Emergency Department Treatment Of Beta Blocker And Calcium-Channel Blocker Poisoning

Abstract

The treatment of a patient who has sustained an overdose of a beta blocker and/or calcium channel-blocking agent can be challenging and time-sensitive, with few proven treatment options beyond supportive care. Such cases present relatively infrequently in the spectrum of emergency medicine and critical care practice. This issue reviews the pharmacology of beta blocker and calcium-channel blocker agents as well as the pathophysiology and clinical course of their associated toxicity. Historically accepted treatment modalities, such as administration of calcium or glucagon, are reviewed. Some newer options, such as high-dose euglycemic insulin therapy and lipid rescue therapy, have shown promising results, but in order to apply these treatments effectively and in a timely fashion, emergency physicians must have a support system prepared to treat these critically ill patients. This system should include ready availability of the agents, defined treatment protocols, and pharmacy and nursing staff familiar with these therapies in advance of patient presentation.
Case Presentation

During a busy evening shift in the ED, EMS providers present you with a 21-year-old patient who reportedly ingested her father-in-law’s “blood pressure pills.” No further identification of the medication is forthcoming, the pill bottles were not found at the scene, and the in-laws are on vacation out of the country. Bystanders report that the ingestion occurred approximately 50 minutes before the patient’s arrival in the ED. On arrival, the patient’s heart rate is 60 beats/min, blood pressure is 105/65 mm Hg, respiration and temperature are normal, and she is alert. The critical care units at your hospital are overloaded, and you are asked to board the patient in your ED for several hours until a bed becomes available. You provide supportive care, but over the next 90 minutes, her clinical condition progressively deteriorates despite attempted interventions. Her heart rate and blood pressure become unresponsive to fluids, calcium, high doses of glucagon, atropine, and vasopressors. Her mental status also deteriorates, and she is endotracheally intubated and placed on mechanical ventilation. Attempts at transcutaneous pacing yield intermittent capture without significant improvement in heart rate or blood pressure. Evidence of tissue hypoperfusion is present, based on your observation of end-organ failure. It seems that her refractory hypotension and bradycardia may be leading to an impending arrest. What salvage options remain? Was there anything that could have been done to avoid this condition?

Introduction

Identification and treatment of patients with significant beta blocker and/or calcium-channel blocker toxicity can be challenging. Optimal management of these patients in the emergency department (ED) can have a meaningful impact on their hospital course. Timely, focused treatment of these patients in the ED sets the stage for successful ongoing management of these challenging critical care cases.

The numbers and potential mortality represented by beta blockers and calcium-channel blockers in the United States are substantial. In 2012, the annual report of the American Association of Poison Control Centers (AAPCC) documented 10,691 cases of reported single-agent exposures to beta blockers and 5076 single-agent exposures to calcium-channel blockers; the sum of these cases more than doubles when considering the number of exposures to these medications in combination with other substances. Of the single-agent exposures to beta blockers reported, outcome data are recorded for 5567 cases, and, of those, 70 experienced a “major” effect and 13 died. The AAPCC defines a major effect of toxin exposure as one in which “the patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement.” For calcium-channel blockers, outcome data have been reported for 2793 exposures; 68 experienced a major effect and 24 died. These data represent collected voluntary reports to regional poison centers, and inherently represent an underestimation of the total number of cases and deaths. Despite the efforts of many poison centers to collect data from medical examiners, it is also likely that poisonings discovered postmortem are underreported in AAPCC data.

When clinicians report cases to regional poison centers, the centers assist in data collection and gain access to the most current patient management guidelines, including real-time toxicology consultation. It is important to note that toxicologists and pathologists are not always in agreement on the cause of death, and the documented cause of death is not always specific to the agent ingested. According to the National Poison Data System (NPDS) 2012 report, cardiovascular drugs accounted for the seventh most frequently found category of substance involved in human exposures, as well as the substance with the third highest rate of exposure increase (closely following analgesics and sedatives/ hypnotics/antipsychotics). Cardiovascular drugs were the fourth most common category of substances involved in adult exposures, and miscellaneous cardiovascular drugs were the category with the second highest number of fatalities.

Critical Appraisal Of The Literature

A literature search was performed using Ovid MEDLINE® and PubMed. Search terms included calcium-channel blocker poisoning, beta blocker poisoning, molecular adsorbent recirculating system, and toxicity. The Poisindex guidelines and references were reviewed. The website www.lipidrescue.org was also reviewed. A search of the National Guideline Clearinghouse (www.guideline.gov) revealed no published guidelines addressing the treatment of beta blocker or calcium-channel blocker overdose.

Human studies in toxicology are often limited by variables that are difficult to control, and a randomized double-blind placebo-controlled study of lethal doses of medications is unethical. Therefore, searches of the literature on human poisoning with beta blockers and calcium-channel blockers yield a preponderance of case reports and animal studies.

Pharmacology Of Beta Blockers And Calcium-Channel Blockers

It is important to be familiar with characteristics of the different classes of beta blockers and calcium-channel blockers in order to anticipate the clinical course that may await the poisoned patient.
**Beta-Adrenergic Blockers**

Beta-adrenergic blockers act by competitive antagonism of catecholamines at beta-adrenergic receptors. Beta blockers vary in their beta, and beta, antagonism, lipid solubility, and other properties. (See Table 1.) In overdose, selectivity is diminished or even lost. The mechanism of action appears not to be restricted to beta-adrenergic receptor-blocking properties. Propranolol, for example, exhibits significant membrane stabilizing activity and is lipid soluble. Propranolol overdose is often lethal; poisoning with this agent may be characterized by seizures, coma, bradycardia, hypotension, abnormal atrioventricular conduction, QRS widening, or ventricular tachydysrhythmias. The central nervous system effects stem, in part, from this lipid-soluble drug’s ability to cross the blood–brain barrier.

The individual properties of beta blockers may influence their effects in overdose. Beta blockers may be classified into 2 groups, according to their solubility and route of elimination: (1) lipid-soluble agents and (2) water-soluble agents. Lipid-soluble agents (such as propranolol and metoprolol) are cleared via the liver, have significant central nervous system distribution, and are well absorbed by the gut. They readily enter the central nervous system and have variable bioavailability and relatively short plasma half-lives. Conversely, water-soluble agents (such as atenolol) are less completely absorbed through the gut, not as well distributed to the central nervous system, have relatively longer plasma half-lives, and are eliminated via the kidneys, unchanged.

