micrograms/kg in children), and if a response is not seen within 15 minutes, a repeat bolus can be given. If a beneficial effect is seen from the glucagon bolus, a continuous infusion of 1 to 5 milligrams/h (20 to 70 micrograms/kg per hour in children) can be used to maintain this effect. Glucagon infusion should be titrated to rate to achieve adequate hemodynamic response. There is no identified maximum therapeutic dose or duration of treatment.

The amount of glucagon required to treat a significant β-blocker overdose may exceed the total amount available at any given hospital. The positive inotropic and chronotropic effects of glucagon may not be maintained for a prolonged period due to possible tachyphylaxis. Nausea and vomiting are commonly reported side effects of high-dose glucagon therapy and may be related to esophageal sphincter relaxation. Intubation prior to glucagon administration may be warranted in any patient with altered mental status to limit the risk of aspiration.

Prior to 1998, glucagon was derived from porcine and bovine pancreas and contained other pancreatic compounds such as insulin and phenol as a preservative. The contribution of this insulin content to the original glucagon's overall efficacy is unclear (see discussion below in "High-Dose Insulin Therapy"). Since 1998, glucagon has been produced via recombinant technology and is devoid of insulin or phenol.

**ADRENERGIC RECEPTOR AGONISTS**
The β-adrenergic receptor agonists—such as norepinephrine, dopamine, epinephrine, and isoproterenol—are used routinely to treat β-blocker toxicity. However, results have been variable even when dosages far exceed those recommended in standard guidelines for cardiac resuscitation. The most effective adrenergic receptor agonists may be norepinephrine and epinephrine due to their chronotropic and vasopressor effects. Phenylephrine may also be beneficial as a vasopressor. Although isoproterenol may increase heart rate, it does so at the expense of vasodilation. Dobutamine has a similar downside: potential improvement in inotropy but worsening of hypotension due to vasodilation.

HIGH-DOSE INSULIN THERAPY

High-dose insulin therapy, sometimes called hyperinsulinemia-euglycemia therapy, is an important treatment modality for β-blocker toxicity. Insulin acts as an inotrope by facilitating myocardial utilization of glucose, the desired energy substrate during stress, in contrast to glucagon, epinephrine, and calcium, which promote free fatty acid utilization. In animal models, high-dose insulin therapy improved survival in severe β-blocker overdose compared with glucagon, epinephrine, or vasopressin administration. The most consistent cardiodynamic effect in these models was an increase in contractility.

High-dose insulin therapy dosing used for treatment of β-blocker toxicity is much higher than that used for traditional glucose control in diabetes (Table 194-5). The initial dose is regular insulin 1 unit/kg IV bolus and is followed by a continuous infusion of 0.5 to 1 unit/kg per hour that is titrated to the desired hemodynamic response of a heart rate at least 50 beats/min and systolic blood pressure of at least 100 mm Hg (13.3 kPa). The maximum dose has not yet been established, although an animal model of propranolol overdose found that cardiac output increased in a dose-response manner when the insulin dose was raised from 1 to 10 units/kg per hour, and human case reports have used doses this high.
TABLE 194-5

Protocol for High-Dose Insulin Therapy in Severe β-Blocker Overdose

Check serum glucose, and if <200 milligrams/dL (<11 mmol/L), administer 50 mL of 50% dextrose (0.5 gram/mL) in water IV (children 1 mL/kg of 25% dextrose).

Administer regular insulin 1 unit/kg IV bolus.

Begin regular insulin infusion at 0.5–1.0 unit/kg per hour along with dextrose 10% (0.1 gram/mL) in water at 200 mL/h (adult) or 5 mL/kg per hour (pediatric).

Titrate infusion rate up to 10 units/kg per hour according the hemodynamic goal of HR >50 beats/min and SBP >100 mm Hg (>13.3 kPa).

Monitor serum glucose every 15–20 min.

Titrate dextrose infusion rate to maintain serum glucose level between 100 and 200 milligrams/dL (5.3 and 10.7 mmol/L).

Once dextrose infusion rates have been stable for 60 min, glucose monitoring may be decreased to hourly.

Monitor serum potassium level and start IV potassium infusion if serum potassium level is <2.8 mEq/L (<2.8 mmol/L).

Maintain serum potassium between 2.8 and 3.2 mEq/L (2.8 and 3.2 mmol/L).

Abbreviations: HR = heart rate; SBP = systolic blood pressure.

The onset of action with high-dose insulin therapy is reported to be 15 to 45 minutes, but a delayed response of several hours has been noted. High-dose insulin therapy is continued until resolution of toxicity; the duration of high-dose insulin therapy infusion described in case reports ranges from 9 to 49 hours. The insulin infusion can be gradually weaned or abruptly halted. Reinject the insulin infusion if the heart rate or blood pressure falls after cessation of high-dose insulin therapy.

