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Calcium-Channel Blocker Overdose

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Calcium-channel blockers (CCB) were first developed in the 1960s. Since then, the list of formulations and variety of uses has increased significantly. Unfortunately, toxic exposures to CCBs have also increased since their debut. This review will discuss the CCBs currently marketed in the United States with a focus on their toxicities and potential management.
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The first calcium-channel blocker (CCB), verapamil, was developed in 1962 [1]. Today, there are 10 CCBs marketed in the United States (Table 1). They are classified in into 4 structural groups: phenylalkylamines, benzothiazepines, dihydropyridines, and diarylaminopropylamines. CCBs are currently used in the management of angina, hypertension, migraine headache, Raynaud phenomenon, hypertrophic cardiomyopathy, and subarachnoid hemorrhage.

When taken in therapeutic doses, CCBs are relatively safe medications. However, therapeutic misadventures and intentional overdoses can cause profound cardiovascular instability and pose a significant management challenge for the emergency department physician. There were 9650 incidents of CCB ingestions reported to National Poison Control Centers in 2003 [2]. Of these, there were 57 deaths. The majority of these deaths resulted from ingestions of verapamil and diltiazem. Death from CCB overdose results from cardiovascular collapse.

Pharmacokinetics

CCBs are well absorbed from the gastrointestinal tract. They undergo extensive first-pass metabolism, predominately by cytochrome CYP 3A of the hepatic P450 system. Verapamil is demethylated in the liver to form an active metabolite, norverapamil, which retains 20% of the activity of the parent compound [3]. Diltiazem is metabolized primarily to desacetyldiltiazem which has approximately 50% of the vasodilatory action of the parent compound [1]. The dihydropyridines and diarylaminopropylamines are metabolized to inactive or minimally active agents [4].

Peak drug levels usually occur within 30 minutes to 2 hours after ingestion of immediate-release preparations but can be delayed up to 6 hours [4,5]. Controlled-release preparations may not reach peak concentrations until 22 hours after ingestion [4]. Amlodipine, isradipine, and felodipine are known for their slow absorption and long duration of action [1].

Mechanisms of Action

CCBs affect the cardiovascular, gastrointestinal, and metabolic systems. Those currently marketed in the United States act by blocking L-type, voltage-sensitive, slow calcium channels. L-type channels are located in cardiac, smooth, and skeletal muscle; however, skeletal muscle is not affected by CCBs because skeletal muscle contractions are not dependent upon calcium influx through L-type voltage channels. However, pacemaker cells of the sinoatrial (SA) and atrioventricular (AV) nodes are influenced by L-type calcium channels.

The most significant and potentially fatal effects of CCBs are those exerted on the cardiovascular system. Under normal circumstances, calcium influx through L-type channels in myocardial cell membranes provides an increase in intracellular calcium. This increase in intracellular calcium triggers the sarcoplasmic reticulum to release calcium. The calcium released from the

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Table 1 Calcium channel blockers.

Class/Generic Name	Trade Name(s)
Phenyalkyamines	
Verapemil	Calan, Verelan, Isoptin
Benzothiazepines	
Diltiazem	Cardiazem, Dilacor
Dihydropyridines	
Amlodipine	Norvasc
Felodipine	Plendil
Isradipine	DynaCirc
Nicardipine	Cardene
Nifedipine	Procardia, Aldat
Nimodepine	Nimotop
Nisoldipine	Baymycard
Diarylaminopropylamine	
Bepridil	Vascor

sarcoplasmic reticulum binds to troponin and allows actin and myosin to slide together to form a contraction. CCBs decrease myocardial contractility by blocking the influx of calcium through L-type channels in cardiac muscle cell membranes. Similar effects occur in vascular smooth muscle (affecting the arterial system more powerfully than the venous system); this causes a decrease in systemic blood pressure and an increase in coronary artery vasodilation. Blockade of L-type channels in the SA and AV nodes promotes a decrease in heart rate and a reduction in intracardiac conduction.

