61: Calcium Channel Blockers

David H. Jang; Francis Jerome DeRoos

HISTORY AND EPIDEMIOLOGY

In 1964, Albretch Fleckenstein described an inhibitory action of verapamil and prenylamine on excitation-contraction coupling that was similar to calcium depletion. By the late 1970s, the clinical use of calcium channel blockers (CCBs) was widely accepted for variety of cardiovascular indications, including hypertension, dysrhythmias, and angina. Later indications, including Raynaud phenomenon, migraine headaches, and subarachnoid hemorrhage, have been adopted. There are currently 10 individual CCBs marketed in the United States that are available as immediate or sustained-release formulations and as combination products with other antihypertensives.

The cardiovascular drug class is one of the leading classes of drugs associated with poisoning fatality. Over the past 5 years of available data, there were more than 12 million poisonings with more than 7000 poisoning-related deaths reported to the American Association of Poison Control Centers Toxic Exposure Surveillance System. Cardiovascular drugs were involved in more than 474,000 of the reported poisonings and accounted for nearly 18% of the overall poisoning fatalities. Within this class, CCBs were the most common cardiovascular drugs involved in poisoning fatalities. CCBs accounted for more than 50,000 cases reported over the past 5 years, with 289 cases resulting in major effects and more than 100 deaths (Chap. 136).

PHARMACOLOGY

Calcium (Ca\(^{2+}\)) ion channels exist as either voltage-dependent or ligand-gated channels. There are many types of voltage-gated Ca\(^{2+}\) channels that include P, N, R, T, Q, and L-type channels (Table 61–1). Ligand-gated Ca\(^{2+}\) channels include IP\(_3\) and ryanodine receptors, which are found intracellularly and play a critical role in cell signaling. Voltage-gated Ca\(^{2+}\) channels are located throughout the body in the heart, nervous system, pancreas, and muscles. The structure of voltage-dependent Ca\(^{2+}\) channels is composed of several components that include α, β, δ, and the ion-conducting α\(_1\)-subunit. The α\(_1\)-subunit is the most important component of the Ca\(^{2+}\) channel as it contains the actual pore through which Ca\(^{2+}\) ions pass and also serves as the binding site of all CCBs. The other subunits such as β and δ act to modulate the function of the α\(_1\)-subunit.

| TABLE 61–1. Voltage-Sensitive Calcium Channel Subtypes |
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The primary action of all CCBs available in the United States is antagonism of the L-type or "long-acting" voltage-gated Ca\textsuperscript{2+} channels. CCBs are often classified into three groups based on their chemical structure (Table 61–2). A fourth class, the tetraols, were developed and included mibefradil, but this drug was withdrawn because of significant adverse drug interactions. Each group binds a slightly different region of the \( \alpha_1 \) subunit of the Ca\textsuperscript{2+} channel and thus has different affinities for the various L-type Ca\textsuperscript{2+} channels, both in the myocardium and the vascular smooth muscle. It is often more logical to classify them as nondihydropyridine versus dihydropyridine CCBs. The former includes verapamil and diltiazem, whereas the latter includes many drugs, the chemical names of which all currently end in –pine, such as nifedipine and amlodipine. Verapamil and diltiazem have inhibitory effects on both the sinoatrial (SA) and atrioventricular (AV) nodal tissue and thus are commonly used for the treatment of hypertension, to reduce myocardial oxygen demand, and also to achieve rate control in a variety of tachydysrhythmias. In contrast, the dihydropyridines have very little direct effect on the myocardium at therapeutic doses and act primarily as peripheral vasodilators. They are therefore commonly used as vasodilators for conditions with increased vascular tone such as hypertension, migraine headaches, and postintracranial hemorrhage–associated vasospasm.

TABLE 61–2. Classification of Calcium Channel Blockers Available in the United States

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Experimental studies suggest an additional vasodilatory effect of some CCBs due to stimulation of nitric oxide release. Amlodipine and other dihydropyridine CCBs release nitric oxide in a dose-dependent fashion from canine coronary microvessels. Although the exact mechanism is uncertain, it is hypothesized that this amlodipine-induced nitric oxide production results from increasing endothelial nitric oxide synthase activity through phosphorylation of this enzyme. Bradykinin B\textsubscript{2} receptors may also be contributory.

PHARMACOKINETICS AND TOXICOKINETICS

Absorption.
All CCBs are well absorbed orally, but many exhibit low bioavailability due to extensive hepatic first-pass metabolism. Once the CCBs reach the liver, they undergo hepatic oxidative metabolism predominantly via the CYP3A4 subgroup of the cytochrome P450 (CYP) enzyme system.

Distribution.
All CCBs are highly protein bound. Volumes of distribution are large for amlodipine (21 L/kg), verapamil (5.5 L/kg), and diltiazem (5.3 L/kg), and somewhat smaller for nifedipine (0.8 L/kg).