Potential adverse effects from high-dose insulin therapy are hypoglycemia and lowered serum potassium. Dextrose infusion is used to prevent hypoglycemia and often required during the duration of therapy. Serum potassium is monitored and supplemental replacement is given if the level is below 2.8 mEq/L (2.8 mmol/L). An increase in the dextrose infusion rate required to maintain serum glucose between 100 and 200 milligrams/dL (5.3 and 10.7 mmol/L), along with signs of clinical improvement, may be an indication that metabolic status is normalizing; that is, that the stress response is diminishing, the heart is reverting back to basal energy substrates, and extra insulin is no longer needed.

INTRAVENOUS LIPID EMULSION THERAPY

Intravenous lipid emulsion therapy, also known as fat emulsion therapy or lipid rescue, is effective in treating toxicity from local anesthetics, calcium channel blockers, typical and atypical antipsychotics, cyclic and other antidepressants, and some β-blockers. The exact mechanism is not fully understood, but the
likely explanation is that lipid emulsion acts as a pharmacologic sink, by sequestering lipophilic drugs into a separate lipid compartment, and the amount of free drug available to target tissues is reduced ("lipid sink" model). Other potential mechanisms may include supplying the myocardium with free fatty acids and phospholipids, increasing myocardial contractility by increasing myocyte calcium concentration, and elevating blood pressure by central sympathetic activation.

Animal models suggest that intravenous lipid emulsion may be most effective in the lipophilic β-blockers (Table 194-2), such as propranolol and carvedilol, and may be less effective in more hydrophilic agents, such as metoprolol and atenolol.

The dosing regimen for intravenous lipid emulsion is based on treatment of local anesthetic systemic toxicity. The standard 20% lipid emulsion is given as a 1.5 mL/kg bolus over 1 minute, followed by a infusion at 0.25 mL/kg per minute. If the blood pressure remains low, an additional 1.5 mL/kg bolus may be repeated followed by an increase in the infusion rate to 0.5 mL/kg per minute. The recommended upper limit is about 10 mL/kg over the initial 30 minutes. If the patient's hemodynamic stability is dependent on continued lipid infusion, the treatment may be continued beyond this level. Duration of therapy has not been fully established. If cardiac arrest occurs, a bolus dose can be given during the resuscitation.

Adverse effects reported with the use of lipid emulsion for the treatment of overdose and toxicity include lipemia causing interference with laboratory analysis, hypertriglyceridemia, pancreatitis, and possibly acute lung injury, acute renal failure, deep vein thrombosis, and cardiac arrest. Lipid emulsion may clog the hemofiltration filter precluding renal replacement therapy during the infusion and until the lipid has been cleared from the blood. Given the current understanding and limited clinical experience using intravenous lipid emulsion as an antidote, this treatment should be reserved for refractory shock.

**ATROPINE**

Atropine, a muscarinic blocker, is unlikely to be effective in the management of β-blocker–induced bradycardia and hypotension, although its use is unlikely to cause harm. Its use may be beneficial for co-ingestants.

**CALCIUM**

Canine studies and limited case reports suggest that calcium therapy may reverse depression of the myocardium via positive inotropic action, although with few chronotropic effects. Calcium administration is not routinely recommended in β-blocker overdose, but may be considered in patients with refractory shock unresponsive to other therapies. Calcium for IV administration is available in two forms, gluconate and chloride, both in a 10% solution. A 10-mL dose of 10% calcium chloride solution contains three times more elemental calcium, 13.6 mEq (6.8 mmol), than 10 mL of 10% calcium gluconate solution, 4.5 mEq (2.23 mmol). Thus, one 10-mL ampule of 10% calcium chloride equals three 10-mL ampules of 10% calcium gluconate.
Potential adverse effects of calcium therapy include hypercalcemia, conduction blocks, worsening bradycardia, and inefficient cardiac energetics during shock (see "High-Dose Insulin Therapy"). Most patients tolerate transient increases in total calcium level without difficulty, and conduction blocks are rare. Severe soft tissue injury associated with inadvertent IV infiltration of the chloride formulation is the most concerning adverse event. Thus, calcium chloride is ideally given via a central line. Calcium gluconate is only rarely associated with tissue injury and is the preferred form for peripheral administration.