Other beta blockers of note have special properties. Some have intrinsic sympathomimetic properties (such as acebutolol and pindolol) and may, therefore, have a less suppressive effect on heart rate. Labetalol has beta-blocker activity combined with substantially less alpha- (than beta) blocking activity. Esmolol is an ultra-short-acting beta blocker whose brief half-life is due to rapid clearance by hepatic and blood esterases. Beta blockers may also demonstrate Vaughan Williams class I sodium channel-blocking properties (similar to quinidine, disopyramide, and procainamide). Sotalol is unique, due to its class III effects (potassium-channel blockade), resulting in prolonged action potential and delayed repolarization of cardiac muscle cells.

The clinical course for a beta blocker overdose will typically involve bradycardia and hypotension. Other possible signs include hypothermia, hypoglycemia (due to inhibited glycogenolysis), and seizures. It may be difficult to determine an occult overdose, since bradycardia is a therapeutic effect of beta blockers. Onset of symptoms can be from 20 minutes to several hours, depending on the patient’s tolerance and cardiovascular reserve as well as the type of agent ingested. Sustained-release agents may take longer to produce clinical effects, but all significant beta blocker overdoses should be clinically apparent within 6 hours. Patients may develop seizures (occurring more commonly with propranolol), but they are usually brief. Finally, bronchospasm can occur with beta blocker overdose, and it is more likely in patients with preexisting bronchospastic disease.

**Calcium-Channel Blockers**

There are 3 classes of calcium-channel blockers available in the United States: (1) dihydropyridines (nifedipine, amlodipine, and nicardipine); (2) phenylalkylamines (verapamil); and (3) benzothiazepines (diltiazem). It is clinically useful, however, to think of calcium-channel blockers as either dihydropyridine agents or nondihydropyridine agents because of their different mechanisms of action and the resulting differences in clinical course following overdose.

Dihydropyridines are smooth-muscle selective agents that have relatively little myocardial depressant activity at therapeutic doses when compared with nondihydropyridines. Dihydropyridines may even increase cardiac output, due to resultant reflex

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Table 1. Pharmacologic Properties Of Selected Beta Blockers

<table>
<thead>
<tr>
<th>Agent</th>
<th>Beta, Selective?</th>
<th>Lipid Solubility</th>
<th>Route of Elimination</th>
<th>Intrinsic Sympathomimetic Activity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>Yes</td>
<td>Moderate</td>
<td>Renal/hepatic</td>
<td>Mild</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Yes</td>
<td>Low</td>
<td>Renal</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>No</td>
<td>Moderate</td>
<td>Hepatic</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Yes</td>
<td>Low</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Labetalol</td>
<td>No</td>
<td>High</td>
<td>Hepatic</td>
<td>Mild</td>
<td>Some alpha blockade</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Yes</td>
<td>High</td>
<td>Hepatic</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pindolol</td>
<td>No</td>
<td>Moderate</td>
<td>Renal/hepatic</td>
<td>High</td>
<td>NA</td>
</tr>
<tr>
<td>Propranolol</td>
<td>No</td>
<td>High</td>
<td>Hepatic</td>
<td>NA</td>
<td>Possible altered glucose metabolism</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable.
tachycardia (as in their role in blood pressure management). Dihydropyridines are efficient antihypertensive agents that act by inhibiting Ca2+ ion movement across cardiac and vascular cell membranes, resulting in dilation of main coronary and systemic arteries and decreased preload and afterload. In overdose, dihydropyridine selectivity may diminish and result in impaired myocardial conduction and myocardial depression. In contrast, nondihydropyridines block L-type calcium channels, causing impaired myocardial contractility and conduction (as in their applications in controlling tachycardia). See Table 2 for the differences between the classes of calcium-channel blockers and their sites of action.

Calcium-channel blockers currently in use bind to the pore-forming subunit of the L-type calcium channel where they prevent calcium influx into all types of muscle cells. Under normal conditions, they allow the calcium ions needed for excitation-contraction coupling to flow intracellularly down electrical and concentration gradients, causing muscular contraction. This ion flow is critical to cardiac muscle excitation. In smooth-muscle cells, this calcium flow indirectly activates myosin, which then binds actin, thereby causing contraction. In cardiac muscle cells, slow inward calcium flow creates the plateau phase of the cardiac action potential, which causes calcium-induced calcium release from the sarcoplasmic reticulum. The additional calcium released binds troponin C, causing a conformational change that removes troponin and tropomyosin from actin. This allows actin and myosin to couple, creating a contraction.

All calcium-channel blocker overdoses may result in hypotension, bradycardia, and death, in part because receptor selectivity may be lost in overdose. Pharmacology and experience indicate that the most severe cardiotoxic effects result from the strong negative inotropic and chronotropic effects of the nondihydropyridines. Verapamil overdoses, in particular, are challenging to manage and carry the potential for high lethality. Calcium-channel blockers are highly protein-bound and verapamil and diltiazem both have large volumes of distribution, making extracorporeal removal via standard hemodialysis or hemoperfusion ineffective.

Other pharmacologic actions of calcium-channel blockers may also contribute to their lethality. When calcium-channel blockers block L-type calcium channels on pancreatic islet cells, calcium entry into those cells is limited. The limited calcium entry can result in decreased insulin release by pancreatic islet cells, low insulin levels, resultant hyperglycemia, and poor glucose utilization by target tissues. Finally, at high doses, calcium-channel blockers may also block sodium channels, resulting in QRS prolongation similar to that induced by Vaughan Williams class Ia antiarrhythmics and cyclic antidepressants.

