Treatment of poisoning caused by β-adrenergic and calcium-channel blockers

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Overdoses with cardiovascular drugs are associated with significant morbidity and mortality.[1] Beta-adrenergic blockers and calcium-channel blockers (CCBs) represent two of the most important classes of cardiovascular drugs. This article will review the toxicity and treatment of β-blocker and CCB overdoses. Overdoses with cardiovascular drugs typically result from exploratory ingestions by children or intentional ingestions by suicidal adults. Other reasons for intoxications include medication errors (e.g., double dosing) or adverse effects. Interactions with drugs that affect cardiac conduction, inotropy, or metabolism via the cytochrome P450 enzymes may also produce toxicity.[2,3]

According to the 2004 Toxic Exposure Surveillance System (TESS) report, 3% ($n = 74,145$) of the total exposures reported in TESS documented by the American Association of Poison Control Centers were due to cardiovascular medications.[1] Poisonings with these drugs resulted in 162 deaths, making cardiovascular drugs the fifth leading cause of death in the TESS database. CCBs and β-blockers accounted for 37% of these exposures and the majority of cases resulting in life-threatening effects or death.[1] The CCB and β-blocker drugs

Purpose. The toxic effects and treatment of β-adrenergic blocker and calcium-channel blocker (CCB) overdose are reviewed.

Summary. Overdoses with cardiovascular drugs are associated with significant morbidity and mortality. Beta-blockers and CCBs represent the most important classes of cardiovascular drugs. In overdose, β-blockers and CCBs have similar presentation and treatment overlaps and are often refractory to standard resuscitation measures. The common feature of β-blocker toxicity is excessive blockade of the β-receptors resulting in bradycardia and hypotension. Poisoning by CCBs is characterized by cardiovascular toxicity with hypotension and conduction disturbances, including sinus bradycardia and varying degrees of atrioventricular block. Therapies include β-agonists, glucagon, and phosphodiesterase inhibitors. However, in β-blocker poisoning where symptomatic bradycardia and hypotension are present, high-dose glucagon is considered the first-line antidote. Traditionally, antidotes for CCB overdose have included calcium, glucagon, adrenergic drugs, and amrinone. For cases of CCB poisoning where cardiotoxicity is evident, first-line therapy is a combination of calcium and epinephrine; high-dose insulin with supplemental dextrose and potassium therapy (HDIDK) is reserved for refractory cases. Health-system pharmacists should be aware that when these drugs are used as antidotes, higher than normal dosing is needed.

Conclusion. Poisoning by β-blockers or CCBs usually produces hypotension and bradycardia, which may be refractory to standard resuscitation measures. For cases of β-blocker poisoning where symptomatic bradycardia and hypotension are present, high-dose glucagon is considered the first-line antidote. For cases of CCB poisoning where cardiotoxicity is evident, a combination of calcium and epinephrine should be used initially, reserving HDIDK for refractory cases.

Index terms: Amrinone; Antidotes; Calcium; Calcium antagonists; Combined therapy; Dextrose; Dosage; Epinephrine; Glucagon; Insulin; Phosphodiesterase inhibitors; Poisoning; Potassium; Sympatholytic agents; Sympathomimetic agents; Toxicity

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most frequently implicated in fatalities are verapamil and propranolol, respectively.[1] Newer agents in both classes have better safety profiles.

Beta-blocker pharmacology

Beta-blockers selectively antagonize β-adrenergic receptors that are linked to G proteins. The β-receptor has three known subtypes.[4] Beta-1 receptors primarily regulate myocardial tissue and affect the rate of contraction via impulse conduction. Beta-2 receptors regu-

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late smooth muscle tone and influence vascular and bronchiolar relaxation. Beta-3 receptors are less well studied but are thought to primarily affect lypolysis and may have effects on cardiac inotropy. Beta-receptor complexes are subject to genetic polymorphisms that may result in variable patient responses.[4] Some β-blockers have relative specificity for different β-subreceptors, and some agents may antagonize α-receptors. Some β-blockers have mixed agonist and antagonist activity; the agonist property is commonly referred to as intrinsic sympathomimetic activity. In an overdose situation, receptor selectivity is lost, and effects not normally seen at therapeutic doses can occur.[3] In addition, some β-blockers may antagonize cardiac sodium channels, producing quinidine-like effects that will increase toxicity in overdose. An important determinant of adverse effects with β-blockers is lipid solubility. Highly lipophilic agents such as propranolol cross the blood–brain barrier and can result in unwanted central nervous system (CNS) effects. Table 1 displays various commonly used β-blockers and their pharmacologic profiles.[5]

