Chapter 195: Calcium Channel Blockers

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FIGURE 195-1.

INTRODUCTION

Calcium channel blockers (CCBs) are commonly used for the treatment of hypertension and angina pectoris and for ventricular rate control in supraventricular dysrhythmias. Less common uses include prophylactic treatment of migraine headaches, treatment of arterial vasospasm due to Raynaud's disease, esophageal spasm, and pulmonary hypertension.¹ For the last 50 years, CCBs have accounted for more poisoning deaths than any other cardiovascular drug and are the second most common cause of prescription drug poisoning death.

PHARMACOLOGY

Intracellular calcium is the primary stimulus for smooth and cardiac muscle contraction and for impulse formation in sinoatrial pacemaker cells. At therapeutic concentrations, CCBs bind to the subunit of the L-type calcium channel, causing the channel to favor the closed state and thereby decreasing calcium entry during the plateau phase (phase 2) of the transmembrane action potential. At very high concentrations, some CCBs (notably verapamil) may occupy the channel canal and completely block calcium entry. The result is profound smooth muscle relaxation, weakened cardiac contraction, blunted cardiac automaticity, and intracardiac conduction delay.¹ Clinically, these effects produce hypotension and bradycardia. Animal data suggest that verapamil overdose also impairs myocardial carbohydrate intake, which contributes to the negative cardiac inotropy.²

The three main pharmacologic classes of CCBs are phenylalkylamines (verapamil and gallopamil), benzothiazepines (diltiazem), and dihydropyridines (nifedipine, amlodipine, and most newer agents—aranidipine, azelnidipine, barnidipine, benidipine, cilnidipine, clevidipine, efonidipine, felodipine, lacidipine, lercanidipine, manidipine, nicardipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, and pranidipine). All of these drugs relax vascular smooth muscle, reduce pacemaker activity, and decrease cardiac contractility; however, these effects occur at different dose ranges for each drug. In addition, all three classes increase coronary blood flow in a dose-dependent fashion.³ Each group binds a different region of the calcium channel and has different affinities for calcium channels in various tissues. Verapamil is the most
potent negative inotrope of all CCBs, causing at least equal depression of heart contraction and vascular smooth muscle dilatation at any concentration. This combined cardiovascular effect may be one reason that verapamil overdose causes more deaths than all other CCBs combined.

Dihydropyridines bind more selectively to vascular smooth muscle calcium channels than to cardiac calcium channels and therefore relax smooth muscle at concentrations that produce almost no negative inotropy. The differences in the effects of these agents is the reason for preferential use of specific agents in particular clinical situations. For example, verapamil and diltiazem are used to manage hypertension, to achieve rate control in atrial flutter and atrial fibrillation, and to abolish supraventricular reentrant tachycardias. Dihydropyridines are typically used to treat diseases with increased peripheral vascular tone such as hypertension, Prinzmetal’s angina, and vasospasm after subarachnoid hemorrhage.

The original three CCBs—verapamil, nifedipine, and diltiazem—all have relatively short serum half-lives (Table 195-1). Consequently, extended-release formulations have been developed for all of these agents. Because extended-release formulations prolong drug absorption, onset of symptoms may be delayed and toxicity may be prolonged following overdose. Several of the newer dihydropyridines have prolonged duration of action, and therefore are generally not formulated as extended-release products. Because newer formulations are released frequently, it is helpful to contact a regional poison control center for help in determining if a given product ingested in an overdose is formulated as an extended-release preparation.
TABLE 195-1
Oral Calcium Channel Blockers

<table>
<thead>
<tr>
<th></th>
<th>Metabolism</th>
<th>Half-Life (standard preparation, not extended-release)</th>
<th>Maximum Recommended Adult Daily Dose (milligrams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
<td>Liver extensively</td>
<td>2–5 h</td>
<td>480</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Liver extensively</td>
<td>3–5 h</td>
<td>480 for regular-release and 540 for extended-release</td>
</tr>
<tr>
<td>Nifedipine*</td>
<td>Liver</td>
<td>2 h</td>
<td>180 for regular-release and 90 for extended-release</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Liver extensively</td>
<td>30–50 h</td>
<td>10</td>
</tr>
<tr>
<td>Felodipine*</td>
<td>Liver extensively</td>
<td>9 h</td>
<td>10</td>
</tr>
<tr>
<td>Isradipine</td>
<td>Liver</td>
<td>8 h</td>
<td>10</td>
</tr>
<tr>
<td>Nicardipine*</td>
<td>Liver extensively</td>
<td>8–14 h</td>
<td>120</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Liver extensively</td>
<td>Early: 1–2 h, Terminal: 8–9 h</td>
<td>360</td>
</tr>
<tr>
<td>Nisoldipine*</td>
<td>Liver extensively</td>
<td>7–12 h</td>
<td>34</td>
</tr>
</tbody>
</table>

*Also available in extended-release preparations.