### Prehospital Care

The mainstays of prehospital care of the poisoned patient revolve around recognizing and confirming the toxidrome, initiating supportive care, and acquiring information and/or orders needed to optimize care from medical control or the regional poison center according to local protocols and practices. Prehospital care providers are often in a unique position to gather history at the scene and from bystanders, as patients are frequently unable or unwilling to relate a reliable ingestion history. A quick search of the scene for pill containers (bedroom, bathroom, kitchen, and trash containers, etc) often yields information regarding the identity of ingestants/co-ingestants, estimated quantity ingested, the presence or absence of emesis, and more. Questioning of fam-

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**Table 2. Pharmacologic Properties Of Classes Of Calcium-Channel Blockers**

<table>
<thead>
<tr>
<th>Agent (L-type Ca2+ Channel Binding Site)</th>
<th>Example Drugs</th>
<th>Peripheral and Coronary Vasodilation</th>
<th>Negative Inotropic Effect</th>
<th>SA Node Suppression</th>
<th>AV Node Suppression</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydropyridine (N site)</td>
<td>Amlodipine</td>
<td>++++</td>
<td>+</td>
<td>0</td>
<td></td>
<td>Potential reflex tachycardia due to arteriolar vasodilation</td>
</tr>
<tr>
<td></td>
<td>Bepridil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Felodipine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isradipine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nicardipine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nisoldipine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzothiazepine (D site)</td>
<td>Diltiazem</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>Possible advantages in chronic kidney disease and diabetic nephropathy</td>
</tr>
<tr>
<td>Phenylalkylamine (V site)</td>
<td>Verapamil</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AV, atrioventricular; SA, sinoatrial.

ily and friends, the identity of pharmacies and prescribing physicians, and the examination of medical records on scene by prehospital providers may assist physicians in the management of these patients. This information may help emergency physicians confirm or refute their working hypotheses, estimate the direction the clinical course may take, and identify and treat mixed toxidromes and ingestants that might otherwise have been missed.

Although prehospital providers may also be in a position to provide the earliest possible gastric decontamination with activated charcoal (where indicated and allowed), the decision to administer activated charcoal should not be taken lightly. Aspiration of charcoal can result in significant morbidity and mortality. If this intervention is considered, it should only be done in patients who will be able to protect their airway throughout transport and early ED management. This condition often applies only to patients with relatively small ingestions, while those with substantial overdoses are at greatest risk for aspiration. Therefore, consultation with an online medical command physician and, potentially, a toxicologist is advised before administration of activated charcoal in the field.

Treatment

Patient Selection

In cases of beta blocker and calcium-channel blocker poisoning, supportive care may include vital sign and cardiac monitoring, fluid resuscitation, endotracheal intubation, and, for calcium-channel blocker toxicity, calcium administration. It is highly recommended that physicians consult their regional poison control centers and an experienced medical toxicologist in all cases of beta blocker and calcium-channel blocker exposure. These resources have the extensive experience required to risk stratify patients and guide therapy and patient disposition. Poison centers in the United States may be reached by calling 1-800-222-1222, 24 hours a day, 7 days a week. Medical toxicologists are available for direct consultation upon request.

Supportive Care

Recognition of the potential for lethal myocardial depression should guide the selection of basic measures to stabilize and support the patient who is poisoned with a beta blocker or a calcium-channel blocker. Excessive fluid administration during resuscitation of patients poisoned with beta blockers and calcium-channel antagonists is not advised due to the myocardial depressant activity of these agents. Once the patient has adequate preload, additional (or aggressive) fluid resuscitation is more likely to result in overload of the failing heart and acute onset of pulmonary edema than in other forms of shock.

For similar reasons, special attention must be focused on the selection of adjunctive medications used in supportive care in order to avoid further (or inadvertent) myocardial depression that may worsen cardiac output. For example, it is important to avoid agents that may cause or worsen hypotension and bradycardia during rapid sequence intubation and subsequent sedation for the maintenance of ventilation. Agents with myocardial depressant effects (such as propofol, thiopental, or dexmedetomidine) should be avoided. Benzodiazepine administration may result in bradycardia and concomitant hypotension, especially in hypotension. Specifically, diazepam and midazolam have a direct myocardial depressant effect at the cellular level, which is mainly mediated by an inhibition of the sarcolemmal L-type Ca2+ channel. In contrast, agents preferred in cardiac anesthesia offer some advantages. Ketamine is an acceptable choice due to its sympathomimetic effect. Fentanyl may be an acceptable choice; however, in cases of multiple ingestions, it can worsen hypotension.

Neuromuscular blockade may be used to improve patient-ventilator synchrony and gas exchange, to lower the risk of barotrauma, to reduce muscle oxygen utilization, and to prevent inadvertent extubation. Succinylcholine, a depolarizing agent, has the potential to cause hyperkalemia, bradycardia, and other ventricular arrhythmias, and it is, perhaps, best avoided in the setting of beta blocker and calcium-channel blocker overdose. The short duration of action is also a limitation. The nondepolarizing agents may offer advantages in this context. For rapid sequence intubation, rocuronium (a short-acting agent) offers the advantage of having few cardiovascular effects. Similarly, vecuronium (an agent of intermediate duration of action) has few cardiovascular effects. For longer duration of paralysis, pancuronium offers the theoretical advantage of vagolysis, which, under ordinary circumstances, may induce tachycardia and hypertension and increase cardiac output. Loss of cardiac responsiveness due to poisoning may negate these potential benefits.

Common Treatment Options

Multiple modalities have been utilized to attempt to restore myocardial conduction and contractility after beta blocker and calcium-channel blocker overdoses. These include infusion of crystalloid solutions, calcium, atropine, sodium bicarbonate, adrenergic agents, glucagon, cardiac pacing, intra-aortic balloon counterpulsation, extracorporeal bypass, and, more recently, euglycemic insulin therapy, infusion of lipid emulsion, and extracorporeal albumin dialysis. The following sections will expand on the treatments typically used by emergency physicians.
**Glucagon Therapy**

Glucagon has been shown to reduce myocardial depression in beta blocker and calcium-channel blocker poisoning, and it should be used early in the course of poisoning.\(^{11-15}\) When glucagon binds to receptors in the liver, the synthesis of cyclic adenosine monophosphate (cAMP) is increased, thereby stimulating gluconeogenesis, glycogenolysis, and ketogenesis.\(^{16}\)

Agonism of cardiac glucagon receptors also increases cAMP concentrations and results in increased inotropy and chronotropy. The effects of a bolus dose of 50 mcg/kg of glucagon last about 15 minutes. Bolus doses often range from 2 mg to 10 mg, depending on the degree of hypotension and the resultant response to therapy. Boluses that do not yield the desired response must be “stacked” in rapid succession, due to the short duration of effect. The effect may be prolonged by the administration of a continuous infusion of glucagon.\(^{17,18}\)

