Management of Beta-Adrenergic Blocker Poisoning

Angela C. Anderson, MD, FAAP

Beta-adrenergic blocking agents or β-blockers are prescribed for the treatment of a broad array of common disorders. Their widespread use, coupled with a narrow therapeutic index, contributes to their being a significant cause of poisoning from overdose and the second most common cause of mortality from cardiovascular agents. This article provides an overview of beta-adrenergic system pathophysiology and the properties and pharmacokinetics of β-blockers. Also discussed are the various effects and management of β-blockers in overdose settings.

Clin Ped Emerg Med 9:4-16 © 2008 Published by Elsevier Inc.

KEYWORDS β-blockers, poisoning, cardiovascular agents, overdose

Beta-adrenergic blocking agents or β-blockers are prescribed for the treatment of a broad array of common disorders. Although the primary targets of beta antagonists are cardiovascular diseases that primarily affect adults (e.g., angina, hypertension, and heart failure), these agents are also used to manage childhood and adolescent disorders including dysrhythmias, behavioral disorders, migraine headaches, and anxiety. The widespread use of β-blockers, coupled with their narrow therapeutic index, contribute to their being a significant cause of poisoning from overdose.

There were 18,207 cases of β-blocker exposures reported by the American Association of Poison Control Centers in 2005 [1]. These agents were responsible for 9,078 visits to health care facilities and 60 deaths—making β-blockers the second most common cause of mortality from cardiovascular agents. Children younger than 6 years were the victims in 4,436 of the reported cases of β-blocker ingestion.

**Beta Receptors**

There are 4 subgroups of beta receptors. Although these receptors may be found in more than one location in the human body (Table 1), β₁ receptors are primarily found on cardiac myocytes, β₂ receptors are located chiefly in vascular and bronchial smooth muscle, β₃ receptors are concentrated in adipocytes (although they are found in cardiac myocytes as well), and β₄ receptors reside in the myocardium.

During stressful conditions, endogenous catecholamine release stimulates β₁ receptors to promote an increase in heart rate and contractility, whereas β₂-receptor stimulation induces bronchial and arteriolar dilation. Simultaneous adrenergic stimulation of α₁ receptors, also located on vascular smooth muscle, causes vasoconstriction thereby providing a counterbalance to the β₂ induced vasodilation. β₂ Agonists also promote insulin release, glycogenolysis, and gluconeogenesis; the net result is an increase in serum glucose concentration [2-4].

The role of the β₁ receptor is not completely understood, although it is thought to be involved in lipolysis and thermoregulation. β₃ Receptors are also believed to mediate negative inotropic effects via activation of Gi proteins (see below) [5-7]. Finally, β₄ receptors are responsible for the partial agonist properties seen in some β-blockers (see intrinsic sympathomimetic activity below) [7].

**Pathophysiology of the Beta-Adrenergic System**

To understand the clinical presentation and management of β-blocker overdose, one must be familiar with the

Pediatric Emergency Medicine, Hasbro Children’s Hospital, Providence, RI 02903.
Warren Alpert Medical School of Brown University, Providence, RI.
Reprint requests and correspondence: Angela C. Anderson, MD, FAAP, Pediatric Emergency Medicine, Hasbro Children’s Hospital, Providence, RI. (E-mail: angela_anderson@brown.edu)

1522-8401/$ – see front matter © 2008 Published by Elsevier Inc.
doi:10.1016/j.cpem.2007.12.001
pathophysiology of the beta-adrenergic system. A cascade of events follows beta-receptor stimulation that allows for the actions of beta agonists. The first of these events involves G proteins, which allow the communication of the beta receptor to the enzyme adenylate cyclase. Gs proteins stimulate adenylate cyclase, whereas Gi proteins inhibit it [6]. β1, β2, and β3 receptors are coupled to Gs proteins, whereas β3 receptors are linked to Gi proteins.

### β1 Activation in Cardiac Muscle

When beta-adrenergic agonists (such as norepinephrine) bind to myocardial β1 receptors, Gs proteins activate adenylate cyclase. Adenylate cyclase then catalyzes the formation of cyclic adenosine monophosphate (cAMP) from adenosine triphosphate. Cyclic AMP, in turn, activates protein kinase A. Phosphorylation of voltage-sensitive L-type calcium channels by protein kinase A causes the channels to open and allow calcium influx into the myocyte. The increase in intracellular calcium promotes calcium release from the sarcoplasmic reticulum. Protein kinase A also phosphorylates the sarcoplasmic reticulum, further augmenting calcium release within the cardiac cell. These mechanisms provide the intracellular calcium required to bind troponin C, which allows excitation-contraction coupling of actin and myosin filaments. Cyclic AMP is broken down by phosphodiesterase (PDE) to 5’-adenosine monophosphate.

### β2 Activation in Smooth Muscle

In the same fashion observed in cardiac myocytes, stimulation of β2 receptors by catecholamines increases cAMP production in vascular and bronchial smooth muscle. Cyclic AMP activates protein kinase A, as it did in cardiac myocytes. However, phosphorylation of smooth muscle cell membranes decreases calcium influx, and phosphorylation of the sarcoplasmic reticulum in smooth muscle causes calcium reuptake rather than calcium release. The overall result is a decrease in intracellular calcium and fewer actin-myosin interactions.