**CLINICAL FEATURES**

The most prominent and life-threatening effects are an extension of the therapeutic effects on the cardiovascular system, particularly myocardial depression and peripheral vasodilation. Hypotension is the most common physiologic abnormality after overdose.\(^8,9\) Patients with moderate verapamil or diltiazem...
poisoning often have sinus bradycardia, varying degrees of atrioventricular block, and hypotension. Atrioventricular block occurs more often with verapamil than with diltiazem or nifedipine.\textsuperscript{10} Mild or moderate dihydropyridine overdoses usually cause peripheral vasodilatation with resultant hypotension and reflex tachycardia.\textsuperscript{10} In severe overdose, any of these agents may cause complete heart block, depressed myocardial contractility, and vasodilatation that ultimately results in cardiovascular collapse.

Pulmonary and CNS effects are generally secondary to decreased myocardial function and impaired organ perfusion. Cardiogenic pulmonary edema is sometimes observed in severe overdoses, especially if large volumes of crystalloid are infused during resuscitation. Acute lung injury (noncardiogenic pulmonary edema) has also been reported.\textsuperscript{11,12} Seizures, delirium, and coma have been described and are presumed to be secondary to cerebral hypoperfusion. Alteration in consciousness in the absence of hypotension should not be attributed to CCB toxicity; prompting an evaluation for other causes. GI symptoms, such as nausea and vomiting, are uncommon.\textsuperscript{13}

**DIAGNOSIS**

**POTENTIAL TOXICITY**

Estimations have been made of the lowest doses and mean doses ingested that produce toxicity (\textit{Table 195-2}).\textsuperscript{7} A history of ingestion that is near these doses should be considered potentially toxic, and doses in excess of the lowest toxic dose reported should be expected to produce toxicity.\textsuperscript{7} Adults receiving long-term therapy with CCBs can develop hypotension, bradycardia, or cardiac conduction abnormalities if they ingest twice their regular daily dose.\textsuperscript{14} It is hypothesized that patients receiving long-term CCB therapy have comorbidities and may be taking additional medications, such as other antihypertensives, that render these patients sensitive to the adverse effects of an additional amount of their CCB. Children may be sensitive to CCB toxicity, and deaths have been reported after ingestion of a single tablet: nifedipine, 10 milligrams, in a 14-month-old child\textsuperscript{15} and verapamil, 25 milligrams, in a 7-day-old infant.\textsuperscript{16} Therefore, all pediatric CCB ingestions should be referred for medical attention and observation.
### TABLE 195-2

**Single-Ingestion Toxicity from Calcium Channel Blockers**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Lowest Toxic Dose (adult)</th>
<th>Mean Toxic Dose (adult)</th>
<th>Mean Toxic Dose (pediatric)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
<td>720 milligrams</td>
<td>2708 milligrams</td>
<td>16 milligrams/kg</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>420 milligrams</td>
<td>2167 milligrams</td>
<td>5.7 milligrams/kg</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>50 milligrams</td>
<td>245 milligrams</td>
<td>8.0 milligrams/kg</td>
</tr>
</tbody>
</table>

Extended-release preparations are increasingly used for patient convenience and enhancing patient adherence to the drug regimen. These preparations complicate the management of overdosed patients by delaying the onset of toxicity. Therefore, it is important to determine the exact formulation of the ingested agent to guide management decisions. If the history cannot identify the exact formulation, the clinician should assume it is extended-release and modify treatment in a conservative way. In a review of CCB overdose cases, 52% of patients ingested extended-release preparations, and of these, 8% had no evidence of toxicity on initial evaluation but developed delayed toxicity 6 hours or later after ingestion. In addition to the exact formulation ingested, other important aspects in the history are the time of ingestion and the possibility of co-ingestants that may contribute to toxicity.

ECG findings include sinus bradycardia, varying degrees of atrioventricular block, and slowing of intraventricular conduction. Reflex tachycardia is commonly seen with low to moderate toxic ingestions of dihydropyridines, whereas junctional rhythms and ventricular escape rhythms are frequently noted in severe overdoses with verapamil or diltiazem.