Typical infusion rates for adults range from 2 to 5 or 10 mg/h. Of note, combining glucagon with the phosphodiesterase inhibitors amrinone and milrinone may result in decreased mean arterial pressure and increased tachycardia, respectively.\(^{19,20}\) It is important to recognize that both hypocalcemia and hypercalcemia lessen the chronotropic effect of glucagon administration; glucagon’s chronotropic effect seems to be optimal in the presence of normal ionized calcium concentrations.\(^{21}\)

Adequate dosing of glucagon is essential to provide the desired increase in mean arterial pressure. Rapid administration of glucagon may result in vomiting, yet slow administration of boluses may not be effective. Boluses and infusions may require some titration to effect. The recommended initial bolus dose is 50 mcg/kg administered over 1 to 2 minutes, but it may range as high as 5 to 10 mg in an adult if the initial bolus does not produce sufficient hemodynamic improvement. The bolus should be followed immediately by a continuous infusion of 2 mg to 10 mg/h, titrated to effect and weaned slowly, as hemodynamics permit.\(^{22,23}\) Infusions may be mixed in 5% dextrose in water after reconstitution of glucagon according to the manufacturer’s instructions. Antiemetic therapy may help to prevent or limit the nausea and vomiting that may result from glucagon use.

In the past, glucagon was supplied with a phenol-containing diluent. Due to the large doses of glucagon necessary for treating beta blocker and calcium-channel blocker poisoning, if the glucagon was reconstituted using the diluent, the cumulative amounts of phenol administered could result in phenol toxicity and exacerbate hypotension. Current United States supplies of glucagon no longer contain phenol.

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**Insulin Therapy**

Insulin works to reverse the effects of beta blocker/calcium-channel blocker overdose by 2 mechanisms. In the toxicity-induced shock state, cardiac cells preferentially use carbohydrate instead of free fatty acid for metabolism, which is compensated by hepatic glycogenolysis. Calcium-channel blockers also inhibit pancreatic insulin secretion via blockade of L-type calcium channels on islet cells. This causes insulin deficiency, hyperglycemia, and acidosis. High-dose insulin/euglycemic therapy enables cardiac cells to metabolize carbohydrates without increasing myocardial oxygen demand. It also allows cells to take in glucose from the bloodstream via activation of the glucose transporter family of receptors, improving both hyperglycemia and acidemia. It is theorized that insulin therapy is more effective than calcium, glucagon, or epinephrine because it does not induce free fatty acid use or increase myocardial work.\(^{24,25}\)

Insulin has also been shown to improve myocardial contractility and vasomotor tone and to increase the uptake of lactate, all of which aid in the resolution of shock in the beta blocker and calcium-channel blocker overdose patient.

**Euglycemic High-Dose Insulin Therapy**

Euglycemic high-dose insulin therapy has improved outcomes in severe cases of beta blocker or calcium-channel blocker poisoning, and, in the authors’ clinical experience, it often succeeds when other modalities (including glucagon) have failed to improve hemodynamic parameters.\(^{24}\) Consultation with a medical toxicologist may help to guide physicians who are not familiar with this therapy and its indications, and consultation is strongly encouraged. This therapy takes effect gradually, often requiring as long as an hour to improve the patient’s hemodynamic status, when dosing is optimized. Because of this slow onset, the need for euglycemic insulin therapy must be anticipated and the infusion should be instituted when it first becomes apparent that the patient will suffer refractory hypotension due to lack of response to standard therapy (including glucagon).

High-dose insulin therapy will require frequent glucose monitoring (as often as every 15 minutes or more frequently) and glucose supplementation until the patient’s serum glucose is stabilized on a given insulin dose. Serum potassium will shift to the intracellular compartment during therapy and back into serum when therapy is terminated, so potassium should be supplemented conservatively and with caution. As with any insulin infusion, the intravenous tubing used must be flushed with insulin-containing solution to saturate binding sites on the tubing with insulin to ensure delivery of prescribed amounts of insulin.

Currently, an insulin bolus of 1 unit/kg body weight has become an accepted starting point, fol-
lowed by insulin infusions started in the range of 1 unit/kg body weight/h and titrated upward to as high as 10 units/kg/h, depending on the degree of hypotension present. Toxicology consultation is advised to assist with dosing. This therapy should be started as early as possible, before the patient is in extremis. Insulin dosing requirements for beta blocker-poisoned patients may be lower than those required to treat calcium-channel blocker-poisoned patients. Insulin therapy requires time to produce hemodynamic improvement, and care should be taken not to taper insulin therapy too rapidly upon hemodynamic improvement or the benefit may be lost.

Gastric Decontamination
Patients who ingest life-threatening amounts of calcium-channel blocker and/or beta blocker agents may potentially be candidates for gastric decontamination. Immediate toxicology consultation is recommended when making this decision, due to significant risks and unproven benefit. Gastric decontamination via activated charcoal may be provided for patients who present within approximately 1 hour after ingestion, and perhaps longer in cases where a co-ingestant (such as an anticholinergic agent) may delay gastric emptying or drug absorption. The patient must remain alert and able to protect his airway (hemodynamics and mental status stability or improving trajectory) or be endotracheally intubated in order to receive activated charcoal therapy, since aspiration of activated charcoal may lead to respiratory failure and death. Endotracheal intubation is not a fail-safe method of preventing charcoal aspiration, however. While activated charcoal administration may decrease the area under the concentration-versus-time curve of a drug, no clinical studies have been performed to assess the effect of activated charcoal on outcome in cases of poisoning. If performed, active charcoal administration should be reserved for recent (usually < 60 min prior) ingestion of a life-threatening amount of a life-threatening agent. It is strongly recommended that emergency physicians caring for patients who have ingested a beta blocker or calcium-channel blocker consult a toxicologist to weigh the theoretical advantage of activated charcoal administration versus the potential life-threatening risk of aspiration of activated charcoal.

Whole-bowel irrigation with polyethylene glycol electrolyte lavage solution is reserved for patients who have ingested sustained-release preparations, with the goal being to speed the passage of the drug through the gut before it can be entirely absorbed. When indicated, polyethylene glycol electrolyte lavage is best administered as early in the course of poisoning as possible, although, given the extended liberation period of many sustained-release agents, there may be some theoretical (but, as yet, clinically unproven) benefit to administration even several hours after ingestion of sustained-release agents.