CCB pharmacology

Voltage-gated calcium channels are found in myocardial cells, smooth muscle cells, and β-islet cells of the pancreas.[2] CCBs prevent the opening of these voltage-gated calcium channels and reduce calcium entry into cells during phase 2 of an action potential. CCBs exhibit different selectivity for cardiac versus vascular channels.[2] Selectivity may relate in part to whether the drug binds to the channel preferentially in the open state or closed states and the affinity of the drug for cardiac versus central α_1 subunits of the L-type channel. Dihydropyridines, such as amlodipine and nifedipine, act predominantly on peripheral vasculature, while verapamil and diltiazem are less selective, exhibiting direct cardiac effects and peripheral vascular activity. Verapamil and, to a lesser extent, diltiazem depress sinoatrial and atrioventricular nodal conduction, decrease myocardial contractility, and decrease peripheral vascular resistance. In myocardial tissue, this results in negative inotropy, chronotropy, and dromotropy. Inotropy is reduced because of the resultant lack of intracellular calcium within the cardiomyocyte. Impaired impulse generation and conduction in the sinoatrial and atrioventricular nodes may slow the heart rate or cause atrioventricular nodal block. By blocking calcium channels in vascular smooth muscle, CCBs prevent arterial contraction. This peripheral action reduces afterload and systemic blood pressure. Because dihydropyridine-type CCBs only act peripherally, the vasodilation they cause may induce a compensatory increase in the heart rate. Within the pancreas, calcium channel antagonism results in decreased insulin secretion. Effects on pancreatic tissue and insulin secretion are less well studied but all three subclasses of CCBs appear to have this effect.[6]

Toxic doses

Any drug may be harmful if the dose is large enough. Determining an exact toxic dose for a given individual is difficult because of the variability in patient-specific factors such as age,

Table 1.
Comparison of Pharmacologic Properties of Various β-Blockers[a]

Agent	Adrenergic Receptor Blocking Activity	Lipid Solubility	Intrinsic Sympathomimetic Activity	Sodium Channel Blocking
Acebutolol	β_1	Low	Yes	Yes
Atenolol	β_1	Low	No	No
Betaxolol	β_1	Low	No	Yes
Bisoprolol	β_1	Low	No	No
Carteolol	β_1, β_2	Low	Yes	No
Carvedilol	$\alpha_1, \beta_1, \beta_2$	High	No	No
Esmolol	β_1	Low	No	No
Labetalol	$\alpha_1, \beta_1, \beta_2$	Moderate	Yes	No
Metoprolol	β_1	Moderate	No	No
Nadolol	β_1, β_2	Low	No	No
Oxprenolol	β_1, β_2	High	Yes	Yes
Penbutolol	β_1, β_2	High	Yes	No
Pindolol	β_1, β_2	Moderate	Yes	No
Propranolol	β_1, β_2	High	No	Yes
Sotalol	β_1, β_2	Low	No	No
Timolol	β_1, β_2	Low to moderate	No	No

[a]Adapted with permission from reference 5.

genetics, health status, and other recently ingested substances. Such factors should be taken into account when establishing a toxic dose, with the realization that some patients will be outliers in either direction. To try to avoid problems with low-dose outliers, safety recommendations are generally set below the lowest dose rather than the mean dose reported to cause harm. A consensus panel recently reviewed the medical literature for toxic doses of β-blockers and CCBs to establish threshold doses for triage and prehospital management of poisonings.[7,8] In general, β-blockers with low lipid solubility that lack membrane-stabilizing effects are much safer than agents that have these effects.[9-11] Among CCBs, the newer agents are generally safer than diltiazem or verapamil.[2] Tables 2 and 3 list the consensus panel's findings of threshold doses for hospital referral and observed minimum toxic doses for common β-blockers and CCBs representing the various subclasses of agents. These values should be used as guidance for decision-making based on the specific circumstances of the case. Elapsed time since ingestion is important for assessment of the clinical situation. Extended-release formulations are common in both classes and have the potential for prolonged toxicity. Also, crushing or chewing these preparations may disrupt the tablet's release mechanisms and result in a larger amount being available for initial absorption. When assessing a potential poisoning in addition to the immediate clinical implications of the ingestion, it is important to assess the patient's intent. Patients with subtoxic ingestions but suicidal intent will require psychiatric care.