All CCBs decrease arterial vascular resistance. Nifedipine and other dihydropyridines are the most potent vasodilators of the CCBs but have little effect on myocardial contractility or AV nodal conduction [6]. Verapamil and diltiazem have moderate vasodilatory properties but have the added effects of decreasing myocardial contractility and slowing conduction through the SA and AV nodes; the combination of these events causes profound hypotension and conduction defects in the overdosed patient. As a result, serious morbidity is most commonly associated with verapamil and diltiazem overdoses. Bepridil has the least effect on systemic blood pressure while still promoting coronary vasodilation [5].

CCBs affect the gastrointestinal tract by inhibiting contraction of smooth muscle; the resultant decrease in gastric motility may delay absorption of the CCB itself and other coingestants. This delay may also prolong toxic effects because of continued absorption and impaired gastrointestinal drug excretion.

Insulin secretion from pancreatic islet cells is also dependent upon the influx of calcium across slow calcium channels. Consequently, CCBs cause hyperglycemia by inhibiting insulin release. Finally, lactic acidosis is common after CCB overdose and is likely the result of tissue hypoperfusion. There is also evidence, however, that CCBs may inhibit mitochondrial pyruvate dehydrogenase activation [7]. This may, in turn, prevent pyruvate from entering the Krebs cycle causing a buildup of lactate and a concomitant metabolic acidosis.

Clinical Manifestations of Overdose

Signs and symptoms of CCB overdose usually occur within 30 minutes to 2 hours of ingestion but may be delayed up to 24 hours with sustained-release (SR) preparations. Bradycardia in the face of hypotension is the hallmark of CCB overdose; AV conduction abnormalities, idioventricular rhythms, junctional escape rhythms, and complete AV block may occur as well. These effects are seen particularly with verapamil and diltiazem which, as described above, slow conduction through the SA and AV nodes, decrease myocardial contractility, and promote arterial vasodilation. Patients with nifedipine or most other dihydropyridine intoxications, however, may present with hypotension and reflex tachycardia because those drugs cause vasodilation while having little to no effect on the SA node. Conduction defects are uncommon in patients with nifedipine overdose because of the absence of AV node blockade. Pediatric ingestions of nifedipine have caused sinus tachycardia alone [8]. Isradipine is the only dihydropyridine that blunts SA node conduction [3]. As a result, it is the only dihydropyridine that may not cause tachycardia, although tachycardia has been reported [9].

Neurological symptoms may include dizziness, lethargy, coma, and seizure activity [8,10]. The etiology of these symptoms is unknown but is presumed to be secondary to cerebral hypoperfusion. Slowed gastric motility may cause nausea and vomiting. Bowel hypoperfusion may cause mesenteric ischemia [11]. Ileus and small bowel obstruction have also been described and may prolong drug absorption and make decontamination efforts challenging [5]. Metabolic features include hyperglycemia and lactic acidosis. Finally, pulmonary edema has also been reported [12,13]. It may result from poor myocardial function, but noncardiogenic pulmonary edema has been described as well [14,15].

Diagnostic Tests

CCBs are not detected on routine qualitative urine toxicology screens. They can be detected in the blood by gas chromatography/mass spectrophotometry. However, clinical outcomes and ingested dosage amounts do not correlate well with serum CCB levels. Consequently, the presence of a CCB on gas chromatography/mass spectrophotometry may confirm the diagnosis, but actual CCB concentrations do not dictate the course of management. A serum digoxin level should be obtained in patients with access to cardiac glycosides because the clinical presentation may be similar to that of CCB intoxication.

An assessment of arterial blood gas values in hemodynamically unstable patients will provide information on the degree of tissue hypoperfusion and guide the need for so-

dium bicarbonate administration. As previously described, a serum glucose analysis may reveal hyperglycemia.

A 12-lead electrocardiogram should be performed to assess rhythm disturbances and interval prolongation. An echocardiogram and central pressure monitoring may aid in evaluating and managing abnormalities in myocardial contractility.

Management

Management of patients with CCB overdose begins, as always, with delivery of adequate oxygenation, ventilation, and appropriate airway protection. Two large-bore intravenous lines should be placed in all hemodynamically unstable patients. Initial management of hypotension is routine with rapid infusion of crystalloid boluses. Early consultation with surgical and anesthesia teams capable of performing cardiac bypass or extracorporeal membrane oxygenation (if available) may be prudent in the severely unstable patient (see below).

