Chapter 60: Calcium Channel Blockers

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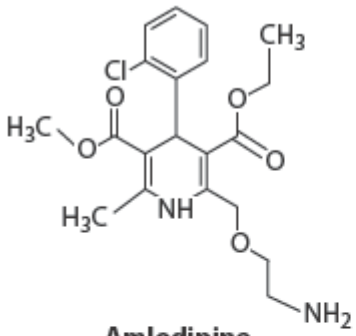
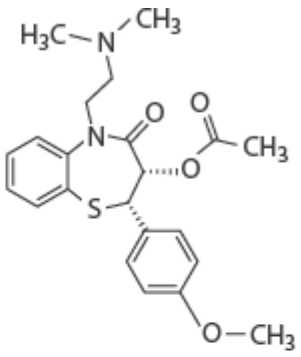
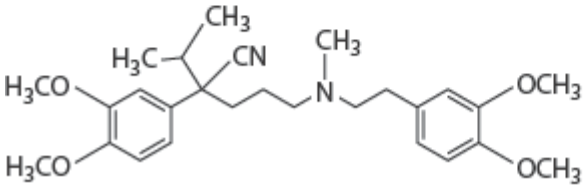
INTRODUCTION



Amlodipine



Diltiazem



Verapamil

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.[3] By the late 1970s, the clinical use of calcium channel blockers (CCBs) was widely accepted for a variety of cardiovascular indications, including hypertension, dysrhythmias, and angina. Later indications for the use of CCBs include Raynaud phenomenon and disease, migraine and cluster headaches and subarachnoid hemorrhage.[1] 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.[31]

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 7,000 poisoning-related deaths reported to the American Association of Poison Control Centers National Poisons Data System (NPDS). Cardiovascular drugs were involved in more than 400,000 of the reported poisonings

and accounted for nearly 15% of the overall poisoning fatalities. Within this class, CCBs were the most common cardiovascular drugs involved in poisoning fatalities. Calcium channel blockers accounted for more than 50,000 cases reported over the past 5 years, with more than 300 cases resulting in major effects and more than 100 deaths (Chap. 130).[15,16,77,78] There is a bimodal distribution within the pediatric population that involves unintentional exposures in young infants and toddlers with intentional ingestions in teenagers.[40]

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 60–1). 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.[106] Voltage-gated Ca^{2+} channels are composed of several components, including α_2, β, δ, and the ion-conducting α_1-subunit. The α_1-subunit is the most important component of the Ca^{2+} channel because it contains the actual pore through which Ca^{2+} ions pass, and it 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.[79,122]

TABLE 60–1

Voltage-Gated Calcium Channel Subtypes

Type	Distribution	Function	Blocked By
T (transient)	Polysynaptic nerve terminals and cardiac nodal tissue	Pacemaker activity	Mibefradil
R	Neural tissue	Neurotransmitter release	Cadmium
Q	Presynaptic nerve terminals	Neurotransmitter release	Agatoxin
P (Purkinje)	Cerebellar Purkinje neurons	Neurotransmitter release	Agatoxin
N (neuronal)	Presynaptic nerve terminals	Catecholamine release	ω-Conotoxin
L (long-acting)	Myocardium and smooth muscle	Muscular contraction	Verapamil, diltiazem, dihydropyridines

The primary action of all CCBs available in the United States is antagonism of the L-type or “long-acting” voltage-gated Ca^{2+} channels. Calcium channel blockers are often classified into three groups based on their chemical structure (Table 60–2).[41,71,79] A fourth class, the diarylaminopropylamines included mibefradil, but this drug was withdrawn because of significant adverse drug interactions.[114] Each group binds a slightly different region of the α_{1c} subunit of the Ca^{2+} channel and thus has different affinities for the various L-type Ca^{2+} channels, both in the myocardium and the vascular smooth muscle.[18] It is often more logical to classify them as nondihydropyridine versus dihydropyridine CCBs. Whereas the former includes verapamil and diltiazem, 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 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.[122] They are therefore commonly used as vasodilators for conditions with increased vascular tone such as hypertension, migraine headaches, and postintracranial hemorrhage–associated vasospasm. Dihydropyridines bind to a site that is formed by amino acid residues in two adjacent S6

segments plus the S5 segment between them, and in some cases, enantiomeric pairs are activators or inhibitors, respectively, indicating that very subtle changes in the drug–receptor interaction are sufficient to convert from agonist to antagonist action.[64]

TABLE 60–2

Classification of Calcium Channel Blockers Available in the United States

Class	Specific Compounds	Volume of Distribution (L/kg)	Time to Peak* Concentrations (h)
Phenylalkylamine	Verapamil	3–5	1–2
Benzothiazepine	Diltiazem	5.3	2–4
Dihydropyridines	Amlodipine	21	6–12
	Clevidipine	0.17	<1
	Felodipine	10	2.5–5
	Isradipine	3	1–2
	Nicardipine	8.3	1–4
	Nifedipine	0.75	2.5–5
	Nimodipine	2	1–2
	Nisoldipine	1.6	>6

*All are oral ingestion of an immediate release formulation: at therapeutic doses.