Metabolism.
Norverapamil, formed by N-demethylation of verapamil, is the only active metabolite and retains 20% of the activity of the parent compound. Diltiazem is predominantly deacetylated into minimally active deacetyldiltiazem, which is then eliminated via the biliary tract. After repeated doses, as well as following overdose, these hepatic enzymes become saturated, reducing the potential of the first-pass effect and increasing the quantity of active drug absorbed systemically. Saturation of metabolism as well as the modified release dosage form contribute to the prolongation of the apparent half-lives reported following overdose of various CCBs.

Excretion.
The majority of CCBs undergo a significant amount of renal excretion after metabolism with a small percentage eliminated in the urine unchanged. This varies depending on the CCB. For example, amlodipine undergoes 60% renal excretion after metabolism to inactive metabolites compared with 70% for verapamil (3.4% as unchanged drug) and 90% for nifedipine as inactive metabolites.

One interesting aspect of the pharmacology of CCBs is their potential for drug–drug interactions. CYP3A4, which metabolizes most CCBs, is also responsible for the initial oxidation of numerous other xenobiotics. Verapamil and diltiazem specifically compete for this enzyme and can decrease the clearance of many drugs including carbamazepine, cisapride, quinidine, various β-hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, cyclosporine, tacrolimus, most human immunodeficiency virus–protease inhibitors, and theophylline (Chap. 13, Appendix). In June 1998, mibebradil, a structurally unique CCB, was voluntarily withdrawn following several reports of serious adverse drug interactions caused in part by its potent inhibition of CYP3A4. Other inhibitors of CYP3A4, such as cimetidine, fluoxetine, some antifungals, macrolide antibiotics, and even the flavonoids in grapefruit juice, raise serum concentrations of several CCBs and may result in toxicity.

In addition to affecting CYP3A4, verapamil and diltiazem also inhibit P-glycoprotein–mediated drug transport into peripheral tissue—an inhibition that results in elevated serum concentrations of xenobiotics such as cyclosporine and digoxin that use this transport system (Chap. 13, Appendix). Unlike diltiazem and verapamil, nifedipine and the other dihydropyridines do not appear to affect the clearance of other xenobiotics via CYP3A4 or P-glycoprotein–mediated transport. Similarly, inhibition of P-glycoprotein–mediated transport by certain xenobiotics such as statins result in increased oral bioavailability of CCBs, which may require enhanced monitoring of appropriate patients.

**PHYSIOLOGY AND PATHOPHYSIOLOGY**

Ca²⁺ plays an essential role in many cellular processes throughout the body as many types of cells depend on the maintenance of a Ca²⁺-concentration gradient across cell membranes in order to function. The extracellular Ca²⁺ concentration is approximately 10,000 times greater than the intracellular concentration. This concentration gradient is important for contraction and relaxation of muscle cells (Fig. 61-1). Ca²⁺-channels located on the cell membrane play a key role to maintain this concentration gradient within muscle cells.
FIGURE 61–1.
Normal contraction of myocardial cells. The L-type voltage sensitive calcium channels (Ca\textsubscript{v}-L) open to allow calcium ion influx during myocyte depolarization. This causes the concentration-dependent release of more calcium ions from the ryanodine receptor (RyR) of the sarcoplasmic reticulum (SR).

Ca\textsuperscript{2+} is driven down a large electrical and concentration gradient through L-type Ca\textsuperscript{2+} channels located in all muscle cell types (cardiac, striated, and smooth). This influx of Ca\textsuperscript{2+} is critical for the function of both cardiac and smooth muscle cells; however, skeletal muscle depends primarily on intracellular Ca\textsuperscript{2+} stores for excitation-contraction coupling and not the intracellular influx of Ca\textsuperscript{2+}. In smooth muscle, the rapid influx of Ca\textsuperscript{2+} binds calmodulin, and the resulting complex stimulates myosin light chain kinase activity. The myosin light chain kinase phosphorylates, and thus activates, myosin, which subsequently binds actin, causing a contraction.

Ca\textsuperscript{2+} plays a similarly important role in myocardial contractility. In myocardial cells, Ca\textsuperscript{2+} influx is slower relative to the initial sodium influx that initiates cellular depolarization, and prolongs this depolarization, creating the plateau phase (phase 2) of the action potential (Chap. 16). The Ca\textsuperscript{2+} subsequently stimulates a receptor operated Ca\textsuperscript{2+} channel on the sarcoplasmic reticulum, known as the ryanodine receptor, releasing Ca\textsuperscript{2+} from the vast stores of the sarcoplasmic reticulum into the cytosol. This is often termed Ca\textsuperscript{2+}-dependent Ca\textsuperscript{2+} release. Ca\textsuperscript{2+} then binds troponin C, which causes a conformational change that displaces troponin and tropomyosin from actin, allowing actin and myosin to bind, resulting in a contraction.