### β-Blocker Actions and Properties

Beta antagonists competitively block beta receptors, thereby inhibiting cAMP formation and preventing the events that routinely follow. β1 Receptor blockade causes a decrease in cardiac inotropy, chronotropy, and automaticity, culminating in a reduction in cardiac output. Blockade of β1 receptors also leads to suppression of renin secretion in the kidney, thereby decreasing production of angiotensin II (a potent vasoconstrictor) and aldosterone (which promotes sodium retention). The combination of renal effects and reduced cardiac output promotes a decrease in blood pressure. Blocking vascular smooth muscle β2 receptors provides a rise in vascular tone that is clinically insignificant in most instances.

A number of β-blockers have been marketed since their initial development in 1962. New applications and adverse side effects stimulated the search for β-blockers with differing attributes. The clinical presentation of β-blocker ingestion (therapeutically and in overdose) may vary depending on the properties that differ among agents.

### Cardioselectivity

Although originally intended for the treatment of cardiovascular conditions, traditional beta antagonists such as propranolol blocked both β1 and β2 receptors causing unwanted side effects. The adverse effects of β2 antagonism (such as bronchospasm in patients with pulmonary disease and hypoglycemia in those with diabetes) prompted the development of more cardioselective agents. Metoprolol and atenolol were the first 2 agents to accomplish that goal [8,9]. They have an affinity for β1 receptors that is 20 times their affinity for β2 receptors [9]. A number of cardioselective agents are now marketed. In overdose, however, cardioselectivity is lost and all beta receptors are at risk for being blocked.

### Vasodilating Activity

Three beta antagonists (nebivolol, labetalol, and carvedilol) have vasodilating properties independent of their beta-blocking activity. Nebivolol is a β1 selective blocker that activates nitric oxide, a known vasodilator [10]. Labetalol and carvedilol promote vasodilation by blocking α1
receptors. The combination of peripheral vasodilation and decreased cardiac output from β2 blockade makes these agents more likely to cause significant hypotension in overdose. Orthostatic hypotension and dizziness are reported in more than 5% of patients taking labetalol therapeutically [11].

In the past, labetalol was touted as a drug of choice for the treatment of tachycardia and hypertension observed in cocaine (a β1-, β2-, α1-agonist) overdose. Nonselective β-blockers potentially exacerbate hypertension by blocking β2 receptors. Blocking β2 receptors without blocking α1 receptors allows for significant increases in vasoconstriction. The therapeutic-blocking property of labetalol was thought to ameliorate those “unopposed alpha” effects. However, its ability to adequately prevent α1-mediated vasoconstriction is questionable [12]. Labetalol is 3 times more effective at blocking beta receptors than alpha receptors after oral ingestion and 7 times more effective after parenteral injection [11]. Labetalol has not been shown to decrease coronary vasoconstriction in cocaine overdose [13].

**Intrinsic Sympathomimetic Activity**

Some β antagonists (acebutolol, carteolol, and pindolol) also have beta-agonist properties (or intrinsic sympathomimetic activity). These agents are able to both stimulate and competitively block adenylate cyclase [14]. As a result, they are capable of causing tachycardia and hypertension [15]. They are particularly useful in patients who are at risk for bradycardia, bronchospasm, or glucose intolerance [16]. Intrinsic sympathomimetic activity is believed to be mediated via stimulation of β4 receptors [7,17] or a subgroup of β1 receptors that have a low affinity for the beta-blocking agent pindolol [18].

Theoretically, medications with intrinsic sympathomimetic activity should be safer in overdose than pure beta antagonists. However, there are other factors that influence β-blocker toxicity, the most significant of which is membrane stabilizing activity (MSA) (see below). Deaths have been reported from acebutolol overdose—an agent that has significant membrane stabilizing effects in addition to its intrinsic sympathomimetic activity [19].

**Membrane Stabilizing Activity**

Membrane stabilizing activity appears to be the most important property of beta-adrenergic antagonists when determining potential for morbidity and mortality. Propranolol, labetalol, acebutolol, metoprolol, pindolol, betaxolol, and oxprenolol have membrane stabilizing effects. These agents block fast sodium channels. Rapid influx of sodium across the myocardial cell membrane is required for depolarization. Sodium channel blockade reduces conduction velocity, prolongs QRS duration, and decreases automaticity. Membrane stabilizing activity is of little consequence for patients in whom drug concentrations are therapeutic; however, it is particularly important in overdose (see cardiovascular effects and electrocardiographic [ECG] changes).

**Potassium Channel Blockade**

Although agents that prevent sodium from rapidly entering the cell prolong QRS duration (see MSA above), drugs that block potassium from leaving the cell cause QT-interval prolongation. Cardiac repolarization depends on potassium efflux via “delayed rectifier potassium current” channels [20]. Sotalol is a nonselective β-blocker that has no intrinsic sympathomimetic activity or MSA. However, it is unique in that it blocks delayed potassium rectifier currents [21,22]. Acebutolol has been shown to cause similar abnormalities, which also may be mediated by interference with potassium egress [19].