Experimental studies suggest an additional vasodilatory effect of some CCBs caused by stimulation of nitric oxide release. Amlodipine and other dihydropyridine CCBs release nitric oxide in a dose-dependent fashion from canine coronary microvessels.[127-129] 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_2 receptors also contribute to vasodilation. Bradykinin is a vasodilator that exerts its action by causing endothelial release of prostacyclin, nitric oxide, and endothelium-derived hyperpolarizing factor.[128]

PHARMACOKINETICS AND TOXICOKINETICS

Absorption

All CCBs are well absorbed orally, but many exhibit low bioavailability because of extensive hepatic first-pass metabolism. When the CCBs reach the liver, they undergo hepatic oxidative metabolism predominantly via the CYP3A4 subgroup of the enzyme system.[76]

Distribution

All CCBs are highly protein bound which limits the role of extracorporeal removal. Volumes of distribution are large for amlodipine (21 L/kg), verapamil (3–5 L/kg), and diltiazem (5.3 L/kg) and somewhat smaller for nifedipine (0.75 L/kg).[47,84]

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.[48,57] After repeated doses, as well as after overdose, these hepatic enzymes become saturated, reducing the potential of the first-pass effect and increasing the quantity of active drug absorbed systemically.[124] Saturation of metabolism as well as the modified-release dosage form contribute to the prolongation of the apparent half-lives reported after overdose of various CCBs.[95]

Excretion

The CCBs undergo a significant, but variable, amount of renal excretion after metabolism with a small percentage eliminated in the urine unchanged. 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.[34,80]

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. 11 and Appendix).[39,92] In June 1998, mibefradil, a structurally unique CCB, was voluntarily withdrawn after several reports of serious adverse xenobiotic interactions caused in part by its potent inhibition of CYP3A4.[66] 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, which results in toxicity.[38,102]

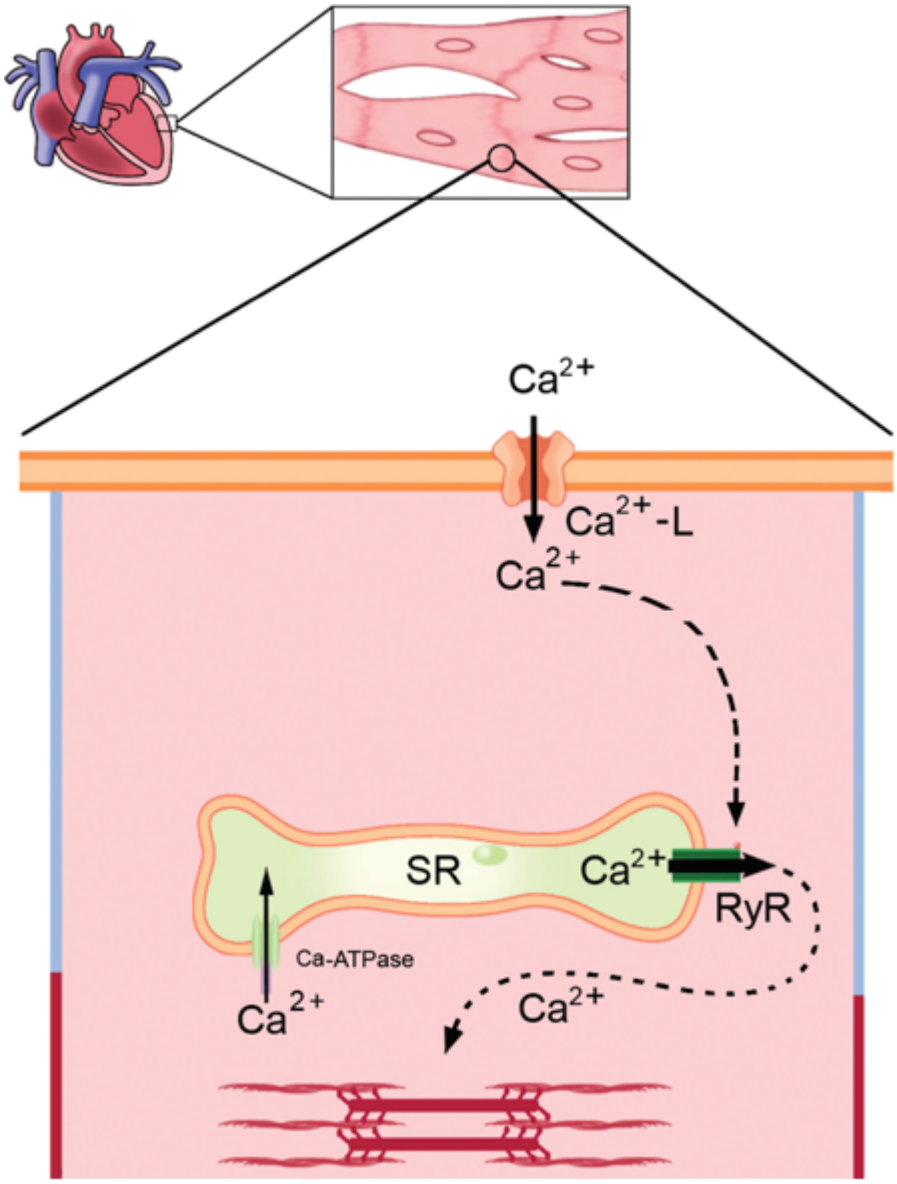
In addition to affecting CYP3A4, verapamil and diltiazem also inhibit P-glycoprotein–mediated drug transport into peripheral tissue that results in elevated serum concentrations of xenobiotics such as cyclosporine and digoxin that use this transport system (Chap. 11 and Appendix). Unlike diltiazem and 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 requires closer outpatient follow-up for the development of bradycardia or hypotension.