Ca\textsuperscript{2+} influx also plays an important role in the spontaneous depolarization (phase 4) of the action potential in the sinoatrial (SA) node. This Ca\textsuperscript{2+} influx also allows normal propagation of electrical impulses via the specialized myocardial conduction tissues, particularly the atrioventricular (AV) node. After opening, the rates of recovery of these slow Ca\textsuperscript{2+} channels, in both the SA and AV nodal tissue, determine the rate of conduction.

The nondihydropyridine CCBs such as verapamil and diltiazem have the greatest affinity for the myocardium, with verapamil considered the most potent. In addition, not only do verapamil and, to a lesser extent, diltiazem impede Ca\textsuperscript{2+} influx and channel recovery in the myocardium, but their blockade is potentiated as the frequency of channel opening increases. Therefore, in a frequently contracting tissue, such as the myocardium, the blockade of verapamil and diltiazem would be augmented.

At therapeutic doses, the dihydropyridine CCBs such as nifedipine have little effect at the myocardium and have most of their effect at the peripheral vascular tissue; thus, they have the most potent vasodilatory effects when compared to the nondihydropyridine CCBs. Dihydropyridines bind the Ca\textsuperscript{2+} channel best at less-negative membrane potentials. Because the resting potential for myocardial muscle (–90 mV) is lower than that of vascular smooth muscle (–70 mV), dihydropyridines bind preferentially in the peripheral vascular tissue.
The toxicity of CCBs in poisoning is largely an extension of their therapeutic effects within the cardiovascular system. Inhibition of the L-type Ca\(^{2+}\) channels within both the myocardium and peripheral vascular smooth muscle results in a combination of decreased inotropy, heart rate, and arterial vasodilation. Because dihydropyridines have limited myocardial effect at therapeutic concentrations, the baroreceptor reflex remains intact and a slight increase in heart rate and cardiac output may occur. Isradipine is the only dihydropyridine whose inhibitory effect on the SA node is significant enough to blunt any reflex tachycardia. CCB poisoning can also result in blockade of L-type Ca\(^{2+}\) channels located in the pancreas. This results in decreased insulin release resulting in hyperglycemia.

**CLINICAL MANIFESTATIONS**

The hallmark of the CCB poisoning is hypotension and bradycardia, which results from depression of myocardial contraction and peripheral vasodilation.\(^{44}\) Myocardial conduction may also be impaired, producing AV conduction abnormalities, idioventricular rhythms, and complete heart block. Junctional escape rhythms frequently occur in patients with significant poisonings.\(^{13,26,28,75,107}\) The negative inotropic effects may be so profound, particularly with verapamil, that ventricular contraction may be completely ablated.\(^{5,10,11,19}\)

Hypotension is the most common and life-threatening finding in an acute CCB poisoning, typically caused by a combination of decreased inotropy, bradycardia, and peripheral vasodilation.\(^{23}\) Patients may also present asymptomatic early following ingestion and subsequently deteriorate rapidly to severe cardiogenic shock.\(^{5,10,44}\) The associated clinical findings reflect the degree of cardiovascular compromise and hypoperfusion, particularly to the central nervous system. Early symptoms include fatigue, dizziness, and lightheadedness. Alteration in mentation in the absence of hypotension should prompt the clinician to consider other causes and ingestions. Severely poisoned patients may manifest syncope, altered mental status, coma, and sudden death.\(^{11,44}\) Gastrointestinal (GI) effects, such as nausea and vomiting, are not a typical feature of CCB poisoning. Acute respiratory distress syndrome (ARDS) may also occur with severe CCB poisoning. This may be due to precapillary vasodilation with a subsequent increase in transcapillary pressure. The elevated pressure gradient results in increased capillary transudates and possible interstitial edema.\(^{26,43}\)

In mild to moderate overdose of dihydropyridine CCBs, the predominantly peripheral effect may induce a reflex tachycardia. However, severe poisoning with any CCBs can result in loss of receptor selectivity resulting in bradycardia. A prospective poison center study noted AV nodal block to occur more frequently with verapamil poisoning.\(^{29}\) While deaths are attributed mainly to the nondihydropyridines, a significant number of dihydropyridine-related deaths are also reported.\(^{58,91}\) This may reflect the wider use of this latter class of CCBs.

There are several factors that ultimately determine CCB toxicity. These include medication formulation, dose, and coingestion with other cardioactive medications such as β-adrenergic antagonists, underlying comorbidities, and age. Elderly patients and those with underlying
cardiovascular disease such as congestive heart failure are more sensitive to CCBs. Even at therapeutic doses, these patients are more susceptible to the cardioactive effects of these medications and may develop symptomatic hypotension.