**Pharmacokinetics**

β-Blockers vary with respect to their bioavailability, body tissue distribution, metabolism, and route of elimination (Table 2). Oral bioavailability is the fraction of an ingested dose of drug that actually reaches the systemic circulation. It is dependent on the degree of absorption from the gastrointestinal tract and first-pass metabolism by the liver. β-Blocker oral bioavailability ranges from 20% for carvedilol to 100% for penbutolol. Medications with high bioavailability are more likely to reach the circulation and cause toxicity.

After absorption into the systemic circulation, β-blockers are distributed throughout the body depending on their degree of lipid solubility. Drugs that are highly lipophilic are more widely distributed throughout the body and consequently have a large volume of distribution. Lipophilic agents are able to cross the blood-brain barrier and are therefore more likely to cause central nervous system effects. The volume of distribution of β-blockers ranges from 0.5 L/kg for penbutolol to 40 L/kg for nebivolol.

Lipid solubility also affects drug metabolism and elimination. Highly lipophilic drugs require hepatic metabolism to produce more water-soluble metabolites that can be excreted by the kidney; metabolism and excretion of these drugs decrease in the event of hepatic dysfunction. Hydrophilic drugs are more confined to the intravascular space and are therefore more capable of reaching the glomerulus to allow renal excretion. A high degree of protein binding interferes with renal excretion and hinders the ability to hemodialyze an agent. The degree of lipid solubility and protein binding for the various β-blockers is listed in Table 2.

**β-Blockers in Overdose**

Although cardiovascular depression is the most commonly anticipated event after β-blocker overdose, other
physiologic and metabolic derangements may occur as well. β₁ blockade is responsible for cardiovascular effects and a variety of electrocardiogram (ECG) abnormalities. β₂ blockade can cause bronchospasm, peripheral vasoconstriction, hypoglycemia, central nervous system abnormalities, and hyperkalemia.

**Cardiovascular Effects and ECG Changes**

Cardiovascular abnormalities, primarily bradycardia and hypotension, are the most common adverse effects observed in β-blocker overdose. β-Blockers bind to adrenoreceptors in cardiac nodal tissue, myocytes, and the conducting system. Significant blockade of β₁ receptors in the sinoatrial node decreases automaticity causing sinus bradycardia, the most common ECG abnormality in β-blocker poisoning; this paired with decreased cardiac contractility results in hypotension.

Inhibition of the conducting system most commonly causes first-degree AV block. However, higher levels of toxicity can promote second- and third-degree AV block, junctional rhythms, and intraventricular conduction delays [23].

Medications that have membrane stabilizing effects block fast sodium channels and cause prolongation of the QRS interval. Excessive slowing of conduction velocity is proarrhythmic and predisposes patients to reentrant arrhythmias [20]. Acebutolol and propranolol have the highest MSA and have been shown to cause QRS prolongation and ventricular tachycardia [24,25]. These agents account for most of the morbidity and mortality seen in β-blocker overdose.

Three β-blockers are known to prolong QTc intervals: sotalol, propranolol, and acebutolol. Sotalol blocks potassium channels, thereby prolonging action potential and repolarization duration. The resultant prolongation of the QTc interval predisposes the patient to ventricular tachyarrhythmias and torsades de pointes [26,27]. These abnormalities have been described after both sotalol overdose and therapeutic administration [27-30]. Sotalol does not affect sodium channels and has no membrane stabilizing effects; QRS duration is not affected. Propranolol overdose has caused QTc prolongation and torsades on rare occasion [23,31].

Acebutolol in overdose prolongs the QTc interval, although the mechanism is not clearly understood [19,32]. The membrane stabilizing effects of acebutolol widen the QRS interval, which contributes to the excess QTc duration. However, because QTc prolongation is rarely seen with β-blockers other than sotalol, it is proposed that acebutolol, similar to sotalol, may block outward potassium rectifier channels [19].

History of a cardioactive co-ingestant (especially calcium channel blockers, tricyclic antidepressants, and neuroleptics) appears to be the single most important factor associated with morbidity [33]. In the absence of a co-ingestant, the presence of membrane stabilizing effects pose the most important significant influence on morbidity [33].

**Central Nervous System Effects**

The ability of β-blockers to affect the central nervous system (CNS) is dependent primarily on the agents’ lipophilicity. Lipid-soluble agents are able to cross the blood-brain barrier and penetrate into the CNS. Central nervous system effects include respiratory depression, seizure activity, and sleep and mood disturbances.

Respiratory depression has been described in overdoses of propranolol and atenolol [34,35]. Whereas respiratory