In overdose, β-blockers and CCBs often have similar presentation and there is much overlap in treatment. Cardiotoxicity characterized by hypotension and bradycardia is the common clinical feature, but other effects may help differentiate the ex-

Table 2.		
Threshold and Toxic Oral Doses of Common β-Adrenergic Blockers[a]		
Drug and Patient Age	**Threshold Dose for Referral**[b]	**Lowest Reported Toxic Dose**
Acebutolol hydrochloride[c]		
Adult	600 mg	4000 mg
Child	12 mg/kg	NC
Atenolol		
Adult	200 mg	500 mg
Child	2 mg/kg	5.3 mg/kg
Carvedilol		
Adult	50 mg	1050 mg
Child	0.5 mg/kg	NC
Labetalol hydrochloride		
Adult	400 mg	6000 mg
Child	20 mg/kg	NC
Metoprolol succinate (ER)		
Adult	400 mg	7500 mg[d]
Child	5 mg/kg	NC
Metoprolol tartrate (IR)		
Adult	450 mg	7500 mg[d]
Child	2.5 mg/kg	NC
Nadolol		
Adult	320 mg	NC
Child	2.5 mg/kg	NC
Propranolol hydrochloride		
Adult	240 mg	800 mg
Child		
IR	4 mg/kg	5 mg/kg
ER	5 mg/kg	12 mg/kg
Sotalol hydrochloride		
Adult	160 mg	560 mg
Child	4 mg/kg	NC
Timolol maleate		
Adult	30 mg	NC
Child	Any dose	NC

[a]Adapted, with permission, from reference 7. Doses are based on the assumption that ingestion was unintentional in an asymptomatic patient without underlying severe medical conditions or concomitant ingestion of calcium-channel blockers. NC = no case reports available, ER = extended-release formulation, IR = immediate-release formulation.
[b]Dose during acute ingestion that should prompt referral to a hospital.
[c]Doses expressed in terms of the drug base.
[d]Dose expressed in terms of metoprolol tartrate equivalents.

posure. It is important to understand the different features of such poisonings by class and specific agents.

Among β-blockers, there is variation of toxic potential. The common feature is excessive blockade of the β-receptors resulting in bradycardia and hypotension.[10] When β-receptors are blocked, the G protein responsible for converting adenosine triphosphate to cyclic adenosine monophosphate is disabled, which results in less

cytosolic calcium being available for muscular contraction (Figure 1). Because β-selectivity is lost in overdose, even "β$_1$-selective" agents can block β$_2$- and β$_3$-receptors and bring about bronchospasm and a reduction in inotropy, respectively. Lipophilicity is a good predictor of CNS depression in β-blocker overdose. Beta-blockers, such as atenolol, that have poor lipid solubility generally will not directly produce sedation. However, if the

Table 3.
Threshold and Toxic Oral Doses of Common Calcium-Channel Blockers[a]

Drug and Patient Age	Threshold Dose for Referral[b]	Lowest Reported Toxic Dose
Amlodipine besylate[c]		
Adult	10 mg	30 mg
Child	0.3 mg/kg	0.4 mg/kg
Bepridil hydrochloride		
Adult	300 mg	NC
Child	Any dose	NC
Diltiazem hydrochloride		
Adult		
IR	120 mg	360 mg
12-hr ER	360 mg	700 mg
24-hr ER	540 mg	NC
Child	1 mg/kg	180 mg[d]
Felodipine		
Adult	10 mg	NC
Child	0.3 mg/kg	NC
Isradipine		
Adult	20 mg	NC
Child	0.1 mg/kg	2.5 mg/kg
Nicardipine hydrochloride		
Adult		
IR	40 mg	260 mg
ER	60 mg	600 mg
Child	20 mg	1.25 mg/kg
Nifedipine		
Adult		
IR	30 mg	50 mg
ER	120 mg	200 mg
Child	Any dose	2.8 mg/kg
Nimodipine		
Adult	60 mg	NC
Child	Any dose	NC
Nisoldipine		
Adult	30 mg	NC
Child	Any dose	NC
Verapamil hydrochloride		
Adult		
IR	120 mg	160 mg
ER	480 mg	720 mg
Child	2.5 mg/kg	12 mg/kg