Vaspressors
Atropine and conventional vaspressors (such as dopamine and norepinephrine) may not yield the expected benefits in significant overdoses due to the myocardial depressant effects of beta blocker and calcium-channel blocker toxicity. Phosphodiesterase inhibitors (such as amrinone and milrinone) have historically been used, but they do not seem to offer any benefit over glucagon and may even decrease mean arterial pressure, when used. The use of cardiac pacing, extracorporeal membrane oxygenation, cardiopulmonary bypass, and intra-aortic balloon counterpulsation have been reported for severe cases of beta blocker/calcium-channel blocker toxicity in order to temporize until further clearance of the toxin occurs. Indications for glucagon, euglycemic insulin therapy, and lipid rescue may be best understood as points along the continuum of progressive hypotension as beta blocker or calcium-channel blocker poisoning progresses.

Using Multispecialty Teams
It is imperative that team members be familiar with advanced therapies before critical cases present in order to initiate timely action when needed. Pharmacists may be unfamiliar with high-dose glucagon, high-dose euglycemic insulin, or lipid rescue therapies. It is best to enlist their assistance in developing institutional guidelines for these infrequently used (but potentially life-saving) treatments. Similarly, nephrologists should be involved regarding available hemoperfusion/molecular adsorbent modalities available and their indications. Cardiologists and cardiothoracic surgeons must become familiar with potential uses for intra-aortic balloon counterpulsation and cardiopulmonary bypass in poisoning. Neurologists may be involved for continuous electroencephalographic monitoring that may be needed to detect subclinical status epilepticus, especially if paralytics are used in the poisoned patient.

The practice of using a multispecialty team to provide care to the severely poisoned patient may prove beneficial for all. Institutions or practitioners with little experience managing these cases may find it advantageous to transfer these patients to a higher level of care. If transfer is contemplated, it should, ideally, be accomplished early in the course of poisoning, before severe hemodynamic compromise increases the risk to the patient. Hospital practice teams should receive education in advance on the need to manage these potentially critically ill patients so that antidotes and other care may be rendered in a timely and efficient manner.
Clinical Pathway For Management Of Beta Blocker And Calcium-Channel Blocker Toxicity

Identify patient with beta blocker or calcium-channel blocker toxicity

Is the patient protecting the airway?

- Intubate patient (Class I)
- Go to “severe toxicity” treatment pathway

NO

Is the patient protecting the airway?

- Intubate patient (Class I)
- Go to “severe toxicity” treatment pathway

YES

Deteriorating vital signs or Signs of systemic shock?

- Immediate resuscitation required (Class I)
- Go to “severe toxicity” treatment pathway

NO

Deteriorating vital signs or Signs of systemic shock?

- Immediate resuscitation required (Class I)
- Go to “severe toxicity” treatment pathway

YES

Determine level of toxicity (clinical presentation)

Mild toxicity; consider:
- Cardiac monitoring
- IV fluids
- Correction of electrolytes
- Calcium
- Glucagon bolus/infusion
- Atropine

Patient improving?

- Continue to monitor
- Consider additional treatment with above
- Consider hospital admission

NO

Moderate toxicity; consider:
- All options in “mild toxicity” pathway and
- High-dose insulin (with glucose)
- Vasopressors

Patient improving?

- Continue to monitor
- Consider additional treatment with above
- Likely hospital admission (consider ICU)

NO

Moderate toxicity; consider:
- All options in “mild toxicity” pathway and
- High-dose insulin (with glucose)
- Vasopressors

Patient improving?

- Continue to monitor
- Consider additional treatment with above
- Likely hospital admission (consider ICU)

Severe toxicity; consider:
- All options in “mild toxicity” and “moderate toxicity” pathways and
- Intubation
- Lipid rescue therapy
- Cardiac pacing
- Intra-aortic balloon counterpulsation
- Cardiopulmonary bypass
- Molecular adsorbent recirculating system

Patient improving?

- Continue to monitor
- Consider additional aggressive treatment
- Obtain toxicology consult, if not already done
- Consider alternate diagnosis

Patient improving?

- Continue to monitor
- Consider additional aggressive treatment
- Obtain toxicology consult, if not already done
- Consider alternate diagnosis

Abbreviations: ICU, intensive care unit; IV, intravenous.
For class of evidence definitions, see page 9.
Continuous monitoring of hemodynamics, serum chemistries (especially glucose and electrolytes), and mental status are essential in order for the physician to anticipate the escalation in doses and therapies that may be required to optimize patient salvage. Hyperglycemia is a hallmark of significant calcium-channel blocker overdose, and in the altered patient presenting without history of ingestion, unexplained hyperglycemia should raise concern for calcium-channel blocker poisoning. While further work is needed to correlate glucose levels with therapies indicated, glucose levels may be a better indicator of the severity of poisoning and of the need for euglycemic insulin therapy.\textsuperscript{29}

In contrast, beta-blocker poisoning may present with hypoglycemia (rarely) or hyperglycemia.\textsuperscript{30} Lactate levels, bicarbonate, and serum pH may help to assess the adequacy of end-organ perfusion. In conjunction with supportive care, escalating doses/infusions of glucagon, insulin/glucose/potassium, and/or parenteral lipid infusion may be required, in succession, as hemodynamics deteriorate. Evidence of cerebral/tissue hypoxemia and/or acidosis indicates the need for escalation of therapy. In the absence of signs of severe hypoperfusion, lower-than-average blood pressures may be acceptable. Middle-aged patients will often tolerate/survive with target blood pressures as low as 80 mm Hg, systolic. In severe cases of cardioactive agent poisoning, it is often impossible to reach optimal perfusion rates. Although suboptimal in terms of optimal cerebral and core organ perfusion goals, blood pressures such as 90/60 mm Hg may be an acceptable pressure in patient with severe beta blocker or calcium-channel blocker poisoning.

### Determining Stability And Identifying And Managing Deterioration

Once the patient with beta blocker/calcium-channel blocker toxicity has been identified, the first priority is to protect the airway, which may require intubation. Vital signs, including hemodynamic stability, will guide the subsequent course of action. If the patient is asymptomatic, activated charcoal or orogastric lavage may be considered if it has been < 1 hour since ingestion. Systolic blood pressure < 100 mm Hg or heart rate < 60 beats/min may mandate fluid boluses and/or atropine. If this does not result in hemodynamic stability or the condition worsens, intubation, glucagon, additional atropine, calcium, and/or high-dose insulin with glucose may be warranted. If glucagon is ineffective in improving the hemodynamics of a calcium-channel blocker-poisoned patient, no time should be lost before advancing to euglycemic insulin therapy.