PHYSIOLOGY AND PATHOPHYSIOLOGY

Calcium plays an essential role in many cellular processes throughout the body, and many types of cells depend on the maintenance of a Ca^{2+} concentration gradient across cell membranes in order to function. The extracellular Ca^{2+} concentration is approximately 10,000 times greater than the intracellular concentration. This concentration gradient is important for contraction and relaxation of muscle cells (Fig. 60–1). Ca^{2+} channels and various exchange pumps located on the cell membrane play a key role in maintaining this concentration gradient within muscle cells.[59,81]

FIGURE 60–1.

Normal contraction of myocardial cells. The L-type voltage-gated Ca^{2+} channels (Cav-L) open to allow Ca^{2+} ion influx during myocyte depolarization. This causes the concentration-dependent release of more Ca^{2+} ions from the ryanodine receptor (RyR) of the sarcoplasmic reticulum (SR).



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Calcium is driven down a large electrical and concentration gradient through L-type Ca^{2+} channels located in all muscle cell types (cardiac, striated, and smooth). This influx of Ca^{2+} is critical for the function of both cardiac and smooth muscle cells; however, skeletal muscle depends primarily on intracellular Ca^{2+} stores for excitation–contraction coupling and not the intracellular influx of Ca^{2+}. In smooth muscle, the rapid influx of Ca^{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 contraction.[74]

Calcium plays a similarly important role in myocardial contractility. In myocardial cells, Ca^{2+} influx is slower relative to the initial Na^{+} influx that initiates cellular depolarization and prolongs this depolarization, creating the plateau phase (phase 2) of the action potential (Chap. 15 and Fig. 15–2). The Ca^{2+} subsequently stimulates a receptor-operated Ca^{2+} channel on the sarcoplasmic reticulum (SR), known as the ryanodine receptor, releasing Ca^{2+} from the vast stores of the SR into the cytosol.[87] This is often termed *Ca^{2+}-induced*

Ca^{2+} release. Calcium 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.[19,28] Calcium influx is also plays important in the spontaneous depolarization (phase 4) of the action potential in the SA node. This Ca^{2+} influx also allows normal propagation of electrical impulses via the specialized myocardial conduction tissues, particularly the AV node. After opening, the rates of recovery of these slow Ca^{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^{2+} influx and channel recovery in the myocardium, but their blockade is also potentiated as the frequency of channel opening increases. Dihydropyridines are modulated by the membrane potential and calcium channel blockade is more pronounced when current is measured from depolarized holding potentials as opposed to verapamil; where this voltage-dependent block occurs in the absence of repetitive depolarizations.[44,89] Therefore, in frequently contracting tissue, such as myocardium, the blockade of verapamil and diltiazem is augmented. Verapamil and diltiazem are therefore commonly used for controlling the ventricular rate in patients with atrial tachydysrhythmia.

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 compared with the nondihydropyridine CCBs. Dihydropyridines bind the Ca^{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.[89]

The toxicity of CCBs 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 and heart rate, as well as arterial vasodilation. Because dihydropyridines have limited myocardial effect at therapeutic concentrations, the baroreceptor reflex remains intact, and slight increases in heart rate and cardiac output often occur. Isradipine is the only dihydropyridine whose inhibitory effect on the SA node is significant enough to blunt any reflex tachycardia. Calcium channel blocker poisoning also results in blockade of L-type Ca^{2+} channels located in the pancreas. This results in decreased insulin release, resulting in hyperglycemia.