---

### Table 2 Pharmacokinetics of various β-blockers.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lipid solubility</th>
<th>Oral bioavailability (%)</th>
<th>Protein binding (%)</th>
<th>Volume of distribution (L/kg)</th>
<th>Route of elimination</th>
<th>Half life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>Low</td>
<td>35-50</td>
<td>25</td>
<td>1.2</td>
<td>Hepatic/renal</td>
<td>3-4</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Low</td>
<td>50-60</td>
<td>5-10</td>
<td>5-22</td>
<td>Hepatic/renal</td>
<td>14-22</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>Low</td>
<td>90</td>
<td>50</td>
<td>3</td>
<td>Hepatic/renal</td>
<td>9-12</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>Low</td>
<td>80</td>
<td>30-50</td>
<td>4</td>
<td>Renal</td>
<td>6</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>High</td>
<td>20-35</td>
<td>98</td>
<td>1-2</td>
<td>Hepatic</td>
<td>6-8</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Low</td>
<td>NA</td>
<td>55</td>
<td>2-3</td>
<td>Red blood cell</td>
<td>9 min</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Moderate</td>
<td>25-40</td>
<td>50</td>
<td>9</td>
<td>Hepatic</td>
<td>6-8</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Moderate</td>
<td>40-50</td>
<td>10</td>
<td>4</td>
<td>Hepatic</td>
<td>3-4</td>
</tr>
<tr>
<td>Nadolol</td>
<td>Low</td>
<td>30-50</td>
<td>25-30</td>
<td>2</td>
<td>Renal</td>
<td>20-24</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>High</td>
<td>12-96</td>
<td>98</td>
<td>10-40</td>
<td>Hepatic</td>
<td>10-32</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>High</td>
<td>20-70</td>
<td>80</td>
<td>1.3</td>
<td>Hepatic</td>
<td>1-2</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>High</td>
<td>100</td>
<td>80-98</td>
<td>0.5-2</td>
<td>Hepatic/renal</td>
<td>5</td>
</tr>
<tr>
<td>Pindolol</td>
<td>Moderate</td>
<td>95</td>
<td>50</td>
<td>2</td>
<td>Hepatic/renal</td>
<td>3-12</td>
</tr>
<tr>
<td>Propranolol</td>
<td>High</td>
<td>30</td>
<td>90</td>
<td>4</td>
<td>Hepatic</td>
<td>3-5</td>
</tr>
<tr>
<td>Sotolol</td>
<td>Low</td>
<td>80-100</td>
<td>0</td>
<td>2</td>
<td>Renal</td>
<td>5-15</td>
</tr>
<tr>
<td>Timolol</td>
<td>Moderate</td>
<td>75-90</td>
<td>10</td>
<td>2</td>
<td>Hepatic/renal</td>
<td>4</td>
</tr>
</tbody>
</table>

NA, not applicable.
depression from propranolol may not be surprising given its high lipid solubility, atenolol is more water soluble. It is proposed that in extreme overdose, atenolol may be able to cause toxicity similar to more lipophilic agents [36]. Respiratory depression from β-blocker overdose may occur in the absence of coma or cardiovascular collapse [35,37]. Infusion of propranolol into the cerebral ventricles induced respiratory arrest in rats, thereby suggesting that β-blocker-induced respiratory compromise may be centrally mediated [37].

Propranolol is known for its ability to cause seizures in overdose [34]. Interestingly, propranolol has both anticonvulsant and convulsant properties. Propranolol’s sodium channel blocking actions have anticonvulsant effects [38,39], whereas convulsant activity seems to be mediated by beta receptors [40]. The risk of seizures from propranolol toxicity appears to increase in patients with QRS intervals of more than 100 milliseconds [34]. Reith et al [34] noted that no seizure activity was observed in adult patients who ingested less than 1.2 g of propranolol and that ingestion of more than 2 g was associated with a higher likelihood of developing seizures. Seizure activity has been observed after metoprolol, sotalol, and oxprenolol overdose, and therapeutic administration of esmolol [34,41,42].

Sleep and mood disturbances have been described in β-blocker ingestions. Lipophilic agents such as metoprolol, propranolol, and pindolol significantly impair sleep continuity when compared to the hydrophilic β-blockers atenolol or sotalol [15]. Similarly, lipophilic beta antagonists are more likely to cause mood depression than hydrophilic drugs [15]. The exact mechanism by which CNS effects are carried out is incompletely understood; however, Maebara et al [43] reported excessive binding of central β2 receptors as a cause for nightmares and panic disorder after an inadvertent overdose of carvedilol, a nonselective β-blocker with lipophilic properties.

**Bronchospasm and Vasospasm**

Bronchospasm, secondary to β2 blockade, rarely occurs in β-blocker overdose. However, it has been described, although usually in patients with preexisting lung disease [44,46]. Historically, one avoided routine beta-antagonist use in patients with pulmonary disease because of the potential risk of bronchospasm. However, a recent Cochrane review determined that therapeutic administration of cardioselective β-blockers to patients with mild to moderate reversible airway disease does not cause clinically significant changes in respiratory status [47]. Similar results have been found in patients with chronic obstructive pulmonary disease [9].

There are reports of mesenteric ischemia in beta-antagonist overdose, possibly due to mesenteric hypoperfusion from unopposed alpha effects or from cardiovascular compromise [48]. Unopposed alpha effects may also cause peripheral cyanosis [49].

**Hyperkalemia**

Another function of β2 receptors is to mediate potassium uptake into skeletal muscle, hepatocytes, and adipose tissue [50]. β2 agonists stimulate Na+/K+ adenosine triphosphatase that promotes potassium uptake into skeletal muscle, the largest pool of potassium in the body. An increase in insulin secretion promoted by betaadrenergic agents may further augment cellular potassium uptake. β2-receptor blockade interferes with these processes and predisposes susceptible patients to hyperkalemia. In fact, labetalol has caused severe hyperkalemia in patients with renal failure [51].