A patient in systemic shock will require aggressive management, including all of the interventions noted previously, and may require vasoactive therapy, lipid rescue, cardiac pacing, or more invasive maneuvers such as intra-aortic balloon counterpulsation, cardiopulmonary bypass, and/or the use of molecular adsorbent recirculating system. Once resuscitation has occurred and the patient is temporarily stabilized, the decision on admission location within the hospital will depend on whether or not intubation has occurred, the patient’s hemodynamic stability, and the resources available at the local institution. Twenty-four-hour inhouse presence of attending-level critical care providers is highly desirable for the management of these complex patients. Transfer of the patient to a tertiary care center should be considered if the patient is hemodynamically unstable or if the anticipated course includes therapies that are not available at the original institution. Continuous hemodynamic monitoring as well as neurologic and airway monitoring are necessary, regardless of therapy applied, in all beta blocker and calcium-channel blocker overdoses. Potential for severe declines in clinical status exists.

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### Class Of Evidence Definitions

Each action in the clinical pathways section of *EM Critical Care* receives a score based on the following definitions.

**Class I**
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

**Level of Evidence:**
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

**Class II**
- Safe, acceptable
- Probably useful
- Level of Evidence:
  - Generally higher levels of evidence
  - Nonrandomized or retrospective studies: historic, cohort, or case control studies
  - Less robust randomized controlled trials
  - Results consistently positive

**Class III**
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments
- Level of Evidence:
  - Generally lower or intermediate levels of evidence
  - Case series, animal studies, consensus panels
  - Occasionally positive results

**Indeterminate**
- Continuing area of research
- No recommendations until further research
- Level of Evidence:
  - Evidence not available
  - Higher studies in progress
  - Results inconsistent, contradictory
  - Results not compelling

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This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient’s individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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even in seemingly stable patients. Such declines may be dependent on time of exposure, immediate versus sustained-release product ingested, comorbidities, time of presentation, and other variables.

Special Circumstances

Mixed or multidrug overdoses are common and present special challenges. Many drugs (such as cyclic antidepressants) have complicating cardiovascular and vasoactive effects, and all warrant supportive care. Opportunities for specific antidote therapy for agents involved should be sought. Lipid rescue should be considered in cases of severe poisoning resulting in hypotension and/or impending arrest, even if other modalities are in place.

Controversies And Cutting Edge

Lipid Resuscitation Therapy

For the treatment of the poisoned patient, lipid resuscitation therapy involves the intravenous injection of a lipid solution. Intralipid®, a solution of soybean oil that also contains egg lecithin and glycerol, is manufactured by Fresenius Kabi (Uppsala, Sweden). Although several concentrations are available, most published animal studies and human case reports concerning lipid resuscitation therapy deal with Intralipid® 20%; thus, it is the American College of Toxicology’s recommended agent for lipid resuscitation therapy. Lipid rescue may be attempted when significant hemodynamic instability unresponsive to traditional therapy is present or if cardiac arrest is impending or has occurred. Intractable lipid-soluble drug-induced seizures (such as those caused by propranolol or tricyclic antidepressants) may also respond to this therapy.

Originally studied as an antidote to local anesthetic toxicity, reports of lipid resuscitation therapy’s efficacy in dire cases of beta blocker and calcium-channel blocker toxicity have surfaced in recent years. Similarly, reports of success in cases of tricyclic antidepressant, anticonvulsant, and antipsychotic drug overdose have also been published. Several hypotheses exist regarding the lipid resuscitation therapy mechanism of action, with the initially accepted theory being the “lipid sink” theory. This theory holds that the injected lipid solution creates an additional lipid compartment into which lipid-soluble toxins will diffuse, thereby making them less available to target organs. Two different possible mechanisms mentioned in the literature include a direct positive inotropic effect from Intralipid® and augmentation of mitochondrial fatty acid oxidation by Intralipid. To date, the mechanism whereby lipid resuscitation therapy exerts its beneficial effects has not been definitively proven. No randomized controlled studies exist to support the use of lipid resuscitation therapy. The very nature of clinical toxicology, however, often precludes the conduction of such studies. Therefore, many therapies are transitioned into widespread use based on a preponderance of available evidence, which, in the case of lipid resuscitation therapy, has shown promise in recent years. No definitive optimal dose or dosing schedule has been proven, as yet. A currently published position statement from the American College of Medical Toxicology is shown in Table 3.

Molecular Adsorbent Recirculating System

The molecular adsorbent recirculating system (MARS) is an albumin-based dialysis system designed to remove both water-soluble and albumin-bound toxins from the blood. Initially developed to treat liver failure by removal of bile acids, amino acids, fatty acids, and ammonia from the bloodstream, MARS has also been shown to remove fentanyl, theophylline, acetaminophen, midazolam, and phenytoin from the blood. More recently, case reports detailing the use of MARS to treat patients with diliazem or verapamil toxicity and refractory cardiogenic shock have been published. In 1 series, not only did all 3 patients survive to hospital discharge, but all were still asymptomatic at 2-year follow-up. While initially designed as a “liver dialysis” system, MARS is approved only for use in the treatment of drug overdose and poisonings in the United States and, currently, has limited availability.