Laboratory testing is done to assess the overall metabolic state of the patient; none is crucial in the acute management of CCB toxicity. Hyperglycemia is often noted after CCB ingestion, which differentiates it from β-blocker ingestion, which is typically euglycemic or sometimes hypoglycemic. CCBs inhibit calcium-mediated insulin secretion from the beta islet cells in the pancreas, impeding the use of carbohydrates, and also increase insulin resistance by unclear mechanisms.

Systemic hypoperfusion may cause a lactate acidosis with an elevated anion gap and low serum bicarbonate level. Hypokalemia may be observed in severe overdoses. Serum calcium levels are usually normal. Ionized serum calcium levels may be followed during treatment with intravenous calcium preparations, but the optimum serum calcium level for patients with severe CCB poisoning is unknown. CCB serum concentrations are not routinely available and are not used in management. Screen blood and urine for other potential toxins after suicidal overdose.

**DIFFERENTIAL DIAGNOSIS**
A few conditions and other drug toxicities can produce bradycardia, atrioventricular block, and hypotension (Table 195-3). Hypothermia should be detected during vital sign assessment. Myocardial infarction may be evident on the initial or subsequent ECG. Suspect hyperkalemia in patients with renal failure.

### Table 195-3

**Differential Diagnosis of Bradycardia, Atrioventricular Block, and Hypotension**

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Cardiac glycoside toxicity</td>
</tr>
<tr>
<td>β-Blocker toxicity</td>
</tr>
<tr>
<td>Antiarrhythmic drugs class IA and IC toxicity</td>
</tr>
<tr>
<td>Central α-adrenergic agonist (clonidine or tetrahydrozoline) toxicity</td>
</tr>
</tbody>
</table>

It may be difficult to distinguish CCB toxicity from cardiac glycoside toxicity; patients may be taking these drugs for the same indications and at the same time (see chapter 193, "Digitalis Glycosides"). In general, patients with chronic digoxin poisoning have greater ventricular excitation, including rate and ectopy, than patients with CCB toxicity. In acute overdose, digoxin toxicity may be distinguished by hyperkalemia. However, because the main manifestation of acute cardiac glycoside poisoning is heart block and bradycardia, bedside differentiation may be difficult.

Toxicity from β-adrenergic antagonists may be clinically indistinguishable from CCB toxicity (see chapter 194, "Beta-Blockers"). In general, β-blocker toxicity is not as severe, and patients tend to have low to normal glucose and normal to elevated serum potassium levels. However, these findings are not consistent enough to have diagnostic value. Fortunately, the treatment for these two poisonings is similar, with calcium, adrenergic agonists, glucagon, insulin, and pacing considered useful therapy for both.¹⁹

### TREATMENT

Institute cardiopulmonary monitoring and obtain an ECG (Table 195-4). Evaluate patients with altered mental status for hypoglycemia and opioid toxicity. Decreased level of consciousness following CCB ingestion is a result of cerebral hypoperfusion or co-ingestion. Administer oral activated charcoal if within 1 hour of ingestion or in cases of extended-release preparations, as long as there are no contraindications such as altered mental status or vomiting. Provide early airway management in patients with mental status change or hemodynamic instability. Endotracheal intubation may minimize the risk of aspiration associated with GI decontamination. Vomiting is not only associated with decontamination, but glucagon administration also often precipitates vomiting. Finally, early airway management allows the physician to concentrate on treating the often-precipitous cardiovascular collapse without having to perform a "crash airway" procedure.
### General Treatment for Calcium Channel Blocker Toxicity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td>Initiate cardiopulmonary monitoring and obtain ECG</td>
</tr>
<tr>
<td>Point-of-care glucose</td>
<td>If altered mental status, and also in anticipation of insulin therapy</td>
</tr>
<tr>
<td>Naloxone</td>
<td>If signs of opioid toxicity</td>
</tr>
<tr>
<td>Single-dose activated charcoal</td>
<td>If ingestion within 1 h and no vomiting or altered mental status; for children even if one tablet ingested</td>
</tr>
<tr>
<td>Multidose activated charcoal</td>
<td>For extended-release preparations</td>
</tr>
<tr>
<td>IV crystalloid for hypotension</td>
<td>Overaggressive treatment can cause pulmonary edema</td>
</tr>
<tr>
<td>Endotracheal intubation</td>
<td>Early intubation if altered mental status or hemodynamic instability</td>
</tr>
</tbody>
</table>

*See Figure 195-1 for treatment of severe toxicity.*

Following airway management, provide cardiovascular stabilization. The goal of treating bradycardia is to increase end-organ perfusion rather than restoring a specific heart rate; some patients with heart rates in the 30 to 40 beats/min range can maintain adequate blood pressure and perfusion, and therefore require only monitoring rather than a specific intervention. Conversely, patients may respond to cardiac pacing with an increase in heart rate to 90 to 100 beats/min without improvement in blood pressure or perfusion and require additional therapy to improve inotropy.