**Hypoglycemia and Intracerebral Glucose Transport**

Most β-blockers impair glycogenolysis and gluconeogenesis; however, hypoglycemia rarely occurs, except in those who are at risk for hypoglycemia: children and those with diabetes [52,53]. Hypoglycemia may be the most commonly reported adverse effect of β-blocker overdose in children; however, it most often occurs after prolonged periods of decreased oral intake [54,55]. Patients may have difficulty recognizing the symptoms of hypoglycemia because β1 receptor blockade masks the sympathetic clues that herald low blood sugar. Carvedilol has insulin sensitizing properties that, in addition to its vasodilating properties, make it an attractive choice for individuals with diabetes [52].

Cerebral glucose concentrations may be affected by β-blockers as well. Glucose administration reversed CNS depression in a euglycemic 2-year-old patient, 24 hours post propranolol ingestion [34]. The authors postulate that propranolol may impair intracerebral glucose transport and ketone use by blocking β2 and β1 receptors.

**Management**

The initial management of β-blocker overdose begins with attention to airway, breathing, and circulation. If intubation is required, one should consider pretreatment with atropine to ameliorate potential vagal-induced bradycardia. Continuous ECG monitoring is essential. Obtain a 12-lead ECG to evaluate possible rhythm disturbances and cardiac conduction interval length. Administer normal saline boluses as needed to ensure full cardiovascular capacity. A chest radiograph may be useful to look for evidence of pulmonary edema or cardiomegaly that may develop with fluid resuscitation and heart failure. If available, use echocardiography or cardiac ultrasound to evaluate cardiac performance. Invasive blood pressure monitoring, in tandem with visualization of cardiac function, may provide clues that help tailor management toward improvement of heart rate, myocardial contractility, vascular tone, or a combination of all 3 (Table 3). Pertinent laboratory studies
## Table 3: Management strategies based on cardiovascular status.

<table>
<thead>
<tr>
<th>SVR/HR</th>
<th>SVR/Normal</th>
<th>SVR</th>
<th>HR</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide QRS</td>
<td>Wide QTS</td>
<td></td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Dobutamine</td>
<td></td>
<td>Carvedilol</td>
<td>Carvedilol</td>
</tr>
<tr>
<td>of Dopamine</td>
<td></td>
<td></td>
<td>Labetalol</td>
<td>Labetalol</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Esmolol</td>
<td></td>
<td>Carvedilol</td>
<td>Carteolol</td>
</tr>
<tr>
<td>Sodium</td>
<td>Magnesium</td>
<td></td>
<td>Carvedilol</td>
<td>Betaxolol</td>
</tr>
<tr>
<td>bicarbonate</td>
<td>Lidocaine</td>
<td></td>
<td>Acebutolol</td>
<td>Acebutolol</td>
</tr>
<tr>
<td>Override</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR = heart rate, SVR = systematic vascular resistance, PDE = Phosphodiesterase.
include blood glucose and serum electrolytes looking for potential hypoglycemia, hyperkalemia, acidosis, or evidence of renal failure. Blood levels of β-blockers are not available from hospital service laboratories. β-Blocker concentrations may confirm ingestion, but they do not correlate with degree of toxicity. Sotalol levels may correlate with QTc length in therapeutic doses [56].

Decontamination and Prevention of Absorption

There are insufficient data to determine if gastric decontamination affects patient outcome; therefore, attention to other life-saving measures takes precedence [57]. It is reasonable to consider gastric lavage in the case of severe overdose of a particularly toxic agent if the patient presents within 1 hour of ingestion [57]. Decontamination efforts may increase vagal tone potentiating bradycardia; therefore, pretreatment with standard-dose atropine is prudent [58]. Avoid gastric lavage if the patient is already bradycardic. Administration of syrup of ipecac is contraindicated [59,60]. Activated charcoal is suggested for patients presenting within 1 hour of significant ingestion [61]. The admission of multidose activated charcoal (charcoal administered every 4-6 hours) moderately increased the elimination of sotalol presumably by interrupting enterohepatic circulation [62]. However, the ability of multidose activated charcoal to change outcome is unknown. Whole bowel irrigation should be considered for significant ingestion of sustained-release products in symptomatic patients, although data to strongly support or refute this practice are lacking [63]. Whole bowel irrigation with polyethylene glycol is usually administered by nasogastric tube at a rate of 500 mL/h for children and 1 to 2 L/h for adults and continued until the rectal effluent is clear.

Elimination Enhancement

Hemodialysis may be effective for water-soluble agents with protein binding less than 25% and a volume of distribution less than 2 L/kg (Table 2) [64]. Hemodialysis has been shown to enhance clearance of atenolol and acebutolol [65-67]. Unfortunately, it is difficult to perform hemodialysis in hemodynamically compromised patients; therefore, its efficacy in overdose may be limited.

Atropine

Atropine blocks acetylcholine stimulation of muscarinic receptors. It is effective in managing bradycardia resulting from increased vagal tone. Muscarinic receptors are not affected in β-blocker overdose; therefore, it is not surprising that atropine has little significant effect on reversing the bradycardia observed after beta-antagonist poisoning.