Decontamination, Prevention of Absorption, and Elimination Enhancement

Induced emesis is contraindicated in patients with CCB overdose because of the potential for rapid deterioration. Gastric lavage may be considered for patients who present within 1 hour of ingestion. Activated charcoal (1 g/kg orally or via orogastric or nasogastric tube) is likely to be most effective if administered within 1 hour of ingestion. However, because of the high potential for significant toxicity and delayed gastrointestinal emptying, the author recommends gastric lavage followed by administration of activated charcoal more than 1 hour after ingestion for those patients who are presumed to have very large ingestions or are critically ill.

Studies evaluating the administration of multidose activated charcoal for CCB overdose are lacking. However, one may consider giving activated charcoal every 4 hours (1 g/kg per dose) especially in the case of CCB intoxications because CCBs have a propensity to form concretions. Maintenance of a protected airway and vigilant observation for the development of an ileus are important to help prevent charcoal aspiration.

Whole bowel irrigation with polyethylene glycol (GoLytely, Colyte) may aid in clearing CCBs from the gastrointestinal tract and should be considered in the symptomatic patient [16]. It is administered as a slow continuous infusion through a nasogastric tube (0.5 L/h for children, 2 L/h for adults) until the rectal effluent is clear. Care must be taken to watch for the development of an ileus which may preclude continued administration [17].

Most CCBs are distributed widely throughout the body and are highly protein bound; as a result, elimination via hemoperfusion is likely to be an ineffective means of drug removal [18]. There is a case report of charcoal hemoperfusion being used successfully to enhance the elimination of diltiazem and metoprolol [19]. However, a recent report of diltiazem overdose failed to find an appreciable decline in diltiazem levels after 2 courses of charcoal hemoperfusion [17].

Calcium Salts

Calcium salts historically have been the first line of therapy for CCB overdose. They are readily available and familiar to health care professionals. Furthermore, it intuitively makes sense to use calcium to reverse calcium-channel blockade. A recent review of the literature, however, suggests that conventional catecholamine-type vasopressors should be used as the initial therapy for CCB overdose (see below) [20]. Descriptions of the efficacy of calcium administration to the CCB-poisoned patient are variable with reports of both success [16,21] and failure [22,23]. A study evaluating the use of calcium chloride to treat verapamil-poisoned rats revealed that calcium improves hypotension primarily by increasing stroke volume; it may have little to no effect on heart rate or peripheral vascular resistance [24].

The recommended dose of calcium chloride is controversial. Those who taut its efficacy attribute their success to adequate dosing (relatively high with respect to routine dosing) [25,26]. One approach is to administer bolus doses of calcium intravenously over 5 minutes and repeat approximately every 5 minutes until an effect is seen (see Table 2 for adult and pediatric doses). As much as 30 g of calcium chloride over the course of 12 hours resulting in a serum calcium concentration of 23.8 mg/dL has been given without adverse effect [25]. Alternatively, one could administer an initial bolus of calcium followed by a continuous calcium infusion (0.2-0.4 mL/kg per hour of 10% calcium chloride or 0.6-1.2 mL/kg per hour of 10% calcium gluconate) [3]. Despite large doses, the response to calcium may be transient or minimal. Therefore, it is important to think ahead and begin other modes

Table 2 Calcium dosing for CCB overdose.

	Bolus Dose	Drip Dose
Children		
10% Calcium gluconate	0.6 mL/kg (60 mg/kg)	0.6-1.2 mL/kg per hour
10% Calcium chloride	0.2 mL/kg (20 mg/kg)	0.2-0.4 mL/kg per hour
Adults		
10% Calcium gluconate	30 mL (3 g)	0.6-1.2 mL/kg per hour
10% Calcium chloride	10 mL (1 g)	0.2-0.4 mL/kg per hour

of therapy if the patient does not respond rapidly to calcium administration.

Precautions for Calcium Administration

Calcium may promote cardiac dysrhythmias in digitalis-toxic patients [3]. Current recommendations are to withhold calcium administration in patients suspected of having cardiac glycoside toxicity and move on to the therapies listed below. This becomes a dilemma for the patient with concomitant CCB and digitalis overdoses. In this situation, it is prudent to administer digitalis antibodies before giving calcium.