Pediatric cases of CCB are commonly from medication errors or unintentional ingestions of pills found at home. Children with CCB poisoning may develop nonspecific clinical effects such as lethargy, emesis, and confusion. While CCB exposure in children is uncommon, there are reported cases of severe poisoning and death.

**DIAGNOSTIC TESTING**

Any patients with suspected CCB poisoning should be considered at risk for cardiovascular collapse and be evaluated with a 12 lead electrocardiogram (ECG), followed by continuous cardiac and hemodynamic monitoring. A chest radiograph, pulse oximetry, and serum chemistry should also be obtained if any degree of hypoperfusion is suspected. Assessment of electrolytes, including magnesium, and a serum digoxin concentration may be useful in a bradycardic patient with unknown exposure history, although a careful history, if possible, may narrow down the etiology. Cardioactive steroids should be a consideration in the setting of hyperkalemia with normal kidney function. Assays for CCB serum concentrations are not routinely available and therefore have no role in the management of patients poisoned with CCBs.

Hyperglycemia is considered a prognostic sign in cases of severe CCB poisoning. The release of insulin from the β-islet cells in the pancreas is dependent on Ca²⁺ influx through the L-type Ca²⁺ channel. CCB poisoning reduces insulin release with resultant hyperglycemia. An additional mechanism may be dysregulation of the insulin dependent phosphatidylinositol 3-kinase pathway. It should be noted that hyperglycemia might also be the result of diabetes or the administration of glucagon for suspected β-adrenergic antagonist poisoning.

A retrospective study suggests that serum glucose concentration correlate with the severity of CCB poisoning. The initial mean serum glucose concentration was 188 mg/dL in patients who met a composite end point of requiring vasopressors, a pacemaker, or death, versus 122 mg/dL in those not requiring intervention. Peak serum glucose concentrations were also significantly different. This finding may become a useful early sign of severity and an indicator for when to initiate hyperinsulinemia-euglycemia therapy.

**MANAGEMENT**

**General Approach**

All patients with suspected CCB poisoning should undergo prompt evaluation even when the initial vital signs are normal. This urgency is due to the potential to initiate early GI decontamination and pharmacologic therapies before patients manifest severe poisoning. This is particularly important with ingestions involving sustained-release formulations. Intravenous access should be obtained and initial treatment should be directed toward aggressive GI decontamination of patients with large
recent ingestions. All patients who become hypotensive should receive a fluid bolus of 10 to 20 mL/kg of crystalloid which should be repeated as needed. Caution is required, as aggressive fluid resuscitation should not be given to patients with congestive heart failure, evidence of ARDS, or chronic kidney disease (CKD).

Pharmacotherapy should focus on maintenance or improvement of both cardiac output and peripheral vascular tone. Although atropine, calcium, insulin, glucagon, isoproterenol, dopamine, epinephrine, norepinephrine, and phosphodiesterase inhibitors have been used with reported success in CCB-poisoned patients, no single intervention has consistently demonstrated efficacy. It is also important to be aware that certain treatment such as vasopressors may be detrimental with long-term use, so these should be avoided when there are more effective and safer treatment options.

Although therapy for hypotension and bradycardia should begin with crystalloids and atropine, most critically poisoned patients will not respond to these initial efforts and will require further pharmacotherapy. While it would be ideal to initiate each therapy individually and monitor the patient’s hemodynamic response, in the most critically ill patients, multiple therapies should be administered simultaneously. A reasonable treatment sequence based on existing data and clinical experience should initially consist of isotonic fluids, atropine, glucagon, and calcium. If the patient does not respond to these initial treatments, hyperinsulinemia-euglycemic therapy should be initiated. In cases of refractory shock or in cardiac arrest, the use of 20% intravenous fat emulsion should be considered. The use of vasopressors such as norepinephrine or dopamine can result in tissue ischemia with long-term use and thus should be avoided. Phosphodiesterase inhibitors such as inamrinone, milrinone, and enoximone have been used to treat CCB poisoning.\textsuperscript{54,59,103} These xenobiotics inhibit the breakdown of cAMP by phosphodiesterase, thereby increasing intracellular cAMP concentrations, resulting in increased cardiac output. Despite some reported success, phosphodiesterase inhibitors are not readily available, and there are other xenobiotics that are more effective and easier to utilize (Fig. 61–2).