Calcium

Beta-blocking agents interfere with calcium influx into the myocyte; therefore, it is reasonable that calcium administra-

Calcium appears to improve inotropy, with little effect on heart rate or conduction disturbances, in rat and canine models [68-70]. A return of pulses was temporally related to calcium administration during electromechanical dissociation in a patient who ingested atenolol, fluoxetine, and hydrochlorothiazide [71]. For patients in whom depressed inotropy is suspected, consider bolus administration of 10% calcium gluconate 0.6 mL/kg or 10% calcium chloride 0.2 mL/kg intravenously over 5 to 10 minutes; more rapid administration may aggravate hypotension. The duration of calcium effects may be temporary; therefore, a continuous infusion of 10% calcium gluconate (1.5 mL/kg/h) or 10% calcium chloride (0.2-0.5 mL/kg/h) should be considered after calcium boluses.

Glucagon

Glucagon promotes chronotropic, dromotropic, and inotropic activities by stimulating the sinoatrial node to increase heart rate, the atrioventricular node to improve cardiac conduction, and the myocardium to increase contractility. It exerts these effects by acting on receptors that are independent from beta receptors; therefore, unlike adrenergic agonists, glucagon activity is not dependent on successful competition for beta receptors [72,73]. Glucagon binding to its receptors activates adenyl cyclase. The events that follow are similar to the ones described previously (see pathophysiology above). Glucagon also augments myocardial glucose uptake, thereby assisting the myocardial metabolic requirements (see insulin below) [74].

To date, all controlled, prospective studies describing the use of glucagon for the treatment of β-blocker poisoning have used an animal model. Most have examined the effects of glucagon on propranolol toxicity in canines. In this model, glucagon improves heart rate, stroke volume, and cardiac output; however, it is less effective at restoring blood pressure [22,75,76]. One study that reviewed the effects of glucagon in both dogs and humans (not poisoned) observed that chronotropic and inotropic improvement was twice as great in dogs as in humans [77].

Studies on survival are mixed. Glucagon was credited for the survival of 4 of 6 dogs poisoned with propranolol; however, survival was statistically better after treatment with insulin (6/6 animals) [74]. The combination of dopamine and glucagon resulted in decreased survival in propranolol-poisoned rabbits and rats, despite a temporary improvement in heart rate and mean arterial blood pressure [78].

Human studies include multiple case reports describing the use of glucagon for the treatment of β-blocker–induced cardiovascular instability; however, rarely is glucagon the only mode of therapy, and commonly non-β-blocker agents are co-ingested. It is neither practical nor ethical to overdose healthy volunteers on β-blockers or any potentially lethal agent; therefore, we only have the
observations of these case reports and series to derive conclusions. There are many reports that credit glucagon for improved hemodynamic function; there are also studies that purport little or no effect [64].

A human study involving nonpoisoned patients undergoing cardiac catheterization observed increases in heart rate, cardiac contractility, and mean arterial blood pressure after glucagon administration [79]. Effects on systemic vascular resistance (SVR) were variable and dependent on the dose of glucagon administered; patients receiving a dose of 1 mg of glucagon experienced a decrease in SVR, whereas doses of 3 to 5 mg (equivalent to 50 μg/kg in this study) caused no significant change [79]. By comparison, another study showed a moderate decrease in SVR in response to a glucagon dose of 50 μg/kg [77].

Glucagon may be able to improve contractility better than chronotropy in the presence of beta-receptor blockade in humans (in contrast to animal studies noted above) [79]. Glucagon has been shown to improve arterial blood pressure without affecting heart rate in a patient on timolol (an ocular beta antagonist) affected by an anaphylactic reaction to radiocontrast dye [80]. One should follow serum calcium concentrations as glucagon’s ability to increase heart rate appears to be dependent on normal physiologic calcium levels: both hyper- and hypocalcemia blunt glucagon’s chronotropic actions [81].

By increasing heart rate or contractility, glucagon also increases myocardial energy requirements (as evidenced by a significant increase in oxygen consumption) [77]. Glucagon appears to promote enough coronary artery vasodilation to allow sufficient blood flow to meet those requirements [77].

The dose of glucagon is 50 to 150 μg/kg (5-10 mg in adults) intravenously over 1 to 2 minutes. Boluses may be repeated every 3 to 5 minutes. Response is usually within 1 to 3 minutes; peak effects occur in 5 to 7 minutes [77,79]. Glucagon has a short elimination half-life (6.6 minutes); therefore, if bolus administration has provided an effect, one can begin a continuous infusion of 0.1 mg/kg/h (2-10 mg/h in adults) and titrate to effect. Alternatively, calculations for a continuous infusion can be extrapolated from the dose of glucagon needed during bolus administration and how frequently repeat doses were required. Glucagon has a short duration of action (10-15 minutes), and therapeutic effects may be transient even during continuous infusion (see insulin/euglycemia below) [74]. It appears that over time, glucagon loses its ability to increase cAMP levels [82]. This results in “inotropic desensitization,” an impaired ability to stimulate cardiac contractility over time. It has been postulated that repeat boluses of glucagon, which allow recovery from inotropic desensitization, may be an alternative method of administration; however, there is currently insufficient data to support this hypothesis [83].

Glucagon administration is associated with a transient 50% to 70% rise in serum glucose and a slight (0.1-0.5 mEq/L) decrease in serum potassium [74,77,79]. Vomiting is commonly reported after glucagon infusion; therefore, it may be wise to pretreat with an antiemetic. Ondansetron is a reasonable agent to use because it is not known to lower the seizure threshold. Fatal ventricular tachycardia has been reported after glucagon therapy for propranolol toxicity in dogs [74,76].