CLINICAL MANIFESTATIONS

The hallmarks of CCB poisoning are hypotension and bradycardia, which result from depression of myocardial contraction and peripheral vasodilation.[100] Myocardial conduction is impaired, producing AV conduction abnormalities, idioventricular rhythms, and complete heart block, most commonly with nondihydropyridine poisoning. Junctional escape rhythms occur in patients with significant

poisonings.[13,45,51,91,125] The negative inotropic effects are often so profound, particularly with verapamil, that ventricular contraction is completely ablated.[5,9,11,23]

Hypotension is the most common and life-threatening finding in acute CCB poisoning, caused by a combination of decreased inotropy, bradycardia, and peripheral vasodilation.[93] Patients can present asymptomatically early after ingestion and subsequently deteriorate rapidly to severe cardiogenic shock.[5,9,54] 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 evaluate for other causes and ingestions. Severely poisoned patients manifest syncope, altered mental status, coma, and sudden death.[97,101] Gastrointestinal (GI) effects, such as nausea and vomiting, are not a typical feature of CCB poisoning. Acute respiratory distress syndrome (ARDS) is also described with severe CCB poisoning. This is due to precapillary vasodilation with a subsequent increase in transcapillary pressure. The elevated pressure gradient results in increased capillary transudates and possible interstitial edema.[33,53]

In mild to moderate overdose of dihydropyridine CCBs, the predominantly peripheral effect induces a reflex tachycardia. However, severe poisoning with any CCBs can result in loss of receptor selectivity, resulting in bradycardia. A prospective poison control center study noted AV nodal block to occur more frequently with verapamil poisoning.[94] Although deaths are attributed mainly to the nondihydropyridines, a significant number of dihydropyridine-related deaths are also reported, which likely reflects the wider use of dihydropyridine CCBs.[94,107]

Several factors ultimately determine CCB toxicity. These include medication formulation, dose, and coingestion with other cardioactive medications such as β-adrenergic antagonists, underlying comorbidities, and age. Older adult patients and those with underlying cardiovascular disease such as congestive heart failure are more sensitive to CCBs.[75] Even at therapeutic doses, these patients are more susceptible to the cardioactive effects of these medications and develop symptomatic hypotension.

Pediatric cases of CCB overdose commonly result from medication errors or unwitnessed ingestions of pills found at home.[12,40] Children with CCB poisoning can develop nonspecific clinical effects such as lethargy, emesis, and confusion. Although CCB poisoning in children is uncommon, there are reported cases of severe poisoning and death.[107]

DIAGNOSTIC TESTING

All 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, end-tidal carbon dioxide ($EtCO_2$), and serum chemistry should also be obtained if any degree of hypoperfusion is suspected. Assessment of electrolytes, including magnesium, and a serum digoxin concentration in a bradycardic patient with unknown exposure history are

indicated, although a careful history, if possible, may narrow down the etiology. Cardioactive steroids should be a consideration in a patient with undifferentiated bradycardia with hyperkalemia but are less likely in the setting of hypotension. 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 Ca^{2+} influx through the L-type Ca^{2+} channel. Calcium channel blocker poisoning reduces insulin release with resultant hyperglycemia. An additional mechanism also includes dysregulation of the insulin-dependent phosphatidylinositol-3 kinase (PI3K) pathway.[11] 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 correlated with the severity of nondihydropyridine CCB poisoning. The initial mean serum glucose concentration was 188 mg/dL in patients who met a composite endpoint of requiring vasopressors, a pacemaker, or death versus 122 mg/dL in those not requiring intervention. Peak serum glucose concentrations were also significantly different.[69] This finding is interpreted to be an early sign of severity and an indicator for when to initiate high dose insulin (HDI) (Antidotes in Depth: A21) therapy.