**FIGURE 61–2.** Myocardial toxicity of calcium channel blockers and use of antidotal therapies. Calcium channel blockers reduce calcium ion influx through the L-type calcium channel (Ca\(_{\text{v}-L}\)) and thus reduce contractility. The entry of calcium via voltage-sensitive channels (Ca\(_{\text{v}-L}\)) initiates a cascade of events that result in actin-myosin coupling and contractions. Mechanisms to increase intracellular calcium include recruitment of new or dormant calcium channels by increasing cyclic adenosine monophosphate (cAMP) by stimulating its formation by adenylyl cyclase (AC) with glucagon (see text). The use of calcium salts may increase the calcium concentration gradient across the cellular membrane to further its influx and improve contractility. The mechanism by which insulin therapy enhances inotropy is not fully known. 5MP = 5’-monophosphate; PDEI = phosphodiesterase inhibitor; PKA = protein kinase A; RyR = ryanodine receptor; SR = sarcoplasmic reticulum.
**Gastrointestinal Decontamination**

Because CCB poisoning is a leading cause of poisoning fatality, attempts to prevent absorption from the GI tract should be strongly considered, assuming there are no contraindications for the described techniques below. This is particularly important if sustained-release CCBs are suspected. Patients who present early with minimal or no symptoms can have delayed cardiovascular toxicity, which can be profound and refractory to conventional treatment, making early GI decontamination a cornerstone in CCB management.

Induced emesis is contraindicated because CCB-poisoned patients can rapidly deteriorate. Orogastric lavage should be considered for all patients who present early (1–2 hours postingestion) after large ingestions and for those who are critically ill and require immediate endotracheal intubation. Although the effects of orogastric lavage following overdose of a sustained-release CCB have not been specifically studied, given the toxicity of CCB poisoning, orogastric lavage should still be strongly considered. When performing orogastric lavage in a CCB-poisoned patient, it is important to remember that lavage may increase vagal tone and potentially exacerbate any bradydysrhythmias. Pretreatment with a therapeutic dose of atropine may therefore be desirable.

All patients with CCB ingestions should receive 1 g/kg of activated charcoal orally or via nasogastric tube as long as the airway is stable or protected. Multiple-dose activated charcoal (MDAC) (0.5 g/kg every 4–6 hours) without a cathartic should be administered for nearly all patients with either sustained-release pill ingestions or signs of continuing absorption. Although data are limited, there is no evidence that MDAC increases CCB clearance from the serum. Rather, its efficacy may be a result of the continuous presence of activated charcoal throughout the GI tract, which adsorbs any active xenobiotic from its slow-release formulation. MDAC should not be administered to a patient with inadequate GI function (eg, hypotension, diminished peristaltism sounds (Antidotes in Depth: A1).

WBI with polyethylene glycol solution (1–2 L/h orally or via nasogastric tube in adults, up to 500 mL/h in children) should be initiated for patients who ingest sustained-release products and for whom there are no contraindications. Administration should be continued until the rectal effluent is clear (Antidotes in Depth: A2).

**Atropine**

Atropine is often first-line medication for patients with symptomatic bradycardia from xenobiotic poisoning such as organic phosphorus compounds, β-adrenergic antagonists, and calcium channel blockers. While the use of atropine improved both heart rate and cardiac output in an early dog model of verapamil poisoning and a few patients with bradycardia from CCB poisoning, reports of patients with severe CCB poisoning demonstrate atropine to be largely ineffective. The decreased effectiveness may be largely due to the negative inotropic effects and/or peripheral vasodilation of CCBs. Given its availability, familiarity, efficacy in mild poisonings, and safety profile, atropine should be considered as initial therapy in patients with symptomatic bradycardia.

Dose.
The dosing of atropine for xenobiotic induced bradycardia is similar to the dose used for Advanced Cardiac Life Support. Dosing should begin with 0.5 to 1.0 mg (minimum of 0.1 mg; 0.02 mg/kg in children) intravenously every 2 or 3 minutes up to a maximum dose of 3 mg in all patients with symptomatic bradycardia. However, treatment failures should be anticipated in severely poisoned patients. In patients in whom whole-bowel irrigation (WBI) or MDAC will be used, the use of atropine must be carefully considered, weighing the potential benefits of improved heart rate, and thus cardiac output, against the anticholinergic effects with potential decreased GI motility.

Calcium
Ca\(^{2+}\) is another treatment often utilized for CCB poisoning to increase in extracellular Ca\(^{2+}\) concentration with an increase in transmembrane concentration gradient. Pretreatment with intravenous verapamil use in reentrant supraventricular tachydysrhythmias.\(^{22,88}\) This also is observed with CCB poisoning where Ca\(^{2+}\) tends to improve blood pressure more than heart rate. Experimental models have also demonstrated the utility of Ca\(^{2+}\) salts with CCB poisoning. In verapamil-poisoned dogs, improvement in inotropy and blood pressure was demonstrated after increasing the serum Ca\(^{2+}\) concentration by 2 mEq/L with an intravenous infusion of 10% calcium chloride (CaCl\(_2\)) at 3 mg/kg/min.\(^{22,88}\)