As always, care must be taken to watch for calcium extravasation into tissues during calcium infusions. Calcium gluconate is less caustic to tissues and therefore is safer to give via a peripheral line than calcium chloride. However, one must administer 3 times more calcium gluconate to deliver the same amount of calcium provided by calcium chloride. Calcium chloride is best administered via a central line.

Vasopressors

Calcium, as previously noted, does not correct the bradycardia or conduction abnormalities that result from CCB toxicity. Conversely, sympathomimetics with α_1-adrenergic properties (namely, epinephrine, norepinephrine, and dopamine) provide improved chronotropism and AV conduction in animal studies [24]. Epinephrine, in addition to improving cardiac output, also provides the most significant increase in heart rate in verapamil-poisoned rats [24]. Epinephrine reversed hypotension from diltiazem overdose in a patient who failed cardiac pacing, volume expansion, calcium, glucagon, and high-dose dopamine infusions [12].

Norepinephrine and phenylephrine have profound effects on enhancing calcium influx through the calcium channels of peripheral vascular smooth muscle causing significant increases in systemic vascular resistance. These agents, therefore, seem most reasonable to use in patients whose hypotension results primarily from vascular dilation—as is usually the case in nifedipine and other dihydropyridine overdoses.

Dopamine exerts its effects by stimulating the release of norepinephrine [1]. Therefore, it may have limited use in the stressed patient who is catecholamine-depleted. In fact, it appears to have little sustained effect in most CCB overdose patients [13].

The use of isoproterenol is appealing for treating severe bradycardia and 3° AV block because of its potent β_1 activity. However, at high doses, isoproterenol has β_2 effects that promote vasodilation which may worsen hypotension, whereas the β_1 effects increase myocardial oxygen consumption. Central venous pressure monitoring may provide valuable information when trying to determine the best vasopressor to use in a given situation.

Insulin and Dextrose Infusion

Insulin is currently under investigation as a treatment of CCB overdose. Results, thus far, have been promising [7,27,28]. Many of the studies evaluating insulin therapy have reviewed its efficacy toward reversing the effects of verapamil toxicity. Verapamil blocks myocardial uptake of free fatty acids. In doing so, it makes the heart dependent on glucose uptake for energy. Unfortunately, verapamil also inhibits pancreatic insulin release which impairs carbohydrate use. This combination of events leads to poor myocardial function that is improved via the administration of exogenous insulin.

Insulin has positive inotropic effects; this is likely the result of improved myocardial carbohydrate metabolism. In addition to improving myocardial contractility, insulin also increases coronary blood flow and myocardial oxygen delivery [29]. Epinephrine and glucagon, on the other hand, augment contractility but worsen myocardial oxygen delivery. Hyperinsulinemia-euglycemia, in verapamil-poisoned canine studies, provided superior myocardial contractility and survival when compared with glucagon, calcium chloride, and epinephrine [29,30]. Improved myocardial contractility paralleled increases in myocardial glucose uptake [29]. Human data, in the form of case series, have supported these findings and have shown insulin-dextrose infusions to be beneficial in treating patients with CCB overdose [7,28]. An intravenous insulin bolus of 1 U/kg is followed by a continuous drip of 0.5 U/kg per hour [4,18,28]. Animal studies report peak inotropic response in 10 to 15 minutes after high doses of insulin (>1 U/kg), whereas smaller doses may require 45 to 60 minutes [7]. Dextrose is administered to prevent hypoglycemia: a 25- to 50-g (0.5-1 g/kg in children) bolus followed by an infusion of 0.5 g/kg per hour provides a reasonable starting dose [4]. Serum glucose concentrations must be followed closely; monitoring should continue for 6 hours after the insulin infusion is stopped because late-onset hypoglycemia has been reported [4]. Intracellular shifts of potassium may also occur as a result of insulin-dextrose infusions; consequently, patients should be monitored for hypokalemia as well.