MANAGEMENT

Overview

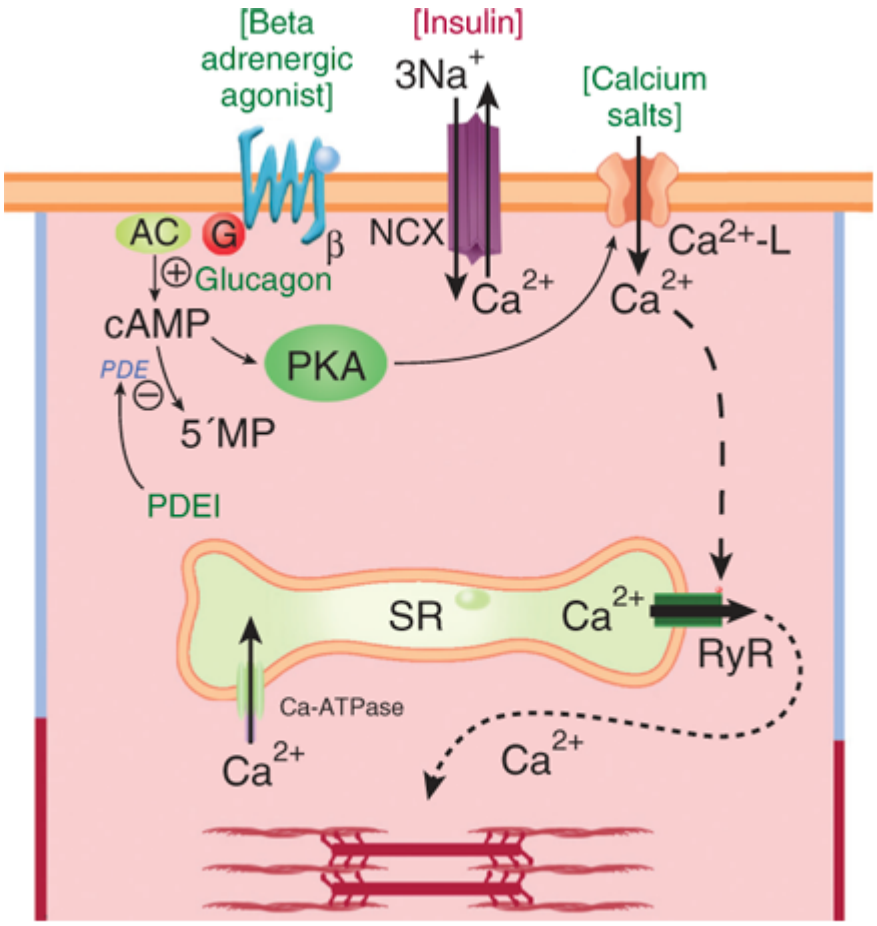
All patients with suspected CCB poisoning should undergo prompt evaluation even when the initial vital signs are normal. This urgency is due to the potential to initiate early GI decontamination and pharmacologic therapies before patients manifest severe poisoning. This is particularly important with ingestions involving sustained-release formulations. Intravenous (IV) 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 initially receive a fluid bolus of 10 to 20 mL/kg of crystalloid. This is repeated as needed with constant monitoring of volume status with repeat serial examinations for volume overload. Caution is required because aggressive fluid resuscitation should not be given to patients with congestive heart failure, evidence of ARDS, or chronic kidney disease. Although there are currently both outpatient and inpatient consensus guidelines in the management of CCB poisoning, there is still no clear pathway for treatment, and the inpatient guidelines are too ambiguous for clinicians unfamiliar with this type of poisoning to be useful.[82,108]

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 (PDE) 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 treatments such as vasopressors are 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 do not respond to these initial efforts and require further pharmacotherapy. Although it would be ideal to initiate each therapy individually and monitor the patient's hemodynamic response, in the most critically ill patients, multiple therapies are administered simultaneously. A reasonable treatment sequence based on existing data and clinical experience should initially consist of isotonic fluids, atropine, calcium, and glucagon (Antidotes in Depth: A20). If the patient does not respond to these initial treatments, HDI therapy should be initiated. Because the onset of effect of HDI is delayed for 15 to 40 minutes and given the relative safety of its use, earlier initiation is preferable. The use of vasopressors such as norepinephrine or dopamine can result in tissue ischemia with long-term use and thus should be avoided, when possible, in favor of HDI therapy. Phosphodiesterase inhibitors such as inamrinone, milrinone, and enoximone have been used to treat patients with CCB poisoning.[65,98,121] These xenobiotics inhibit the breakdown of cyclic adenosine diphosphate (cAMP) by PDE inhibition, thereby increasing intracellular cAMP concentrations, resulting in increased cardiac output. Despite some reported success, PDE inhibitors are not readily available, other xenobiotics are more effective and easier to use and we do not recommend routine use (Fig. 60–2).

FIGURE 60–2.

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



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Gastrointestinal Decontamination

Because CCB poisoning is a leading cause of poisoning fatality, attempts to prevent absorption from the GI tract are recommended, assuming there are no contraindications for the described techniques in this chapter. 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.

We recommend that all patients with CCB ingestions should receive 1 g/kg of activated charcoal (AC) 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 is reasonable 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.[95] Rather, its efficacy is a result of the continuous presence of AC throughout the GI tract, which adsorbs any active xenobiotic from its slow-release formulation. Multiple-dose activated charcoal should not be administered to a patient with inadequate GI function (eg, hypotension, diminished peristaltism sounds (Antidotes in Depth: A1).