Therapies to increase heart rate include medications and cardiac pacing. Atropine alone is rarely effective for CCB-induced bradycardia, but administration is commonly recommended. Calcium salts may improve both heart rate and blood pressure, but the response is variable. Transcutaneous and transvenous pacing may be attempted and are often successful in restoring an acceptable rate but may have little to no effect in correcting hypotension. However, pacing is indicated for hypotensive patients with severe bradycardia (heart rate <30 beats/min).
Administer IV crystalloid for hypotension, but overaggressive fluid administration may produce or worsen pulmonary edema. Persistent hypotension after treatment of bradycardia, administration of calcium salts, and infusion of crystalloid should be treated with adrenergic vasopressors. Recommendations for additional therapies are based on animal data and human case reports or series, with the caution that case reports often document the use of multiple therapies simultaneously.19,20,21

GI DECONTAMINATION

CCBs bind well to charcoal, and activated charcoal should be given to adults following any potentially significant ingestion if within an hour of ingestion.22 Give activated charcoal after accidental ingestion of verapamil in children, because life-threatening toxicity has been reported following ingestion of a single tablet. Multiple-dose activated charcoal may be considered in the setting of ingestion of an extended-release preparation.

Ipecac syrup to induce emesis is not recommended.22 Routine gastric lavage has no proven benefit in CCB ingestions. However, because large CCB overdoses are often life-threatening and may not respond to therapy, some toxicologists recommend gastric lavage for a patient who presents within 60 minutes of ingesting an amount significantly in excess of toxicity (Table 195-2) or for any patient who requires intubation after CCB ingestion. However, evidence for improvement in outcomes after gastric lavage is lacking.

Whole-bowel irrigation is frequently advocated for ingestion of extended-release CCBs.23 Case reports note that a large amount of medication may be recovered. Given the potential for severe toxicity, consider whole-bowel irrigation for patients with large ingestions of extended-release products, although complications from whole-bowel irrigation may contribute to hemodynamic instability.24

CALCIUM SALTS

Exogenous calcium increases the extracellular calcium concentration and increases the transcellular gradient, driving calcium intracellularly through unblocked calcium channels. Administration of calcium salts has improved blood pressure in animal models and in human case reports of CCB toxicity.23,25,26,27,28 However, the effect of calcium salts on the heart rate of patients with CCB toxicity is variable.

Calcium chloride is preferred to calcium gluconate because it provides triple the amount of calcium on a weight-to-weight basis. However, calcium chloride is best administered through a central venous line, because peripheral extravasation can result in severe soft tissue necrosis. Calcium chloride is usually given as a 1-gram (10 mL of 10% solution) IV bolus over 5 minutes in adults (pediatric dose is 15 milligrams/kg or 0.15 mL/kg of the 10% solution). Calcium gluconate can be given at three times this amount. The effects of calcium administration may be transient, and repeat dosing up to every 10 to 20 minutes is commonly required. Alternatively, a continuous infusion of calcium chloride 2 to 6 grams/h may also be used in adults (pediatric dose is 10 to 40 milligrams/kg per hour). Serum calcium levels should be measured every 1 to 2 hours, and a calcium concentration goal of approximately 1.5 to 2 times normal should be achieved.
However, for patients who do not respond to other therapies, it is reasonable to continue calcium administration even when serum calcium levels are considerably elevated.

An acceptable level for hypercalcemia has not been defined. Published case reports of CCB poisoning describe survival following administration of 30 grams of calcium chloride over 12 hours resulting in a serum calcium level of 23 milligrams/dL (5.94 mmol/L)\(^23\) and death from iatrogenic hypercalcemia with a serum calcium level of 32.3 milligrams/dL (8.07 mmol/L).\(^29\) A safe but effective dose of calcium salts to use in the treatment of CCB toxicity is unclear. If repeat dosing or continuous infusions are used, hypercalcemia and/or hypophosphatemia can occur. Although monitoring of serum calcium and phosphorus concentrations during repeated or prolonged calcium therapy is recommended, it is unclear if such electrolyte abnormalities have clinical consequence or should be treated.