Table 3. American College Of Medical Toxicology Position Statement On Lipid Resuscitation Therapy

| 1. | If the treating clinician deems use of lipid resuscitation therapy appropriate, a 1.5 mL/kg bolus of 20% lipid emulsion (Intralipid®) should be used. |
| 2. | The bolus should be followed by an infusion at 0.25 mL/kg/min. |
| 3. | The bolus dose may be repeated for patients in pulseless electrical activity or asystole who do not respond to the initial bolus. |
| 4. | If an initial response to the bolus is observed and the patient redevelops hemodynamic instability, the physician may increase the infusion rate or repeat the bolus dose. |
| 5. | When possible, treatment with lipid resuscitation therapy should last no more than 1 h, but the duration may be extended if the patient’s stability is dependent on such therapy. |
ylene blue in this case followed the unsuccessful use of calcium, glucagon, euglycemic insulin therapy, and 3 vasopressors. The patient suffered 2 cardiac arrests, and a transvenous pacer was placed. Despite these measures, the patient remained severely hypotensive. Initiation of a methylene blue infusion was reported to have resulted in a dramatic improvement in blood pressure.\textsuperscript{58} The methylene blue dose reported was a 1 mg/kg bolus over 10 minutes, followed by an infusion at 1 mg/kg/h that was continued for 10 hours. Improvement in blood pressure was noted 20 minutes after the bolus. The mechanism of action of methylene blue in this context is thought to result from interference with the action of endothelial nitric oxide. Calcium-channel blockers (such as amloidipine) block transmembrane influx of Ca\textsuperscript{2+} into vascular smooth muscle and increase endothelial nitric oxide levels. Nitric oxide binds with guanylate cyclase to form nitric oxide-activated guanylate cyclase (NO-GC). NO-GC increases conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP), leading to smooth-muscle relaxation in the arterioles. Methylene blue inhibits guanylate cyclase, and, in turn, decreases cGMP and vascular smooth-muscle relaxation. In addition, methylene blue scavenges nitric oxide and inhibits nitric oxide synthesis. In sum, methylene blue counteracts the effect that calcium-channel blockers (such as amloidipine) have on smooth muscle.\textsuperscript{58}

**Disposition**

All symptomatic beta blocker and calcium-channel blocker overdose patients should be admitted to a high level of care (intensive care unit, critical care unit, or step-down unit, as appropriate), with continuous cardiac monitoring. Timely gastric decontamination with activated charcoal (and possibly whole-bowel irrigation with polyethylene glycol electrolyte lavage in the case of extended-release formulations) should be considered and discussed with a toxicologist. Patients who have intentionally ingested overdoses of these potentially lethal agents with suicidal ideation or intent must be continuously attended (eg, by a “sitter”) to prevent further attempts at self-harm, and then they should be evaluated by psychiatry when clinically cleared. Patients who remain asymptomatic may, on occasion, be cleared for psychiatric evaluation or they may be discharged with the caveat that patients who ingest sustained-release products must be admitted for observation because of a potential delayed effect of the medication. Co-ingestions of agents that may delay absorption of beta blockers and calcium-channel blockers (such as opioids and anticholinergics) and patients with significant gastrointestinal disease or postsurgical changes may also warrant prolonged observation after ingestion and may be exceptions to the general disposition guidelines that follow.

**Observation Periods For Beta Blocker Ingestion**

In general, beta blocker toxicity from ingestion of immediate-release agents begins within 6 to 8 hours after ingestion (with the exception of sotalol). Therefore, patients who have ingested an immediate-release beta blocker (except sotalol) may be medically discharged after 6 to 8 hours of observation if they remain asymptomatic. Patients who have ingested sotalol are at risk for delayed onset of ventricular arrhythmias and must be monitored for a minimum of 12 hours (preferably longer). After this time, they may be released from a monitored setting if they remain stable and without QTc prolongation or other symptoms.\textsuperscript{59} Patients who intentionally ingest extended-release formulations of a beta blocker must be admitted to a closely monitored environment (step-down or critical care) with immediate access to a critical care unit capable of advanced airway management for 24 hours due to the potential for delayed onset of life-threatening symptoms.\textsuperscript{59} For patients with unintentional ingestion of a sustained-release beta blocker who have no symptoms, routine 24-hour admission is not recommended.\textsuperscript{59} The same literature suggests that an 8-hour period of observation may be sufficient in this instance, with the caveats that the patient: (1) should have no predisposing factors for orthostasis, (2) has ingested only a therapeutic/near-therapeutic dose, and (3) is asymptomatic throughout the course of observation.\textsuperscript{59}

**Observation Periods For Calcium-Channel Blocker Ingestion**

Following presumed calcium-channel blocker ingestion, patients who remain asymptomatic for 8 hours following ingestion of immediate-release products, 12 to 24 hours following ingestion of modified- (sustained) release nonphenylalkylamine (nonverapamil) products, and 24 hours following ingestion of modified- (sustained) release verapamil are generally regarded as unlikely to develop

**Time- And Cost-Effective Strategies**

Given the complexity and potential severity of beta blocker and calcium-channel blocker ingestions, there are no broadly applicable cost-effective pathways aside from sequential and timely institution of the interventions described in this review. Fortunately, this intensity of care is relatively infrequently needed. The most effective plan in managing overdoses is to get ahead of potential decline in clinical status early on, with glucose and insulin, to minimize complications and the need for other therapies. As noted earlier, aggressive care in the face of cardiovascular collapse can yield good outcomes in this population.
significant symptoms. All other patients should be admitted to a high level of care for close observation and treatment. Toxicology and poison control center consultants may help individualize disposition and treatment options on a case-by-case basis.

**Summary**

Beta blocking and calcium-channel blocking agents are common in overdose situations, and efficient action can mean the difference in outcome for patients. Table 4 summarizes the treatment modalities available for beta blocker and calcium-channel blocker poisoning. In general, early use of more-aggressive therapeutic options (eg, glucagon, high-dose insulin/euglycemic therapy, lipid resuscitation therapy) improves outcome. It is advisable to consult with a poison control center to assist in optimizing early and supportive care.

It is important to be aware of the class of the beta blocker or calcium-channel blocker involved. Beta blockers are either lipid soluble or water soluble. Lipid-soluble agents are more dangerous in that they are well absorbed by the gut and have significant central nervous system distribution. Water-soluble agents are not as completely absorbed through the gut, are not as well distributed in the central nervous system, and are eliminated by the renal system unchanged.

Calcium channel blockers fall into 2 broad categories: dihydropyridines or nondihydropyridines. Dihydropyridines have a less significant myocardial depressant action, and may even increase cardiac output due to reflex tachycardia. Nondihydropyridines will cause decreased myocardial contractility and conduction. However, either one of these classes can cause hypotension, bradycardia, and death in an overdose situation.

Common treatment options for the emergency physician include glucagon, insulin therapy, high-dose insulin therapy, and, in certain cases, gastric decontamination. Vasoactive agents may become necessary in the setting of hemodynamic instability, and this may progress to requiring invasive efforts such as hemoperfusion, molecular adsorbent therapies, intra-aortic balloon counterpulsation, or cardiopulmonary bypass. Methylene blue has been reported to reverse refractory shock.