Orogastric lavage is recommended 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 after overdose of a sustained-release CCB are not specifically studied. When performing orogastric lavage in a CCB-poisoned patient, it is important to remember that lavage increases vagal tone and potentially exacerbates any bradydysrhythmias; we routinely pretreat with atropine.[111] It is important to note that although AC is less invasive than lavage, orogastric lavage followed by AC may be more practical in critically ill patients who are intubated[68,110]

Whole-bowel irrigation (WBI) with polyethylene glycol solution (1–2 L/h orally or via nasogastric tube in adults, up to 500 mL/h in children) is recommended for patients who ingest sustained-release products and for whom there are no contraindications. Although the benefit is uncertain, in patients with severe poisoning. The risk of WBI is limited in these cases. It should be continued until the rectal effluent is clear (Antidotes in Depth: A2).[17,24]

Atropine

Atropine is often first-line therapy for patients with symptomatic bradycardia from xenobiotic poisoning such as organic phosphorus compounds, β-adrenergic antagonists, and CCBs. Although 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,[37,94] reports of patients with severe CCB poisoning demonstrate atropine to be largely ineffective.[56,90,105] The decreased effectiveness is largely due to the negative inotropic effects or peripheral vasodilation of CCBs. Given its availability, familiarity, efficacy in mild poisonings, and safety profile, atropine is recommended 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 in children >5 kg; 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 and other therapies such as calcium and glucagon should be administrated. In patients in whom WBI or MDAC will be used, the use of atropine should also be administered particularly if increased vagal tone is apparent.

Calcium

Calcium is another treatment often used for CCB poisoning to increase extracellular Ca^{2+} concentration with an increase in transmembrane concentration gradient. Pretreatment with IV Ca^{2+} prevents hypotension without diminishing the antidysrhythmic efficacy before therapeutic verapamil use in reentrant supraventricular tachydysrhythmias.[29,104] This also is observed with CCB poisoning in which Ca^{2+} tends to improve blood pressure more than heart rate. Experimental models demonstrate 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 IV infusion of 10% calcium chloride ($CaCl_2$) at 3 mg/kg/min.[37,45]

Clinical experience demonstrates that Ca^{2+} reverses the negative inotropy, impaired conduction, and hypotension in many humans poisoned by CCBs.[67,72,95] Unfortunately, this effect is often short lived, and more severely poisoned patients do not improve significantly with Ca^{2+} administration alone.[22,56,99] 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.[51,67] The excessive use of Ca^{2+} can result in significant complications such as vasoconstriction and renal failure, particularly if a Ca^{2+} infusion is used.[103] Caution should be exercised in the administration of Ca^{2+} in patients suspected of an acute cardioactive steroid poisoning as a cause of their bradycardia.[14] The use of Ca^{2+} in the setting of cardioactive steroid poisoning is reported to result in cardiac complications such as dysrhythmia (Chap. 62).

Dose

For poisoned adults, an initial IV 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) is given over 10 minutes followed by repeat doses every 10 minutes up to two doses then every 20 to 60 minutes as needed. It is important to monitor [Ca^{2+}] every 30 to 60 minutes (Antidotes in Depth: A32). 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, 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 we recommend administration through a central venous line, intraosseous line or peripheral line if no other route is accessible. Adverse effects of IV Ca^{2+} include nausea, vomiting, flushing, constipation, confusion, hypercalcemia, and hypophosphatemia.

Glucagon

Glucagon is an endogenous polypeptide hormone secreted by the pancreatic α cells in response to hypoglycemia and catecholamines. In addition, it has significant inotropic and chronotropic effects (Antidotes in Depth: A20).[20,21,109,126] Glucagon is a therapy of choice for β-adrenergic antagonist poisoning (Chap. 59) because of its ability to bypass the β-adrenergic receptor and activate adenylate cyclase via a G_s protein in the myocardium.[123] Thus, glucagon is unique in that it is functionally a "pure" β_1 agonist, with no peripheral vasodilatory effects (Fig. 60–2). Although there are reports of both successes and failures of

glucagon in CCB-poisoned patients who failed to respond to fluids, Ca^{2+}, or dopamine and dobutamine, the authors recommend a trial of glucagon.[23,30,46,56]

Dose

Dosing for glucagon is not well established.[6] An initial dose of 3 to 5 mg IV, slowly over 3 to 5 minutes and if there is no hemodynamic improvement within 5 minutes, and retreatment with a dose of 4 to 10 mg is effective. The initial pediatric dose is 50 mcg/kg. Because of the short half-life of glucagon, repeat doses are often required. A maintenance infusion should be initiated after a desired effect is achieved. Adverse effects include vomiting and hyperglycemia, particularly in patients with diabetes or during continuous infusion. In other models repeat administration leads to tachyphylaxis, which is an acute decrease in response to a drug after repeated administration.