Clinical experience demonstrates that Ca\(^{2+}\) reverses the negative inotropy, impaired conduction, and hypotension in many humans poisoned by CCBs.\(^{22,45,56}\) Unfortunately, this effect is often short lived, and more severely poisoned patients may not improve significantly with Ca\(^{2+}\) administration alone.\(^{18,45,46}\) Although some authors believe that these failures might represent inadequate dosing, optimal effective dosing of Ca\(^{2+}\) is unclear and they recommend repeat doses of Ca\(^{2+}\) to markedly increase the serum ionized Ca\(^{2+}\) concentrations.\(^{22,88}\) The excessive use of Ca\(^{2+}\) can result in significant complications, particularly if a Ca\(^{2+}\) infusion is used.\(^{87}\) Caution should be exercised in the administration of Ca\(^{2+}\) in patients who may have suspected acute cardioactive steroid poisoning as a cause of their bradycardia.\(^{14}\) The use of Ca\(^{2+}\) in the setting of cardioactive steroid poisoning may result in cardiac complications such as asystole (Chap. 65).

Dose.
Recommendations for poisoned adults include an initial intravenous infusion of approximately 13 to 25 mEq of Ca\(^{2+}\) (10–20 mL of 10% CaCl\(_2\) or 30–60 mL of 10% Ca\(^{2+}\) gluconate) followed by either repeat boluses every 15 to 20 minutes up to three to four doses or a continuous infusion of 0.5 mEq/kg/h of Ca\(^{2+}\) (0.2–0.4 mL/kg/h of 10% CaCl\(_2\) chloride or 0.6–1.2 mL/kg/h of 10% Ca\(^{2+}\) gluconate) (Antidotes in Depth: A29). Careful selection and attention to the type of Ca\(^{2+}\) used is critical for dosing. Although there is no difference in efficacy of CaCl\(_2\) or calcium gluconate, 1 g of CaCl\(_2\) contains 13.4 mEq of Ca\(^{2+}\), which is about three times the 4.65 mEq found in 1 g of calcium gluconate. Thus, in order to administer equal doses of Ca\(^{2+}\), three times the volume of calcium gluconate compared with that of CaCl\(_2\) is required. The main limitation of using CaCl\(_2\), however, is that it has significant potential for causing tissue injury if extravasated, so administration should
ideally be via central venous access. Adverse effects of intravenous Ca\textsuperscript{2+} include nausea, vomiting, flushing, constipation, confusion, hypercalcemia, and hypophosphatemia.

**Glucagon**
Glucagon is an endogenous polypeptide hormone secreted by the pancreatic alpha-cells in response to hypoglycemia and catecholamines. In addition, it has significant inotropic and chronotropic effects (Antidotes in Depth: A18).\textsuperscript{17,68,154} Glucagon is a therapy of choice for \(\beta\)-adrenergic antagonist poisoning (Chap. 62) because of its ability to bypass the \(\beta\)-adrenergic receptor and activate adenylate cyclase via a G. protein in the myocardium.\textsuperscript{155} Thus, glucagon is unique in that it is functionally a “pure” \(\beta\), agonist, with no peripheral vasodilatory effects (Fig. 61–2). There are reports of both successes and failures of glucagon in CCB-poisoned patients who failed to respond to fluids, Ca\textsuperscript{2+}, or dopamine and dobutamine.\textsuperscript{18,22,44}

**Dose.**
Dosing for glucagon is not well established.\textsuperscript{6} An initial dose of 3 to 5 mg IV, slowly over 1 to 2 minutes, is reasonable in adults, and if there is no hemodynamic improvement within 5 minutes, retreatment with a dose of 4 to 10 mg may be effective. The initial pediatric dose is 50 μg/kg. Because of the short half-life of glucagon, repeat doses may be useful. A maintenance infusion should be initiated once a desired effect is achieved. Adverse effects include vomiting and hyperglycemia, particularly in diabetics or during continuous infusion. In addition, patients who receive repeat administration develop tachyphylaxis, which is an acute decrease in response to a drug after repeated administration.

**Insulin-Euglycemia Therapy**
Insulin-euglycemia or high-dose insulin-euglycemia (HIE) therapy has become the treatment of choice for patients who are severely poisoned by CCBs. Healthy myocardial tissue relies predominantly on free fatty acids for its metabolic needs, and CCB poisoning forces it to become more carbohydrate dependent.\textsuperscript{49,50,52,53} At the same time, CCBs inhibit Ca\textsuperscript{2+}-mediated insulin secretion from the \(\beta\)-islet cells in the pancreas, making glucose uptake in myocardial cells dependent on passive diffusion down a concentration gradient rather than insulin-mediated active transport.\textsuperscript{20} In addition, there is evidence that the CCB-poisoned myocardium also becomes insulin resistant, possibly by dysregulation of the phosphatidylinositol 3 kinase pathway (Antidotes in Depth: A17). This may prevent normal recruitment of insulin-responsive glucose transporter proteins. The combination of inhibited insulin secretion and impaired glucose utilization may explain why severe CCB toxicity often produces significant hyperglycemia.\textsuperscript{51,52}