Historically, glucagon preparations were packaged with a phenol-containing diluent for reconstitution, posing a risk of phenol toxicity when given in large doses. However, in 1998, the formulation was changed to contain a phenol-free diluent [84]. Additionally, the former glucagon preparations were derived from bovine or porcine pancreatic extracts. Because the pancreas stores both glucagon and insulin, previous “glucagon” homogenates also contained insulin. As a result, it is difficult to determine how much of the effects of the studies before 1998 was due to glucagon vs the effects of insulin.

**Insulin Euglycemia**

Insulin has a number of properties that make it an attractive antidote for β-blocker toxicity. It affects myocardial function, catecholamine release, the inflammatory cascade, and apoptosis, all of which are important determinants in reducing morbidity and mortality after β-blocker overdose. The simple use of insulin to prevent hyperglycemia may be important as well.

Propranolol blocks myocardial free fatty acid uptake [85,86]. As a result, the heart becomes dependent on glucose and lactate as energy substrates. Insulin augments myocardial glucose uptake, and in doing so assists the heart with its metabolic demands [74].

Insulin promotes norepinephrine release, which stimulates alpha receptors causing an increase in mean arterial blood pressure [87]. This effect on vascular tone is only observed if normal blood glucose concentrations are maintained [87]. Finally, insulin has direct anti-inflammatory activity (decreases cytokine production) and apoptotic effects that protect the myocardium [88].

In a study by Kerns et al [74], a combination of high-dose insulin and glucose increased coronary blood flow, reversed myocardial failure, and improved survival in β-blocker poisoning in dogs. This study observed no effect on heart rate. However, insulin/dextrose infusion gradually restored contractility to baseline by 120 minutes of infusion. This was in contrast to glucagon (bolus followed by continuous infusion), which improved contractility within 30 minutes of infusion; however, by 120 minutes, contractility decreased significantly lower than controls. Similar effects were observed with epinephrine infusion: transient improvement within 90 minutes but decline below controls at 120 minutes. Survival with insulin infusion was superior to that from either glucagon or epinephrine.

Administration of insulin should begin with a 1 U/kg bolus dose of regular insulin followed by a continuous
intravenous infusion of 0.5 U/kg/h. The infusion can be titrated upward every 30 minutes as needed to improve contractility or blood pressure. Doses as high as 10 U/kg/h have been beneficial in pigs [89]. One must provide contractility or blood pressure. Doses as high as 10 U/kg/h titrated upward every 30 minutes as needed to improve intravenous infusion of 0.5 U/kg/h. The infusion can be 12 A.C. Anderson mild hypokalemia may be beneficial in \( \beta \) to intracellular shift in potassium rather than actual \( \beta \) patients receiving insulin and glucose therapy for the effects of insulin may persist for hours. Unfortunately, there are limited data investigating dobutamine use in \( \beta \)-blocker overdose [94].

Norepinephrine and phenylephrine have significant \( \alpha \) agonist effects, which provide vasoconstriction. Consequently, it is reasonable to administer either of these agents to hypotensive patients intoxicated with beta antagonists that have vasodilating properties such as labetolol, carvedilol, or nebivolol.

The obvious disadvantage of catecholamines is that they depend on successful competition with \( \beta \)-blockers for beta receptors. As a result, herculean doses of agents are often required to affect a result. Catecholamine infusions should be initiated using recommended dose ranges; however, rapid increases to doses as a high as 10 to 30 \( \mu \)g/min for epinephrine, 1660 \( \mu \)g/min for isoproterenol, 4800 \( \mu \)g/min for dopamine, and 500 \( \mu \)g/min for dobutamine have been required [95-97].

**Phosphodiesterase Inhibitors**

Phosphodiesterase (PDE) inhibitors increase myocardial contractility by blocking the breakdown of cAMP. These agents also decrease systemic vascular resistance. Like glucagon, PDE inhibitor effects are independent of beta-receptor stimulation. Milrinone, inamrinone (formerly amrinone), and theophylline are PDE inhibitors that have shown promise in the treatment of \( \beta \)-blocker overdose. These agents have increased stroke volume and cardiac output in canine \( \beta \)-blocker toxicity [75,76,98]. Effects on heart rate have been mixed [75,76,98]. By comparison, milrinone was superior to glucagon, inamrinone was as effective as glucagon, and aminophylline was faster than amrinone in improving the aforementioned parameters [75,76,98].

Use of PDE inhibitors may be limited by peripheral vasodilation. In addition, these agents have relatively long half-lives (1.5-10 hours for aminophylline, 2-4 hours for inamrinone, and 2 hours for milrinone) making them difficult to titrate or discontinue in the event of adverse reaction. Consequently, PDE inhibitors are considered second- or third-line therapy for \( \beta \)-blocker overdose.

**Sodium Bicarbonate**

Sodium bicarbonate has successfully reversed QRS prolongation after overdoses of agents that have MSA and block fast sodium channels. Sodium bicarbonate reversed ventricular tachycardia in a human overdose of acebutolol,
and instituted QRS interval narrowing and restoration of cardiac output after propranolol overdose [24,25].