**ADRENERGIC AGENTS**

Patients who do not respond to calcium administration or who require repeated doses are usually given adrenergic agonists (Figure 195-1).\(^{19,20,21}\) Although animal data suggest that other therapies may lead to better metabolic function and better survival in severe poisonings, adrenergic agonists have several advantages. Physicians and nurses are familiar with these agents, therapy can be initiated quickly, and most patients respond favorably. This prevents a period of nontreatment while the supplies for more esoteric therapies are gathered. Given the availability of adrenergic agonists and the familiarity of clinicians with their use, adrenergic agonists are the first line of treatment for persistent hypotension following CCB ingestion.

**FIGURE 195-1.**

Treatment algorithm for severe calcium channel blocker toxicity, for stepwise or simultaneous therapy.

*Calcium chloride provides three times as much elemental calcium as calcium gluconate; monitor for ventricular arrhythmias in concomitant digoxin toxicity. D10W = 10% dextrose in water.
No single adrenergic vasopressor is consistently effective. A response may occur with dopamine, epinephrine, norepinephrine, vasopressin, dobutamine, and isoproterenol.\(^{30,31,32}\) Patients with decreased contractility and peripheral vasodilatation, especially in the face of relative bradycardia, may benefit from an agent with both \(\alpha\) - and \(\beta\) -agonist effects, such as epinephrine or norepinephrine (Figure 195-1). Phosphodiesterase inhibitors such as amrinone, milrinone, and enoximone have also been reported to improve blood pressure in animal studies and human case reports.\(^{33,34,35,36}\)

When standard doses are inadequate, it is reasonable to use high doses or multiple agents titrated to achieve a systolic blood pressure >90 mm Hg (>12 kPa), although there is the risk of ischemic complications.\(^{32}\) Alternatively, another approach, such as high-dose insulin, glucagon, or lipid-emulsion, can be considered.

**HIGH-DOSE INSULIN THERAPY**

High-dose insulin therapy, also known as hyperinsulinemia-euglycemia therapy, is a promising treatment for the myocardial suppression associated with CCB poisoning.\(^{37-46}\) Potential mechanisms of action include positive inotropic effects of insulin, increased calcium entry, and improved myocardial use of carbohydrates as an energy source.\(^{18}\) Insulin increases intracellular transport of glucose into cardiac and skeletal muscle.
and has inotropic properties.\(^{39}\) There are no clinical trials comparing high-dose insulin therapy directly to other treatments, but multiple human case reports show that high-dose insulin therapy improves perfusion in CCB poisoning unresponsive to other therapies, with a therapeutic response noted within 15 to 30 minutes.\(^{39,40,41,42,43,44,45}\) The main adverse effect is potential hypoglycemia, which is easily detected with point-of-care glucose testing and treated with dextrose. When to institute therapy is unclear; some toxicologists recommend high-dose insulin therapy if the patient is refractory to standard doses of vasopressors, and others advocate it as first-line therapy. **Given benefit seen in animal models and clinical reports, high-dose insulin therapy should be considered if the patient does not respond to vasopressor therapy (Figure 195-1).**

Doses of insulin used for high-dose insulin therapy are greater than that for diabetic treatment (Table 195-5).\(^{46}\) An initial insulin bolus is followed by a continuous infusion along with a dextrose infusion to prevent hypoglycemia (Table 195-5). The hemodynamic response to high-dose insulin therapy is usually seen in 15 to 45 minutes, so the infusion rate may be increased if no clinical improvement is seen within that time. Monitor the serum glucose concentrations and adjust the dextrose infusion to maintain an acceptable glucose range. Monitor serum potassium and replace as needed. Maintain the high-dose insulin therapy infusion until toxicity has resolved; durations of 9 to 49 hours may be necessary. The insulin infusion may either be weaned gradually or stopped abruptly and reinstituted if toxicity recurs. Dextrose supplementation may be required for up to 24 hours after the infusion is discontinued due to persistent elevated insulin concentrations.

**TABLE 195-5**

**Protocol for High-Dose Insulin Therapy in Severe Calcium Channel Blocker Overdose**

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

Administer regular insulin 1 unit/kg IV bolus.

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

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

Monitor serum glucose every 15–20 min.