[a]Adapted, with permission, from reference 8. Doses are based on the assumption that ingestion was unintentional in an asymptomatic patient without underlying severe medical conditions or concomitant β-adrenergic blockers. NC = no case reports available, IR = immediate-release formulation, ER = extended-release formulation.
[b]Dose during acute ingestion that should prompt referral to a hospital.
[c]Doses expressed in terms of the drug base.
[d]Formulation unknown.

possible, they appear to be uncommon following overdose.[10,11]

CCB overdose is characterized clinically by cardiovascular toxicity, with hypotension and conduction disturbances, including sinus bradycardia and varying degrees of atrioventricular block.[2] These effects are extensions of normal CCB pharmacology.[12] Hyperglycemia is a common finding in cases of CCB poisoning that is not normally seen with therapeutic dosing.[3,8,13] At high doses, CCBs cause a significant decrease in insulin release by blocking calcium influx into pancreatic islet cells. This lack of circulating insulin decreases cardiac carbohydrate metabolism by preventing glucose uptake and use by cardiac muscle (Figure 1).[14] This results in a lack of fuel for aerobic energy production, causing a shift to fatty acid oxidation within the cells. Impaired energy production coupled with decreased entry of calcium into the cell results in negative inotropy and chronotropy. Poor pumping by cardiac tissue and peripheral vasodilation result in profound shock. Metabolic acidosis then develops systemically because of the resulting decrease in tissue perfusion. Similarly, CNS effects, including drowsiness, confusion, agitation, and seizures, are likely to occur as less oxygen is delivered to the brain.

Treatment

Pharmacologic distinctions between β-blockers and CCBs may not be evident upon presentation; therefore, initial treatment efforts should be similar regardless of the type of drug involved. Based on general overdose treatment guidelines, after assuring that the airway, breathing, and circulation are intact, functional decontamination with orogastric lavage, activated charcoal, or whole-bowel irrigation should be administered based on the situation.[15,16] Lavage and charcoal should be used in cases where the history or clinical picture indicates a life-threatening

brain is poorly perfused because of hypotension, lethargy can result. The presence of quinidine-like sodium-channel blocking can greatly increase the cardiotoxicity by causing cardiac conduction delays that prolong the QRS interval, which increases the risk of ventricular arrythmia. This combination of effects, as seen with propranolol, can greatly increase toxicity and complicate treatment. Although glucose derangements are