Many CCB-poisoned patients have been successfully treated with HIE therapy as demonstrated by improved hemodynamic function, mainly resulting from improved contractility, with little effect on heart rate. There are also reports of the failure of this treatment, but this may represent initiation of therapy in terminally ill patients with multiple organ failure.\textsuperscript{28,45}

**Dose.**
Although the dose of insulin is not definitively established, therapy typically begins with a bolus of 1 unit/kg of regular human insulin along with 0.5 g/kg of dextrose. If blood glucose is greater than 300 mg/dL (16.65 mmol/L), the dextrose bolus is unnecessary. An infusion of regular insulin should follow the bolus starting at 1.0 units/kg/h titrated up to 2 units/kg/h if no improvement after 30 minutes. Some authors advocate the use of even higher doses (10 units/kg) of insulin. A continuous dextrose infusion, beginning at 0.5 g/kg/h, should also be started. Glucose should be monitored every 30 minutes for the first 4 hours and titrated to maintain euglycemia. The response to insulin is typically delayed for 15 to 60 minutes, so the use of HIE should be considered very early in the patient’s course if severe CCB poisoning is suspected. Primary complications of HIE include hypoglycemia and hypokalemia from intracellular shifting of potassium. It is essential to note that the development of hypoglycemia is an indication to increase glucose delivery rather than decrease the insulin infusion rate.

**Intravenous Fat Emulsion**

Intravenous fat emulsion (IFE) has been used as a source of parenteral nutrition and as a diluent for intravenous drug delivery of highly lipophilic medications such as propofol and liposomal amphotericin. The use of IFE as an antidote is most extensively studied for the treatment of local anesthetic toxicity, specifically from bupivacaine, but has been utilized in overdoses from other lipophilic drugs such as psychiatric medication, calcium channel blockers, and β-adrenergic antagonists.

IFE is a white, milky liquid composed of two types of lipids, triglycerides and phospholipids. It is sterile and nonpyrogenic with a pH of about 8 (range, 6–9). IFEs are isotonic solutions (260–310 mOsm/L) and are available in 5%, 10%, 20%, and 30% solutions. There are three proposed mechanisms of action for IFE: activation of ion channels (calcium); enhancement of intracellular metabolism; and acting as a lipid sink to sequester lipid-soluble drugs. The latter mechanism is the most likely explanation based on existing literature.

An important property of medications that may determine the effectiveness of IFE is lipophilicity. Lipophilicity means the tendency of a drug to partition between lipophilic organic phase and the polar aqueous phase, and value of lipophilicity most commonly refers to logarithm of partition coefficient P (logP) between these two phases. For ionizable compounds, the partition is changed as a function of pH; this relationship is called a distribution constant (logD) or sometimes also as an apparent partition coefficient. Drugs that are highly lipophilic may benefit more from the use of IFE in severe poisoning. Table 61–3 lists major CCBs with their logD and logP values.

**TABLE 61–3. LogP and LogD of Commonly Available Calcium Channel Blockers**

| View Large | Favorite Table |

Existing experimental evidence supports that IFE decreases the toxicity of a few lipid-soluble drugs, most notably bupivacaine. Pretreatment with IFE also increased the dose of certain medications.
to cause toxicity. Other models suggest that IFE is an effective therapy for CCB-poisoned patients.

In a controlled study of rodents that were poisoned with verapamil, the use of IFE resulted in both increased survival and heart rate when compared to the control groups. IFE was also used on a patient with severe verapamil poisoning who failed Ca\(^{2+}\) and HIE but when given IFE showed improvement and survival. Serum verapamil concentrations were measured before and after IFE treatment. There was a decrease in verapamil after IFE administration once the lipid was removed from the samples, which demonstrate sequestration of verapamil (Antidotes in Depth: A20).

**Dose.**

The recommended dose of IFE is a 1.5 mL/kg bolus. The bolus can be repeated several times for persistent asystole followed by an infusion of 0.25 mL/kg/min or 15 mL/kg/h to run for 30 to 60 minutes. IFE has only traditionally been given to patients in extremis from an overdose, but at this time IFE should be considered in patients who are persistently unstable despite the use of other therapies such as HIE.

**Adjunctive Pharmacologic Treatment**

Other pharmacotherapies have been studied in the setting of CCB poisoning. There are limited data with these therapies, and they should be considered only when all of the above treatments have failed. Digoxin has been experimentally evaluated in CCB poisoning since it raises the intracellular Ca\(^{2+}\) concentration. In a canine model of verapamil poisoning, digoxin, in conjunction with atropine or Ca\(^{2+}\), improved both systolic blood pressure and myocardial inotropy. However, because digoxin requires a significant amount of time to distribute into tissue, and because limited efficacy data and no safety data have yet been collected, more evaluation is needed before digoxin is administered to patients with CCB poisoning. Another xenobiotic that has been utilized as a treatment for CCB poisoning is levosimendan. Levosimendan is a Ca\(^{2+}\) sensitizer used in the management of acutely decompensated congestive heart failure. While there are reported cases of success with the use of this drug, there is also existing experimental evidence that does not support its use.