High-Dose Insulin Therapy

High-dose insulin (HDI) therapy is the treatment of choice for patients who are severely poisoned by CCBs. The mechanisms of action for HDI are varied and include utilization of free fatty acids for myocardial metabolic needs; CCB poisoning forces the myocardium to become more carbohydrate dependent.[60,61,63] At the same time, CCBs inhibit Ca^{2+}-mediated insulin secretion from the β-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.[27] In addition, there is evidence that the CCB-poisoned myocardium also becomes insulin resistant, possibly by dysregulation of the PI3K pathway (Antidotes in Depth: A21). This prevents 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.[61,62] However, the current accepted mechanism is that insulin impairs the Na^{+}-Ca^{2+} antiporter, resulting in an increase in the intracellular [Ca^{2+}]. This increase of calcium results in an increase in the Ca^{2+} load from the SR, leading to increased cardiac contractility.[52,113]

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 represents initiation of therapy in terminally ill patients with multiple organ failure and delayed initiation of treatment.[35]

Dose

We recommend to begin therapy 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 units/kg/h titrated up to 2 units/kg/h if there is no improvement after 30 minutes. Even higher doses (10 units/kg h) of insulin have been successfully reported, and we recommend escalating to this dose if 1 to 2 units/kg/h is not successful.[32] 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 40 minutes, so early use of HDI should be initiated very early in the patient's course if severe CCB poisoning is suspected. Primary complications of HDI 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. The blood glucose should be monitored every 15 to 30 minutes until stable and then every 1 to 2 hours. Kidney failure will alter the pharmacokinetics of insulin elimination and we recommend closer glucose monitoring and to use the dosing of insulin as recommended. Concentrating the insulin infusion to 10 units/mL prevents fluid overload from large doses of insulin.

Intravenous Lipid Emulsion

The use of intravenous lipid emulsion (ILE) as an antidote is best studied for the treatment of local anesthetic systemic toxicity with expanded use for the treatment of nonlocal anesthetic overdose such as with CCBs. Xenobiotics that are highly lipophilic may benefit more from the use of ILE in severe poisoning (Antidotes in Depth: A23).

There is controversy whether ILE is a valuable treatment for CCB poisoning because of inconsistent reported outcomes.[43] Existing experimental evidence supports that ILE decreases the toxicity of several intravenously administered lipid-soluble drugs, most notably bupivacaine.[117,118] Pretreatment with ILE also increased the dose of certain medications to cause toxicity, but its generalizability to CCBs in debatable.[119]

Intravenous lipid emulsion was used on a patient with severe verapamil poisoning who failed Ca^{2+} and HDI but when given ILE showed improvement and survival. Serum verapamil concentrations were measured before and after ILE treatment. There was a decrease in verapamil after ILE administration after the lipid was removed from the samples, which demonstrate sequestration of verapamil.[35] However, there are also reports that ILE enhances intestinal absorption of other xenobiotics and lacks clinical benefit.[85,86] Intravenous lipid emulsion has the potential for interfering with the circuitry of extracorporeal membrane oxygenation (ECMO), and it is not clear what interaction ILE has on other medications being used as treatment. The Lipid Emulsion Workgroup is composed of representatives of all major toxicology associations' published evidence-based recommendations in which ILE was recommended for cardiac arrest from bupivacaine toxicity. At this time, the Workgroup's evidence-based recommendation on the use of ILE in CCB poisoning state that in the setting of life-threatening and non–life-threatening CCB poisoning, ILE should not be used as first-line therapy. The use of ILE is reasonable for CCB induced severe cardiovascular toxicity that persists despite maximal treatment with standard resuscitative measures (including GI decontamination) and ECMO and other ECLS are not available.[42,43]

Adjunctive Pharmacologic Treatment

Other pharmacotherapies are studied in the setting of CCB poisoning. There are limited data with these therapies, and therefore we do not recommend routine use. Digoxin was evaluated experimentally in CCB poisoning because it raises the intracellular Ca^{2+} concentration.[8] In a canine model of verapamil poisoning, digoxin, in conjunction with atropine or Ca^{2+}, improved both systolic blood pressure and myocardial inotropy.[7] 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, we do not recommend use of digoxin in CCB poisoning. Another xenobiotic that was used as a treatment for CCB poisoning is levosimendan. Levosimendan is a Ca^{2+} sensitizer used in the management of acutely decompensated congestive heart failure. Although there are reported cases of success with the use of this drug, there is also existing experimental evidence that does not support its use.[2,83,112]