Figure 1. Proposed actions in cardiac muscle of calcium, epinephrine (EPI), glucagon, amrinone, and insulin in the treatment of β-blocker (BB) and calcium-channel blocker (CCB) toxicity: (a) Calcium enters open voltage-sensitive calcium channels to promote the release of calcium from the sarcoplasmic reticulum. The released calcium combines with troponin to cause muscle contraction via actin and myosin fibers. (b) EPI binds to β-receptors (β) that are not occupied by a BB. Stimulation of the receptors, which are coupled to a G protein (G_s), brings about the activation of adenylate cyclase (AC). AC catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), which activates protein kinase A (PKA), which promotes the opening of dormant calcium channels, enhances release of calcium from the sarcoplasmic reticulum, and facilitates release of calcium by troponin during diastole. Therapies that promote cAMP formation generally have transient effects in CCB overdose due to the myocyte running out of carbohydrates. (c) Glucagon bypasses β-receptors and acts directly on G_s to stimulate conversion of ATP to cAMP. (d) Amrinone inhibits phosphodiesterase (PDE) to prevent the degradation of cAMP. (e) Insulin promotes the uptake and use of carbohydrates as an energy source. It also promotes antiinflammatory effects that may correct problems caused by inefficient energy production. The associated influx of potassium may also provide benefit by prolonging repolarization and allowing calcium channels to remain open longer. Illustration by Marie Dauenheimer, CMI. Adapted, with permission, from reference 16.
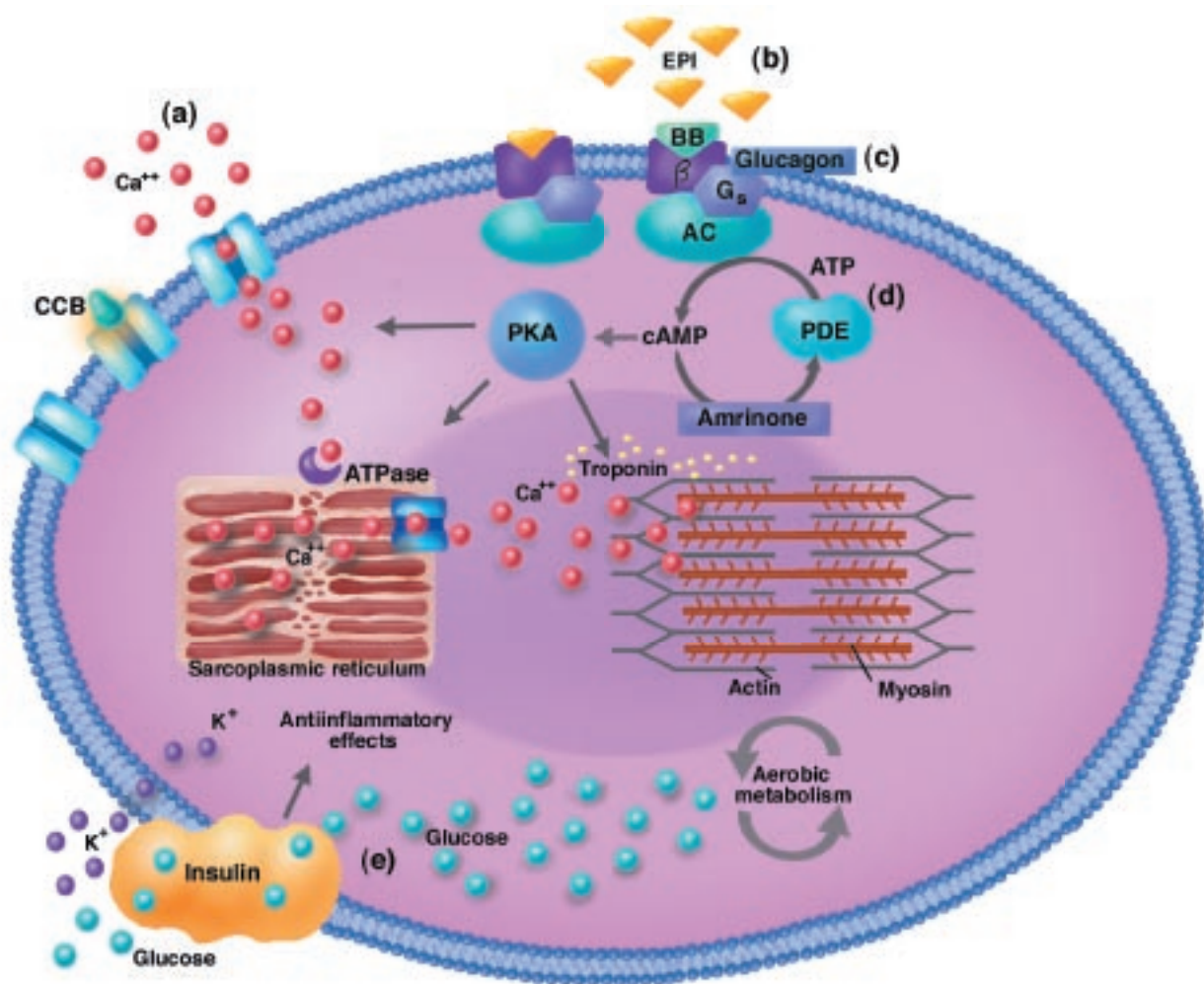
overdose and the ingestion occurred within one hour of presentation. Lavage's effectiveness may be limited for extended-release tablets because they may be too large to be removed via the lavage tube and will not fully dissolve in the stomach. Charcoal may be given alone for cases with less than life-threatening potential or delayed presentation (up to six hours) if charcoal is capable of binding the ingested substance. Gram per kilogram dosing is often recommended so as not to exceed the volume of the stomach, but it is important to understand that such dosing has nothing to do with how much charcoal needs to be given to effectively bind the amount of toxin ingested. The dose of activated charcoal should be based on the amount of drug ingested and the capacity of the stomach. In general, the amount needed for binding is a 10:1 ratio of charcoal to

toxin. In practical terms, 50–150 g for adults or 12.5–25 g for young children usually provides a suitable dose. Whole-bowel irrigation with polyethylene glycol in a balanced electrolyte solution has shown promise for cases of delayed presentation and cases of ingestion of extended-release products. It should be administered orally or by nasogastric tube at a rate of 1–2 L/hr and continued until the rectal effluent is clear or the ingested substance is recovered.