The standard emergency medicine modalities of protecting the airway and addressing other comorbidities that may confound the situation are key. The cardioactive overdose patient will require monitoring, and emergency physicians should err in favor of admission and observation to a high level of care (such as an intensive care unit) because of the potentially dire consequences of these overdoses. The key to excellent patient outcome is early recognition of potentially severe toxicity and focused treatment, taking into consideration the agent(s) ingested.

**Case Conclusion**

It was ultimately determined that the 21-year-old patient who took her father-in-law’s blood pressure pills had ingested a large dose of sustained-release metoprolol, a long-acting beta blocking agent. In addition to intubation, she required vasoactive agents to support hemodynamic stability and CNS perfusion. You followed this with high-dose insulin therapy, as vasopressors alone began to be incapable of maintaining adequate perfusion. This resulted in a period of stability, followed by recurrent hypotension. You initiated lipid emulsion therapy, which was successful, though the patient required vasoactive agents and intensive critical care for 48 hours. The efficient action of the emergency medicine team, along with consultation by the regional poison center, identification of the cardiovascular poison toxidrome, toxicologic consultation, and anticipatory support of hemodynamics helped to stabilize this patient and avoid cardiac collapse.

**Must-Do Markers Of Quality ED Critical Care**

- Recognition of the toxidrome of depressive cardiotoxicity.

- Timely initiation of monitoring and cautious fluid resuscitation, as discussed in the “Supportive Care” section (see page 5).

- Correct patient selection for glucagon therapy, and, if warranted, correct dosing of glucagon and timely initiation of continuous glucagon infusion.

- Early institution of high-dose insulin euglycemic therapy for patients with hypotension unresponsive to other measures.

- Identification of refractory cases that may benefit from lipid resuscitation therapy (or MARS, where available).

**Table 4. Types Of Interventions For Beta Blocker And Calcium-Channel Blocker Toxicity**

<table>
<thead>
<tr>
<th>Basic Supportive Care</th>
<th>Toxin-Specific Interventions</th>
<th>Mechanical Assistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cardiac monitoring</td>
<td>• Calcium (for calcium-channel blocker)</td>
<td>• Cardiac pacing</td>
</tr>
<tr>
<td>• Intravenous fluids</td>
<td>• Glucagon bolus and infusion</td>
<td>• Intra-aortic balloon counterpulsation</td>
</tr>
<tr>
<td>• Correction of electrolytes</td>
<td>• High-dose insulin and glucose</td>
<td>• Cardiopulmonary bypass</td>
</tr>
<tr>
<td>• Atropine</td>
<td>• Lipid rescue therapy</td>
<td></td>
</tr>
<tr>
<td>• Vasopressors</td>
<td>• Molecular adsorbent recirculating system</td>
<td></td>
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<tr>
<td>• Endotracheal intubation</td>
<td></td>
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</tbody>
</table>

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References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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1. Which of the following beta-adrenergic antagonists is MOST likely to cause central nervous system effects in moderate overdose?
   a. Acebutolol
   b. Atenolol
   c. Pindolol
   d. Propranolol

2. Which of the following calcium-channel antagonists is associated with the greatest likelihood of mortality in significant overdose?  
   a. Amlodipine  
   b. Nicardipine  
   c. Nifedipine  
   d. Verapamil
3. Excessive fluid resuscitation is not advised for patients with beta blocker or calcium channel blocker poisoning. Which of the following is the reason for this recommendation?
   a. The electrolyte concentrations in most crystalloid solutions cause untoward interactions with antidotal therapies, such as glucagon and insulin.
   b. Excessive administration of normal saline (0.9%) can cause a non-anion-gap metabolic acidosis, which may inhibit myocardial function.
   c. Most patients who present with beta blocker or calcium channel blocker poisonings are already hypervolemic.
   d. Patients who have been poisoned with these agents have depressed myocardial function and, therefore, have a lower tolerance for excessive preload (fluids).

4. Which of the following is the MOST acceptable agent to induce anesthesia during rapid sequence intubation of a patient with severe beta blocker or calcium-channel blocker poisoning?
   a. Propofol
   b. Ketamine
   c. Thiopental
   d. Midazolam

5. Which of the following is the mechanism by which glucagon exerts its effects on myocardial tissue that has been poisoned by beta blockers or calcium-channel blockers?
   a. It increases cAMP concentrations within cardiac myocytes, thereby increasing inotropy and chronotropy.
   b. It binds to myocardial beta-adrenergic receptors, thereby preventing beta-blocking agents from binding to these receptors.
   c. It decreases expression of beta-adrenergic receptors on the myocardial surface.
   d. It inhibits the activation of L-type calcium channels.

6. Which of the following would prolong the absorption of beta blocking or calcium-channel blocking agents?
   a. Alcohol ingestion
   b. Concomitant opioid ingestion
   c. Seizures
   d. Diabetes

7. Assuming adequate fluid resuscitation, supportive care, and glucagon administration for progressive signs of hypotension, the most promising life-saving antidotal therapy for patients with severe beta-adrenergic antagonist poisoning is likely to be:
   a. Amrinone infusion
   b. Atropine bolus
   c. Euglycemic insulin therapy
   d. Octreotide injection

8. What is the recommended bolus dose of insulin when initiating euglycemic high-dose insulin therapy?
   a. 0.1 units/kg
   b. 0.5 units/kg
   c. 1 unit/kg
   d. 2 units/kg

9. Successful patient salvage in cases of severe calcium-channel blocker and beta blocker poisoning has been reported with the use of lipid emulsion. Theories about potential mechanisms for this beneficial effect include all of the following EXCEPT:
   a. Direct effect on cAMP-mediated inotropic mechanisms
   b. “Lipid sink” effect (in which lipid-soluble drug partitions into the expanded lipid compartment, leaving poisoned compartments)
   c. Increased volume of distribution for the lipid soluble drug
   d. Augmentation of mitochondrial fatty acid oxidation by the administered lipid

10. For cases in which lipid resuscitation therapy is used, what is the recommended initial bolus dose of 20% lipid emulsion, according to the American College of Medical Toxicology?
    a. 0.5 mL/kg body weight
    b. 1 mL/kg body weight
    c. 1.5 mL/kg body weight
    d. 2 mL/kg body weight

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