Methylene blue (Antidotes in Depth: A43) was reported in a confirmed ingestion of amlodipine poisoning in a patient who failed conventional therapy, including HIE treatment. A Swan-Ganz catheter confirmed pure vasodilatory shock, which responded to methylene blue (2 mg/kg).[56] Methylene blue is also reported with success in a case of a mixed β-adrenergic antagonist and CCB overdose,[4] and it is used in other causes of refractory vasodilatory shock such as anaphylaxis and sepsis caused by inhibition of methylene blue along the nitric oxide–cyclic guanosine monophosphate pathway and contributes electrons to mitochondrial glycerophosphate dehydrogenase to improve mitochondrial respiration. Experimental evidence also shows improvement in hemodynamics with no change in mortality rate.[55] Some evidence suggests that certain dihydropyridines, such as amlodipine mediate, their 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.[115]

Inotropes and Vasopressors

Catecholamines are often administered after 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 inotropes and vasopressors, including epinephrine, norepinephrine, dopamine, isoproterenol, dobutamine, and vasopressin.[22,46,50,73] Based on experimental and clinical data, no single inotrope or vasopressor is consistently effective. The variability in response is from the differences of CCB involved, coingestants with other cardioactive medications, and patient response. Calcium channel blocker poisoning often involve the myocardium (verapamil and diltiazem) resulting in negative chronotropy or inotropy or peripheral smooth muscle relaxation (dihydropyridines) with vasodilation mediated by α_1-adrenergic receptors. In a retrospective study in a series of patients with nondihydropyridine poisoning, they were managed with the use of multiple vasopressors and without HDI in all but three cases. Despite high doses of vasopressors, ischemic complications were uncommon and were attributed to the hypotension related to the poisoning. In this study, the use of vasopressors after nondihydropyridine poisoning was associated with good clinical outcomes.[70] 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. The authors therefore recommend avoiding their use if possible or using as a bridge to HDI.

Adjunctive Hemodynamic Support

The most severely CCB-poisoned patients will not respond to any pharmacologic intervention. Transthoracic or IV cardiac pacing is reasonable to improve heart rate, as several case reports demonstrate.[105,116] However, in a prospective cohort of CCB poisonings, two of four patients with significant bradycardia requiring electrical pacing had no electrical capture.[93] In addition, even if electrical pacing is effective in increasing the heart rate, blood pressure often remains unchanged.[49,50]

Intraaortic balloon pump (IABP) is another invasive supportive option that is reasonable to attempt in CCB poisoning refractory to pharmacologic therapy.[58] Because IABPs are ECG gated, in patients with very low heart rates, IABP is often not effective with increasing cardiac output with counterpulsation. Insertion of an IABP successfully improved cardiac output and blood pressure in a patient with a mixed verapamil and atenolol overdose.[36]

Severely CCB-poisoned patients have also been supported for days and subsequently recovered fully with much more invasive and technologically demanding ECMO and emergent open and percutaneous cardiopulmonary bypass.[49,96] Extracorporeal membrane oxygenation has been increasingly used in pharmacology-refractory CCB poisoning.[26,120] The advantage of ECMO over IABP is that it is independent of cardiac electrical and mechanical activity. There are currently two ECMO modalities available, which include venovenous EMCO (VV-EMCO) and venoarterial ECMO (VA-ECMO). Venovenous-extracorporeal membrane oxygenation is used primarily for patients with refractory respiratory failure and is not adequate in shock from severe CCB poisoning. Venoarterial-extracorporeal membrane oxygenation is recommended in severe circulatory shock. Reported complications of VA-ECMO include bleeding at the cannulation site, leg ischemia, and clotting of the machine circuitry, especially if ILE is given.[10,25]

Molecular adsorbents recirculating system (MARS) therapy is a specific extracorporeal albumin dialysis that is reported in the treatment of patients with severe CCB poisoning. Molecular adsorbents recirculating system 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 used in three patients with severe nondihydropyridine CCB poisoning.[88] Despite potential application, we recommend the use of VA-ECMO or some other form of ECLS. The major limitation of all these technologies, however, is that they are available only at tertiary care facilities.

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 they are 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 stability 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 and clinical findings of hypoperfusion, such as lightheadedness, nausea, or fatigue, within hours of a significant ingestion, ingestion of sustained-release formulations result in significant delays in any hemodynamic consequences with prolonged 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.

Because HDI therapy has a delay to onset on action, it should be instituted early in the clinical course in an attempt to avoid the use of vasopressors.

Patients who fail to respond to all pharmaceutical interventions should be considered for lipid emulsion adjunctive hemodynamic support, such as VA-ECMO, whenever available.

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