In addition to decontamination, therapies to support perfusion are often needed in cases of overdose. I.V. fluids (10–20 mL/kg as a bolus dose) should be used as first-line therapy for patients who develop hypotension. Atropine sulfate 0.5–1 mg i.v. is usually the first-line agent for symptomatic bradycardia. However, these treatments yield poor response in moderate to severe β-blocker or CCB overdose.[3] In addition to general supportive measures, several antidotal therapies are available. Hospitals that provide emergency care are required to stock antidotes, but surveys have indicated that many hospitals stock a limited variety of antidotes in insufficient quantities.[17] Unfortunately, there is no exact standard describing how much to stock.[18] Factors such as annual patient volume, geography, and referral status can cause stocking needs to vary. At a minimum, enough stock to treat one patient for 24 hours should be available. It is desirable to have enough to treat multiple patients at once.

Antidotes for β-blockers. Current antidotal therapy for β-blocker poisoning is based on animal studies and case reports. Unfortunately, no prospective human study evaluating optimal therapy has been performed. These therapies include β-agonists, glucagon, and phosphodiesterase inhibitors. Of these agents, glucagon is generally recognized as first-line therapy. Animal studies comparing these agents demonstrated that glucagon was superior to isoproterenol

and amrinone.[19,20] Although glucagon appears to consistently increase the heart rate, it does not consistently improve survival, particularly against propranolol intoxication.[20] A recent study compared glucagon to vasopressin in a porcine model of propranolol toxicity.[21] In that study, both drugs had similar effects on hemodynamic parameters and poor overall survival.

Case reports dating back to the 1970s describe hemodynamic improvement in patients treated with glucagon following β-blocker overdose.[22] A large number of case reports cite success with glucagon when used in conjunction with other agents, but fewer reports of success exist when it is used as the sole antidote.[3,20] However, several reports of glucagon failure also exist.[3] Variability in response to glucagon therapy is likely due to the differences in the type and β-blocker ingested, patient-specific factors, and the timing or content of therapy.[20]

Glucagon is a hormone synthesized and secreted by the α_2 cells of the pancreatic islets of Langerhans. Glucagon is thought to activate adenylate cyclase in cardiac tissue by directly stimulating a G protein on the β-receptor complex (Figure 1). High-dose glucagon is recommended for cardiotoxicity produced by β-blocker poisoning.[20] An initial bolus dose of 50–150 µg/kg should be administered i.v. over one to two minutes.[9,20] This initial dose will have a transient effect that should occur within approximately five minutes. If a benefit is seen, the initial dose should be followed by a continuous i.v. infusion at a rate of 2–5 mg/hr (maximum: 10 mg/hr) diluted in 5% dextrose injection. The infusion rate can then be tapered downward as the patient improves.[9,20] If improvement is not seen with the initial bolus dose, consider increasing the initial dose.

Glucagon is lyophilized powder for injection that requires reconstitution. Older formulations had dilu-

ents that contained small amounts of phenol that could produce toxicity in the doses needed for overdose therapy.[3] The current diluent should contain glycerin, water for injection, and hydrochloric acid for pH adjustment.[23] Reconstitution requires adding 1 mL of sterile diluent to a vial containing 1 mg of the drug, to provide solutions containing 1 mg of glucagon/mL. The bolus dose can be administered using the provided diluent or sterile water for injection. The prepared solution should be used immediately after reconstitution but may be kept at 5° C for up to 48 hours if necessary. For stocking purposes, one patient will require approximately 50 mg of glucagon over a 24-hour period. It is recommended that 20 mg be available in the emergency department and 30 mg in the main pharmacy.[18]

Propranolol or other β-blockers with effects on cardiac sodium channels can produce quinidine-like dysrhythmias (prolonged QRS interval) that may respond to an i.v. bolus dose of sodium bicarbonate.[10] High-dose insulin therapy (described in the CCB section) for β-blocker poisoning has been evaluated in one animal study and may offer benefits.[24] Current thought is that insulin therapy may be considered if the patient has failed to respond to the traditional antidotes or if hyperglycemia is present.

Antidotes for CCBs. Traditionally, antidotes for CCB overdose have included calcium, glucagon, adrenergic drugs (dopamine, norepinephrine, epinephrine), and amrinone.[2,3] Figure 1 shows these agents' potential sites of action. Unfortunately, in severely intoxicated patients with life-threatening clinical effects, these agents do not consistently improve hemodynamic parameters or ensure survival. Vasopressin has been suggested as a potential antidote, but it worsened the cardiac index and failed to improve the mean arterial pressure in a dog model of verapamil-induced

shock.[25] A more promising antidote is high-dose insulin.