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

Once dextrose infusion rates have been stable for 60 min, glucose monitoring may be decreased to hourly. Monitor serum potassium level and start IV potassium infusion if serum potassium level is <2.8 mEq/L (<2.8 mmol/L).

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

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

Glucagon, a hormone synthesized by the pancreas, is the therapy of choice for β-adrenergic blocker poisoning because of its ability to bypass the β-adrenergic receptor and stimulate cardiac activity (see chapter 194). In CCB poisoning, the inhibition is downstream from glucagon's binding site, and therefore, glucagon theoretically offers no advantage over other agents. Nevertheless, glucagon administration improves blood pressure in animal models, and several case reports have also noted improvement in hemodynamics after glucagon therapy. However, failure to respond has also been reported.

The recommended glucagon dose is an IV bolus of 3 to 10 milligrams in adults and 0.03 to 0.05 milligram/kg in children (Figure 195-1). A response is usually seen within 15 minutes. If there is no response, the bolus dose may be repeated. If there is hemodynamic improvement, a maintenance infusion should be initiated at 1 to 5 milligrams/kg per hour in adults and 0.02 to 0.07 milligram/kg per hour in children.

The main adverse effects of glucagon are vomiting and hyperglycemia. Therefore, endotracheal intubation should be strongly considered prior to initiation of glucagon therapy in a patient with altered mental status. Also, an antiemetic such as ondansetron may be empirically administered. Because of the large amounts of glucagon required, hospital supplies of the drug are often rapidly depleted, and it may be necessary to contact other institutions for additional drug.

INTRAVENOUS LIPID EMULSION THERAPY

Lipid emulsion therapy was first described in the management of local anesthetic toxicity. Lipid emulsions appear to create a pharmacologic sink for fat-soluble drugs. Therapy may also provide fatty acid substrate for cardiac energy supply and improve myocyte function by increasing intracellular calcium levels. Lipid emulsion therapy prolongs survival in an animal model of verapamil poisoning, and several case reports also describe benefit in CCB ingestions unresponsive to standard therapy. There are many different commercial lipid emulsion preparations, with the major components typically being soybean oil, egg yolk phospholipids, and glycerin. Consult with the poison control center or pharmacist when considering lipid emulsion therapy.

The recommended dose is a 20% lipid emulsion given as a 1.5 mL/kg bolus over 2 to 3 minutes, followed by an 0.25 mL/kg per minute infusion. If the blood pressure remains low, an additional 1.5 mL/kg bolus may be repeated followed by an increase in the infusion rate to 0.5 mL/kg per minute. The recommended upper limit for lipid emulsion infusion is about 10 mL/kg over the initial 30 minutes. If the patient's hemodynamic stability is dependent on continued lipid infusion, the treatment may be continued. Case reports suggest that if sudden cardiac arrest occurs in the setting of overdose, a bolus can be given in the hope of restoring spontaneous circulation. In addition to interference with laboratory parameters, there are rare adverse effects such as hypertriglyceridemia, hypoxemia (with high doses), and hyponatremia.

EXTRACORPOREAL CIRCULATORY SUPPORT
Patients who do not respond to the aforementioned therapies may benefit from circulatory support measures, such as the placement of intra-aortic balloon pumps, the use of left ventricular assist devices, and even extracorporeal circulatory support, which may provide adequate blood pressure to allow clearance of the drug and resolution of symptoms.\textsuperscript{21,56,57} Hemodialysis or hemoperfusion is not beneficial in the treatment of CCB overdoses.\textsuperscript{58}

**DISPOSITION AND FOLLOW-UP**

In general, patients usually manifest toxicity within 6 hours of ingestion of non–extended-release products. Therefore, those who are asymptomatic and who have normal vital signs after a 6-hour observation period can be discharged after appropriate psychiatric evaluation.\textsuperscript{22} Toxicity may be delayed for up to 12 hours after ingestion of extended-release products.\textsuperscript{6,7} As a rule, patients who ingest potentially toxic amounts of extended-release products should be monitored for 12 to 24 hours. Contact the regional poison control center for assistance with management.

**REFERENCES**


[PubMed: 8517581]

[PubMed: 10802424]

[PubMed: 14514004]

[PubMed: 18570172]

[PubMed: 16436797]

[PubMed: 19282085]

[PubMed: 21320947]

[PubMed: 21327839]

[PubMed: 2669572]

[PubMed: 10628632]

[PubMed: 18592256]