Glucagon

Glucagon has been used to treat CCB toxicity with varying rates of success [31-37]. Its efficacy is attributed to the fact that glucagon stimulates adenyl cyclase which results in the formation of cyclic adenosine monophosphate (cAMP); furthermore, it does so by stimulating receptor sites that are distinct from catecholamine receptors and L-type calcium channels. (Catecholamines act by stimulating adenyl cyclase via β-adrenergic receptors [38]). Increases in intracellular cAMP promote calcium influx which stimulates release

of calcium from the sarcoplasmic reticulum (see Mechanisms of Action); glucagon's effects on adenyl cyclase also cause stimulation of the SA and AV nodes. As a result, glucagon has inotropic, chronotropic, and dromotropic properties.

Glucagon for CCB overdose is given as an intravenous bolus of 50 to 150 μg/kg (1-10 mg in adults) followed by a constant infusion of 0.1 mg/kg per hour titrated to effect [39]. Historically, glucagon preparations were accompanied by a phenol-containing diluent. Therefore, there was a risk of phenol toxicity if glucagon was mixed with that diluent and administered in the high concentrations needed to treat CCB overdoses. However, in 1998, the formulation was changed to contain a phenol-free diluent [40].

Phosphodiesterase Inhibitors

As previously described, glucagon stimulates adenyl cyclase to increase cAMP production; phosphodiesterase inhibitors (PDEs), on the other hand, work by inhibiting cAMP breakdown. PDEs currently marketed in the United States include amrinone (now called inamrinone), milrinone, and aminophylline. These drugs directly stimulate myocardial contractility but, unfortunately for the case of CCB overdoses, promote arterial and venous dilation as well [1]. Scattered case reports describe successful treatment of CCB ingestions with amrinone and aminophylline [36,41,42]. An animal study that compared aminophylline to inamrinone found aminophylline to be a superior agent: the aminophylline group had a shorter time to improved heart rate and systemic blood pressure [43].

Milrinone appears to cause less vasodilation compared with inamrinone; therefore, it may be a safer drug (than inamrinone) to use for CCB toxicity [44]. There is insufficient data that recommend PDEs as routine therapy for CCB intoxication. Similarly, there are no current recommendations for dosing these agents in CCB-poisoned patients. The usual dose of milrinone for patients with heart failure is 50 μg/kg intravenously followed by a continuous infusion of 0.25 to 1 μg/kg per minute; the inamrinone dose is typically a bolus of 0.75 mg/kg over 2 to 3 minutes followed by a continuous drip of 2 to 20 μg/kg per minute.

Vasopressin

A recent study evaluated the administration of vasopressin for verapamil poisoning in dogs [45]. This concept is interesting in light of the recent recommendations for septic shock. The authors hypothesized that vasopressin levels would be low in CCB toxicity—similar to that seen in states of vasodilatory shock (eg, sepsis, late hemorrhagic shock, and post–coronary bypass graft cardiogenic shock). Their findings, however, did not support their theory; vasopressin levels were actually increased, and administration of exogenous vasopressin worsened the cardiac index. Therefore, vasopressin cannot be recommended for use in CCB poisoning at this time.