The evidence supporting high-dose insulin with supplemental dextrose and potassium (HDIDK) therapy in CCB overdose has increased over the past few years and its use is becoming more common.[13] There are several studies using verapamil in a canine model that indicate that HDIDK is likely to be an effective therapy through enhanced cardiac carbohydrate metabolism and direct inotropic effects.[12,14,26-28] In these studies, HDIDK increased survival compared to high-dose epinephrine, glucagon, and calcium. Calcium did not offer any benefits. Epinephrine and glucagon initially improved heart rate and blood pressure but ultimately failed to reverse the toxicity.

The beneficial effects of HDIDK therapy are attributed to the promotion of carbohydrate metabolism during verapamil-induced shock rather than direct effects on the calcium channel. In dogs poisoned with verapamil, insulin appears to stimulate more efficient myocardial carbohydrate metabolism during shock compared to standard therapies. HDIDK increases carbohydrate uptake and oxidation for sustainable benefits, while glucagon or epinephrine enhances fatty acid metabolism, which promotes ketosis.[12,28] The initial benefits seen with glucagon and epinephrine are lost after the myocardial cells switch from aerobic to anaerobic metabolism, resulting in acidosis and free radical formation. Unfortunately, there are no studies investigating combinations of insulin and other therapies to identify if a synergistic effect exists. In a recent review of 13 human cases of CCB poisoning, HDIDK appeared safe and provided some clinical benefit in 12 or 13 cases.[13]

HDIDK should be considered if there is an inadequate response to fluid resuscitation.[13] It should be administered with calcium and epinephrine. Calcium should be dosed as 10–20 mL of 10% calcium gluconate via peripherial venous access or 5–10 mL of 10% calcium chloride via central venous access. Epinephrine is given i.v. at a rate of 1 μg (as the hydrochloride) per minute and increased as necessary. Before initiation of insulin therapy, blood glucose and potassium concentrations should be checked. If they are <200 mg/dL and <2.5 meq/L, respectively, then dextrose (adults, 50 mL of 50% dextrose injection; children, 0.25 g/kg of 25% dextrose injection) and potassium chloride (40 meq orally or i.v.) should be administered.[13] Regular insulin is administered as a 1-unit/kg bolus dose, followed by 0.5–1.0 unit/kg/hr adjusted to clinical response. Total insulin requirements for 24 hours of therapy for one adult patient are approximately 1500 units of regular insulin. For emergency stocking purposes, 200 units should be initially available in the emergency department. Because of the need to adjust the insulin dose, long-acting insulin products should be avoided.

The goal of therapy in adults is a systolic blood pressure above 100 mm Hg and a heart rate above 50 beats/min. Potential adverse effects of insulin infusion include hypoglycemia and hypokalemia. Capillary glucose should be monitored every 20 minutes for the first hour. Next, serum potassium and capillary glucose should be checked hourly. Infusions of dextrose should be started with the insulin bolus dose to maintain adequate blood concentrations. Administering 10% dextrose and 0.45% sodium chloride injection at a rate equal to 80% of the maintenance rate is appropriate for most patients. More concentrated dextrose solutions may be used if volume needs to be limited, but this may require central-line administration. Potassium should be readministered if the blood concentration falls below 2.5 meq/L. The insulin infusion may be tapered off once signs of cardiotoxicity begin to resolve.

Conclusion

Poisoning by β-blockers or CCBs usually produces hypotension and bradycardia, which may be refractory to standard resuscitation measures. For cases of β-blocker poisoning where symptomatic bradycardia and hypotension are present, high-dose glucagon is considered the first-line antidote. For cases of CCB poisoning where cardiotoxicity is evident, a combination of calcium and epinephrine should be used initially, reserving HDIDK for refractory cases.