**Therapies for Tachycardias and Hypertension**

Therapies for patients who develop torsades de pointes include magnesium, lidocaine, and transvenous overdrive pacing. [27,28,99] Nonmalignant tachycardias and hypertension may require observation with no pharmacologic treatment. However, if there is evidence of end-organ failure, one should consider using short-acting drugs that can be more easily discontinued in case of an adverse reaction; these might include agents such as esmolol for tachycardia or nitroprusside for hypertension.

**Nonpharmacologic Therapies**

Intra-aortic balloon pumps, cardiac pacing, and extracorporeal circulatory support (cardiac bypass and extracorporeal membranous oxygenation) have all been used for the treatment of β-blocker overdose refractory to pharmacologic treatments with varying degrees of success [100-102]. Although these methods are last resorts in most instances, it is important to think of them early because they may take time and special teams to institute.

**Therapies Specific to Other Clinical Findings**

Bronchospasm may respond to albuterol nebulizer therapy, epinephrine administration, or aminophylline infusion [46,75]. Intravenous glucose administration may improve depressed mental status even in the presence of euglycemia [34]. Seizure activity may be treated with diazepam or lorazepam.

**Disposition**

Factors that must be considered in determining patient disposition include the following: type of agent(s) ingested, preexisting conditions, intent, and time of ingestion. Co-ingestion of other cardioactive drugs, particularly cyclic antidepressants, calcium channel blockers, or neuroleptics, is the single most important factor associated with increased morbidity [33]. In the absence of a cardioactive co-ingestant, is the single most important factor associated with increased morbidity. In the absence of a cardioactive co-ingestant, is the single most important factor associated with increased morbidity.

The emergency physician is frequently faced with the dilemma of 2 challenging questions: how much is too much, and how long should I monitor the asymptomatic patient? To date, there have been no reports of toxicity in patients who ingested doses less than the maximum recommended single therapeutic dose (Table 4) [61]; therefore, it is reasonable to monitor all patients who ingest more than that amount. It is important to remember that the history regarding the dose and type of medication ingested may be incorrect; hence, it is practical to err on the side of safety if either is questionable. There is growing evidence that ingestion of 1 or 2 beta-antagonist tablets is rarely problematic in children younger than 6 years [55]. However, it is important to keep in mind that ingestion of an agent with membrane stabilizing effects, a sustained-release product, or another cardioactive medication may significantly increase the risk of morbidity.

Most patients who develop beta-antagonist toxicity develop clinical evidence within 2 to 4 hours of ingestion [103]. In a study by Love et al [33], all patients who died from beta-antagonist overdose developed symptoms within 6 hours of ingestion. Sotalol has been associated with delayed toxicity: the greatest risk of ventricular tachyarhythmias has occurred as late as 20 hours post ingestion [26]. Onset of toxicity beyond 6 hours of ingestion may occur if sustained-release tablets have been ingested.

A reasonable approach to the disposition of asymptomatic patients, described in an evidence-based review by Wax et al [61], offers the following principles: (1) observe all patients who ingest more than the maximum recommended single therapeutic dose; (2) monitor all who ingested an immediate-release preparation for at least 6 hours after ingestion; (3) monitor those who ingested sustained-release agents for 8 hours or more; (4) patients who ingested sotalol should be observed for at least 12 hours. Admit all patients who present with or develop any signs or symptoms of toxicity.

**Table 4** Threshold dose for recommended observation in Emergency Department.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>&gt;600 mg</td>
<td>&gt;12 mg/kg</td>
</tr>
<tr>
<td>Atenolol</td>
<td>&gt;200 mg</td>
<td>&gt;2 mg/kg</td>
</tr>
<tr>
<td>Carvedolol</td>
<td>&gt;50 mg</td>
<td>&gt;0.5 mg/kg</td>
</tr>
<tr>
<td>Labetolol</td>
<td>&gt;400 mg</td>
<td>&gt;20 mg/kg</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>&gt;450 mg</td>
<td>&gt;2.5 mg/kg (IR)</td>
</tr>
<tr>
<td></td>
<td>&gt;400 mg</td>
<td>&gt;5 mg/kg (SR)</td>
</tr>
<tr>
<td>Nadolol</td>
<td>&gt;320 mg</td>
<td>&gt;2.5 mg/kg</td>
</tr>
<tr>
<td>Propranolol</td>
<td>&gt;240 mg</td>
<td>&gt;4 mg/kg (IR)</td>
</tr>
<tr>
<td></td>
<td>&gt;320 mg</td>
<td>&gt;5 mg/kg (SR)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>&gt;160 mg</td>
<td>&gt;4 mg/kg</td>
</tr>
<tr>
<td>Timolol</td>
<td>&gt;30 mg tabs</td>
<td>No safe dose</td>
</tr>
</tbody>
</table>

IR-immediate release.
SR-sustained release.
Adapted from Wax, PM et al [61] with permission.

Assumes unintentional ingestion in an asymptomatic patient with no underlying significant medical condition or cardioactive co-ingestant.
Summary

β-Blocker ingestions can cause significant morbidity and mortality when taken in overdose, especially if another cardioactive agent has also been ingested. Agents with membrane stabilizing effects are particularly dangerous. Severe cases potentially benefit from the use of cardiac ultrasound and invasive pressure monitoring to guide management.

References