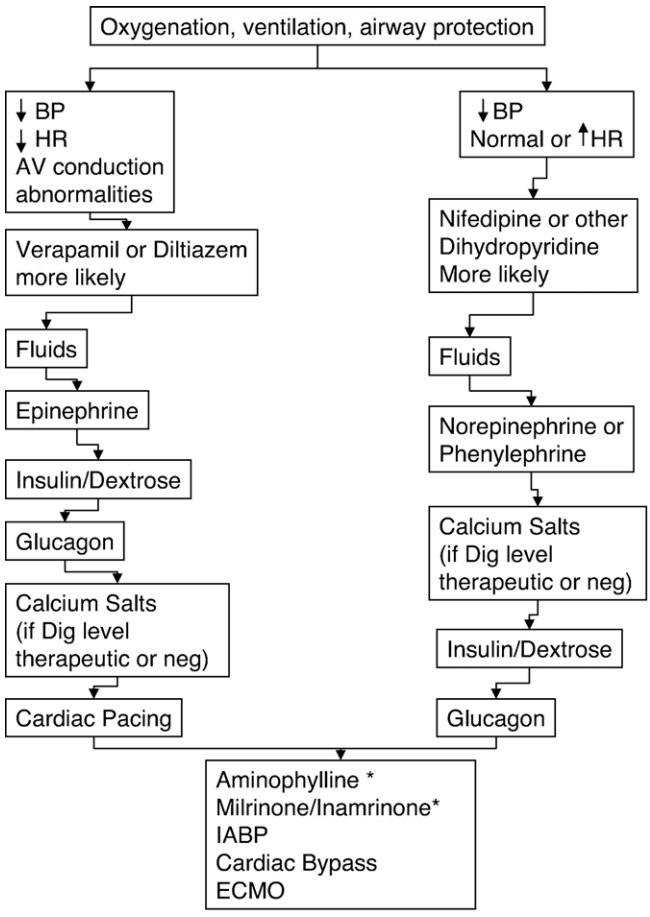

Figure 1 A treatment algorithm based on the evidence in the current literature. Although cardiac bypass and ECMO are listed last, involve teams needed to support those therapies early. Asterisk indicates little supporting data; BP, blood pressure; HR, heart rate; IABP, intra-aortic balloon pump.

Extracorporeal Membrane Oxygenation and Percutaneous Cardiopulmonary Bypass

Extracorporeal membrane oxygenation (ECMO) and percutaneous cardiopulmonary bypass (CBP) have been successfully used to treat patients with CCB overdose (diltiazem and verapamil, respectively) [17,42]. The patient sustained by ECMO survived after a prolonged arrest and a 48-hour course of ECMO [17]. The patient resuscitated by CBP was revived after having 2.5 hours of external chest compressions and 3 hours and 50 minutes of extracorporeal circulation [42]. These modalities were maintained until CCB levels spontaneously decreased to subtoxic concentrations. Although there are no controlled studies evaluating the use of ECMO or CBP for the treatment of CCB poisoning, the author recommends early consideration of these therapies because of the potential lethality of CCB overdose (Figure 1).

Cardiac Pacing and Intra-aortic Balloon Counterpulsation

Transvenous or intracardiac pacing has been attempted for CCB overdose with varying outcomes [18]. Failure to capture can be common in severe overdose [7,17,46]. Intra-aortic balloon pumps have also been used to treat CCB poisoning. They are placed via the femoral artery. Inflation occurs during diastole which enhances coronary artery perfusion. Deflation just before systole provides a vacuum that reduces afterload. Regular cardiac electrical activity is required if synchronized inflation and deflation of the balloon pump is to occur. It may be necessary to attempt cardiac pacing before balloon insertion. Intra-aortic balloon counterpulsation, along with high-dose vasopressors, was credited with patient survival after a mixed verapamil SR and atenolol overdose [47].

Disposition

Disposition of the asymptomatic toddler who presents to the emergency department after the suspected ingestion of 1 or 2 CCB pills can pose somewhat of a dilemma for the emergency physician. Case series reviewing the outcome of CCB ingestions in children propose that the effects of small doses of CCB in toddlers are minimal [10,48]. Belson et al [10] suggest that children who ingest less than 2.7 mg/kg of nifedipine SR or less than 12 mg/kg of verapamil SR may be monitored at home. However, the authors of these studies admit that the validity of their results is limited by small sample size and recognize the need for much larger scale evaluations before sound recommendations can be made.

In addition, the literature is speckled with case reports of death after ingestion of 1 nifedipine (10 mg) pill and serious cardiovascular toxicity from less than 2 doses of verapamil [46,49]. For these reasons, this author currently recommends hospital observation for asymptomatic children believed to have ingested 1 or more pills of immediate-release CCBs for 8 hours, SR products for 12 to 24 hours, and SR verapamil for 24 hours. All symptomatic patients should be admitted to an intensive care unit for cardiac monitoring. Remember that amlodipine, felodipine, and isradipine are known for their delayed times to peak plasma levels and delayed onset of action [18].

Summary

CCBs are relatively safe when taken in therapeutic doses. However, they have the potential to cause significant morbidity and potential mortality if taken in overdose. Cardiovascular collapse and death may occur despite the availability and use of multiple therapies.

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