References

1. Watson WA, Litovitz TL, Rodgers GC Jr. et al. 2004 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med.* 2005; 23:589-666.
2. Salhanick S, Shannon M. Management of calcium channel antagonist overdose. *Drug Saf.* 2003; 26:65-79.
3. Kerns W II, Kline J, Ford MD. Beta-blocker and calcium channel blocker toxicity. *Emerg Med Clin North Am.* 1994; 12:365-90.
4. Buscher R, Herrmann V, Insel PA. Human adrenoceptor polymorphisms: evolving recognition of clinical importance. *Trends Pharmacol Sci.* 1999; 20:94-9.
5. Leikin JB, Paloucek FP. Leikin & Paloucek's poisoning & toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp; 2002.
6. Sunaga K, Ogihara M. Effects of calcium channel blockers and hydralazine on plasma glucose levels in streptozotocin-induced diabetic rats in vivo. *Jpn J Pharmacol.* 1990; 52:449-55.
7. Wax PM, Erdman AR, Chyka PA et al. Beta-blocker ingestion: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol.* 2005; 43:131-46.
8. Olson KR, Erdman AR, Woolf AD et al. Calcium channel blocker ingestion: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol.* 2005; 43:797-822.
9. Critchley JA, Ungar A. The management of acute poisoning due to beta-adrenoceptor antagonists. *Med Toxicol Adverse Drug Exp.* 1989; 4:32-45.
10. Reith DM, Dawson AH, Epid D et al. Relative toxicity of beta blockers in overdose. *J Toxicol Clin Toxicol.* 1996; 34:273-8.
11. Love JN, Howell JM, Litovitz TL et al. Acute beta blocker overdose: factors associated with the development of cardiovascular morbidity. *J Toxicol Clin Toxicol.* 2000; 38:275-81.
12. Kline JA, Raymond RM, Leonova ED et al. Insulin improves heart function and metabolism during non-ischemic cardiogenic shock in awake canines. *Cardiovasc Res.* 1997; 34:289-98.

13. Shepherd G, Klein-Schwartz W. High dose insulin therapy for calcium channel blocker overdose. *Ann Pharmacother.* 2005; 39:923-30.

14. Kline JA, Raymond RM, Schroeder JD et al. The diabetogenic effects of acute verapamil poisoning. *Toxicol Appl Pharmacol.* 1997; 145:357-62.

15. Krenzelok E, Vale A. Position statements: gut decontamination. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol.* 1997; 35:695-786.

16. American College of Emergency Physicians. Clinical policy for the initial approach to patients presenting with acute toxic ingestion or dermal or inhalation exposure. *Ann Emerg Med.* 1995; 25:570-85.

17. Dart RC, Stark Y, Fulton B et al. Insufficient stocking of poisoning antidotes in hospital pharmacies. *JAMA.* 1996; 276:1508-10.

18. Dart RC, Goldfrank LR, Chyka PA et al. Combined evidence-based literature analysis and consensus guidelines for stocking of emergency antidotes in the United States. *Ann Emerg Med.* 2000; 36:126-32.

19. Love JN, Leasure JA, Mundt DJ et al. A comparison of amrinone and glucagon therapy for cardiovascular depression associated with propranolol toxicity in a canine model. *J Toxicol Clin Toxicol.* 1992; 30:399-412.

20. Bailey B. Glucagon in beta-blocker and calcium channel blocker overdoses: a systematic review. *J Toxicol Clin Toxicol.* 2003; 41:595-602.

21. Holger JS, Engebretsen KM, Obetz CL et al. A comparison of vasopressin and glucagon in beta-blocker induced toxicity. *Clin Toxicol.* 2006; 44:45-51.

22. Ward DE, Jones B. Glucagon and beta-blocker toxicity. *Br Med J.* 1976; 2:151.

23. Glucagon for injection package insert. Indianapolis, IN: Eli Lilly Co; 2006 Apr.

24. Kerns W II, Schroeder D, Williams C et al. Insulin improves survival in a canine model of acute beta-blocker toxicity. *Ann Emerg Med.* 1997; 29:748-57.

25. Sztajnkrycer MD, Bond GR, Johnson SB et al. Use of vasopressin in a canine model of severe verapamil poisoning: a preliminary descriptive study. *Acad Emerg Med.* 2004; 11:1253-61.

26. Kline JA, Tomaszewski CA, Schroeder JD et al. Insulin is a superior antidote for cardiovascular toxicity induced by verapamil in the anesthetized canine. *J Pharmacol Exp Ther.* 1993; 267:744-50.

27. Kline JA, Leonova E, Williams TC et al. Myocardial metabolism during graded intraportal verapamil infusion in awake dogs. *J Cardiovasc Pharmacol.* 1996; 27:719-26.

28. Kline JA, Leonova E, Raymond RM. Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized canine. *Crit Care Med.* 1995; 23:1251-63.