The optimum dose of calcium in β-blocker toxicity is unknown. Animal studies and limited human studies suggest that large amounts of calcium are needed to treat drug-induced cardiac toxicity, but these data come from experience derived from treating calcium channel blocker toxicity. The recommended dose of 10% calcium gluconate is 0.6 mL/kg given over 5 to 10 minutes, followed by a continuous infusion of 0.6 to 1.5 mL/kg per h. The equivalent dosage of 10% calcium chloride is 0.2 mL/kg given via central line over 5 to 10 minutes, followed by a continuous infusion of 0.2 to 0.5 mL/kg per h. Ionized calcium levels should be checked every 30 minutes initially and then every 2 hours to achieve an ionized calcium level of twice the normal value.

**PHOSPHODIESTERASE INHIBITORS**

Phosphodiesterase inhibitors such as milrinone have been used to treat β-blocker toxicity. These agents inhibit the breakdown of cyclic adenosine monophosphate, thereby sustaining intracellular calcium levels (Figure 194-1). In animal models, phosphodiesterase inhibitors produce positive inotropic effects without increasing myocardial oxygen demand but have no appreciable effect on heart rate. Compared with glucagon, phosphodiesterase inhibitors do not provide any additional benefit and therefore have no advantage over glucagon. However, if glucagon is not available or pharmacy stores have been exhausted, a phosphodiesterase inhibitor is a reasonable alternative. In the setting of a β-blocker overdose, milrinone is administrated as a continuous IV infusion, starting with a 50 micrograms/kg IV bolus, followed by an IV infusion of 0.375 to 0.75 micrograms/kg per minute for milrinone.

**SODIUM BICARBONATE**

Sodium bicarbonate is used to treat severe acidosis and wide QRS-interval dysrhythmias secondary to sodium channel blockade. β-Blockers with sodium channel–blocking ability (Table 194-2) can interfere with ventricular depolarization, predisposing to cardiac dysrhythmias. When the QRS interval is longer than 120 to 140 milliseconds, it is reasonable to administer sodium bicarbonate. The suggested dose is a rapid bolus of 2 to 3 mEq/kg over 1 to 2 min. Thus, a 70-kg adult receives a bolus of 140 to 210 mEq of sodium bicarbonate, or three to four ampules (50 mL each) of 8.4% sodium bicarbonate. Repeat boluses or an infusion may be required to maintain the QRS interval at <120 milliseconds.

**CARDIAC PACING**
Internal or external pacing may be considered to treat bradycardia in the setting of β-blocker toxicity. Electrical capture and restoration of blood pressure is not always successful, potentially due to the lack of intracellular calcium needed for contraction. Cardiac pacing may be most beneficial in treating torsades de pointes associated with sotalol toxicity.

EXTRACORPOREAL ELIMINATION (HEMODIALYSIS)

The high degree of protein binding and lipid solubility of β-blockers, as well as their large volume of distribution, renders extracorporeal drug removal useless for most drugs in this class. Acebutolol, atenolol, nadolol, and sotalol may be amenable to removal through hemodialysis owing to their lower protein binding, water solubility, and lower volume of distribution.

EXTRACORPOREAL CIRCULATION

Occasionally, extreme means of resuscitation, including extracorporeal circulation (extracorporeal membrane oxygenation) and intra-aortic balloon pumps, have been successful when pharmacologic measures have failed to reverse cardiogenic shock.

TREATMENT OF SOTALOL TOXICITY

Treatment of sotalol toxicity may require pharmacologic measures different from those required for other β-blockers due to its potassium channel effects. In addition to the therapies discussed above, magnesium supplementation, lidocaine, and cardiac overdrive pacing may be of specific benefit.

SUMMARY

No one particular treatment is consistently effective in cases of β-blocker toxicity, and multiple simultaneous treatment measures may be required to resuscitate the critically ill patient. Tailor therapy based on the ECG, bedside cardiac US, and/or central hemodynamic monitoring. The goal of resuscitation is to improve hemodynamics and organ perfusion. Specific end points of therapy may include a cardiac ejection fraction of 50% or greater, a reduction of the QRS interval to <120 milliseconds, a heart rate of >50 to 60 beats/min, a systolic blood pressure of >90 to 100 mm Hg (12.0 to 13.3 kPa) in an adult, a urine output of 1 to 2 mL/kg per hour, and improved mentation.

DISPOSITION AND FOLLOW-UP

Patients who develop altered mental status, bradycardia, conduction delays, or hypotension should be managed in an intensive care unit. A patient who ingests a sustained-released β-blocker product warrants admission and monitoring for the development of delayed toxicity. Patients ingesting an overdose of regular-release β-blocker tablets who remain asymptomatic and have normal vital signs for 6 hours after ingestion can be deemed medically safe for discharge or admission to a psychiatric facility.
REFERENCES