Most recently, methylene blue was reported in a confirmed ingestion of amlodipine poisoning in a patient that failed conventional therapy, including HIE treatment. A Swan-Ganz catheter confirmed pure vasodilatory shock, which responded to methylene blue (2 mg/kg). Methylene blue is also reported with success in a case of a mixed \(\beta\) blocker and CCB overdose, and it is used in other states of refractory vasodilatory shock such as anaphylaxis and sepsis due to inhibition of methylene blue along the nitric oxide–cyclic guanosine monophosphate pathway. There is some evidence to suggest certain dihydropyridines such as amlodipine mediate its vasodilatory effects via nitric oxide, but the importance of this pathway in acute poisoning is unclear. Further investigation is required before methylene blue can routinely be recommended in patients with CCB poisoning.

**Inotropes and Vasopressors**

Catecholamines are often administered once first-line therapy such as atropine, Ca\(^{2+}\), glucagon, and isotonic fluids fail. There are numerous cases that describe either success or failure with various agents, including epinephrine, norepinephrine, dopamine, isoproterenol, dobutamine, and
Based on experimental and clinical data, no single xenobiotic is consistently effective. The variability in response is from the differences of CCB involved, coingestants with other cardioactive medications, and patient response. CCB poisoning may involve the myocardium (verapamil and diltiazem) mediated by β₁-adrenergic receptors, resulting in negative chronotrophy/inotrophy and/or peripheral smooth muscle relaxation (dihydropyridines) with vasodilation mediated by α₁-adrenergic receptors. Despite variable success in CCB poisoning, the existing data described previously show that all vasopressors are generally inferior with significantly more adverse effects such as tissue ischemia with long-term use.

**Adjunctive Hemodynamic Support**

The most severely CCB-poisoned patients may not respond to any pharmacologic intervention. Transthoracic or intravenous cardiac pacing may be required to improve heart rate, as several case reports demonstrate. However, in a prospective cohort of CCB poisonings, two of four patients with significant bradycardia requiring electrical pacing had no electrical capture. In addition, even if electrical pacing is effective in increasing the heart rate, blood pressure often remains unchanged. Intraaortic balloon counterpulsation is another invasive supportive option to be considered in CCB poisoning refractory to pharmacologic therapy. Intraaortic balloon counterpulsation was used successfully to improve cardiac output and blood pressure in a patient with a mixed verapamil and atenolol overdose.

Severely CCB-poisoned patients have also been supported for days and subsequently recovered fully with much more invasive and technologically demanding extracorporeal membrane oxygenation (ECMO) and emergent open and percutaneous cardiopulmonary bypass. The major limitation of all these technologies, however, is that they are available only at tertiary care facilities.

Molecular adsorbents recirculating system (MARS) therapy is a specific extracorporeal albumin dialysis that is reported in the treatment of severe CCB poisoning. MARS therapy has the unique ability to selectively remove from circulation protein-bound xenobiotics that are not cleared by conventional hemodialysis. The use of MARS therapy is under current investigation with *Amanita* poisoning but reportedly was successfully utilized in three patients with severe nondihydropyridine CCB poisoning.

**DISPOSITION**

Patients who manifest signs or symptoms of toxicity should be admitted to an intensive care setting. Because of the potential for delayed toxicity, patients who ingest sustained-release products should be admitted for 24 hours to a monitored setting, even if asymptomatic. This precautionary approach is particularly important for toddlers and small children in whom even one or a few tablets may produce significant toxicity. Criteria for safe discharge or medical clearance apply only to patients with a reliable history of an ingestion of an “immediate-release” preparation who have received adequate GI decontamination, had serial ECGs over 6 to 8 hours that have remained unchanged, and are asymptomatic.
SUMMARY

- The hallmarks of CCB toxicity include bradydysrhythmias and hypotension, which are an extension of their pharmacologic effects.

- Although most patients develop symptoms of hypoperfusion, such as light-headedness, nausea, or fatigue, within hours of a significant ingestion, ingestion of sustained-release formulations may result in significant delays in any hemodynamic consequences and may prolong toxicity.

- Aggressive decontamination of patients with exposures to sustained-release products should begin as soon as possible and should not be delayed while awaiting signs of toxicity.

- The early use of high-dose insulin therapy should be instituted with attempts to avoid the use of vasopressors as it requires time for the effects to occur. In cases of severe toxicity, the use of intravenous fat emulsion therapy should be considered.

- Patients who fail to respond to all pharmaceutical interventions should be considered for adjunctive hemodynamic support whenever available.

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