

Calcium channel blocker toxicosis

by

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Calcium channel blockers have become widely used in human and veterinary medicine since their introduction in the 1960's. This heterogeneous group of drugs is used routinely for treating cardiac arrhythmias, systemic hypertension, and hypertrophic cardiomyopathy in small animals.¹ Three of five major classes are commonly used in the United States: phenylalkylamines, benzothiazepines, and dihydropyridines.² One newer class, the diarylaminopropylamines, operates through a slightly different mechanism (T-type channels) and is not discussed in this article. The structural differences among these classes are associated with distinct binding sites on the "slow" calcium channel, resulting in various potencies and tissue affinities.³ These agents may exert profound effects on the cardiovascular system in therapeutic doses and overdoses.⁴ Since 1995, veterinarians at the ASPCA Animal Poison Control Center (APCC) have consulted on more than 350 cases of calcium channel blocker ingestion (ASPCA APCC Database: Unpublished data, 2000).

Mechanism of action

Most currently available calcium channel antagonists exert their actions on voltage-operated, L-type channels within the plasma membrane. The L-type channel was first isolated from cardiac muscle and has since been found in vascular smooth muscle (both arteriolar and venous), nonvascular smooth muscle (bronchial, gastrointestinal, genitourinary, and uterine), and noncontractile tissues (pancreas, pituitary, adrenal glands, salivary glands, gastric mucosa, and lacrimal tissue).⁵ Blockade of L-type channels in vascular tissue results in the relaxation of vascular smooth muscle, and blockade of these channels in cardiac tissue results in negative inotropic and chronotropic effects.⁶

In vitro, all classes of calcium channel blockers cause concentration-dependent decreases in myocardial contractility, depression of sinus-node activity, and slowing of atrioventricular conduction.⁶ In vivo, however, only the phenylalkylamines and benzothiazepines have these effects at therapeutic doses. The differences between in vitro and in vivo effects of the dihydropyridines are thought to be a result of sympathetic activation in response to vasodilation, overriding their negative effects.⁶ This accounts for the more common signs seen in moderate overdoses of the dihydropyridines. The phenylalkylamines and benzothiazepines have more of an effect on nodal conduction, causing hypotension and bradycardia.⁷ Hypotension also results from the dihydropyridines, and tachycardia has also been reported.⁴

Pharmacokinetics

Calcium channel blockers are rapidly and completely absorbed after ingestion.⁴ Times to peak plasma concentrations for immediate-release forms are 20 to 45 minutes. For sustained-release formulations and amlodipine besylate, which has a much slower absorption rate,² peak plasma concentrations occur at four to 12 hours in dogs, and similar rates have been reported in cats.³ Onset of action varies with the formulation. An animal that bites into and swallows a sustained-release product can show signs within five minutes, while one that swallows the product whole may not show signs for several hours.

Distribution is extensive in all the classes, and protein binding is high, ranging from 70% to 98%.^{3,4,8} Interactions with highly protein-bound drugs may result from competition for binding sites.⁴ In people, these drugs are all metabolized extensively in the liver by oxidative pathways, predominantly by cytochrome P450 CYP3A.⁹⁻¹¹ The phenylalkylamines and benzothiazepines are potent inhibitors of hepatic microsomal enzymes, which accounts for many drug interactions.⁴ Elimination half-lives vary from two to 30 hours in dogs and cats, depending on the formulation (i.e. immediate vs. sustained-release) and dosage.³ Excretion occurs primarily through urine and, to a lesser extent, bile and feces.²

The clearance of all the calcium channel blockers is expected to be prolonged in such disease states as congestive heart failure, cardiomyopathy, or hypotensive overdose in which hepatic blood flow is reduced.⁴ Elimination can be slowed by drugs that inhibit hepatic enzymes (*e.g.* cimetidine), potentially increasing its cardiovascular effects and producing toxicity.⁴

Manifestations of overdose

The most common signs reported to the ASPCA APCC after calcium channel blocker ingestion are hypotension, bradycardia, seizures, tachycardia, and pulmonary edema (ASPCA APCC Database: Unpublished data, 2000). Deaths have been reported to the ASPCA APCC with amlodipine and nifedipine overdose. The dihydropyridines produce the greatest vasodilatory effects of the calcium channel blockers both therapeutically and in overdoses. This most commonly manifests as profound hypotension and reflex tachycardia in cases of moderate overdose. Nodal conduction may be depressed in cases of massive overdose, resulting in bradycardia.⁴

Dihydropyridine ingestions of 1mg/kg have resulted in clinically relevant signs of depression and hypotension (ASPCA APCC Database: Unpublished data, 2000). Since phenylalkylamines and benzothiazepines can cause conduction changes at therapeutic doses, these signs are amplified in cases of overdose (*e.g.* severe hypotension, bradycardia, and potential heart block). For this reason, any exposure above therapeutic concentrations should be treated. Ventricular tachyarrhythmias are not typical of calcium channel blocker overdose, and their presence suggests underlying cardiac disease or effects of other drugs.⁴ Hyperglycemia is a common finding because of the inhibitory effect on insulin release from pancreatic β cells.¹² It is reversible and usually resolves within 24 hours but may require insulin therapy.^{6,12} Metabolic acidosis, as a result of tissue hypoperfusion, can be seen in severe cases. Seizures are rare but have been reported in overdoses in people¹³ and animals (ASPCA APCC Database: Unpublished data, 2000).

Treatment

Asymptomatic patients

Within 15 minutes of ingestion, vomiting may be induced with 3% hydrogen peroxide (1 to 5 ml/kg; 45 ml maximum) or apomorphine hydrochloride subconjunctival solution followed by rinsing.¹⁴ After nausea is resolved, administer 1 g/kg activated charcoal with a cathartic such as 70% sorbitol (3 ml/kg).¹⁴ In cases of massive overdose (≥ 25 mg/kg), perform gastric lavage. Repeated administration of activated charcoal every four to six hours for two to four doses is indicated if a sustained-release product is ingested. Monitor the patient's electrocardiogram, blood pressure, and blood glucose concentrations for 24 hours; further treatment will be symptomatic and supportive.

Symptomatic patients

As with any emergency situation, establish an airway and provide adequate ventilatory and circulatory support. If the ingestion occurred within one hour, consider administering activated charcoal via a stomach tube. This time frame may be extended in cases involving sustained-release products or with the ingestion of a large number of pills. Airway protection is essential in these patients, and the risks vs. benefits of activated charcoal use must be considered.

In critically hypotensive patients, administer 0.9% sodium chloride or lactated Ringer's solution for volume expansion and 10% calcium gluconate at 0.5 to 1.5 ml/kg slowly intravenously.¹⁵ Calcium reverses the myocardial depression and improves atrioventricular nodal conduction.⁴ If hypotension persists, dopamine hydrochloride (10 to 20 μ g/kg/min), dobutamine hydrochloride (2 to 20 μ g/kg/min), or inamrinone lactate (Inocor - Sanofi Winthrop [Canada]; 30 to 100 μ g/kg/min) by intravenous infusion can be started.^{15,16} Glucagon, a polypeptide hormone with positive inotropic and chronotropic actions unaffected by adrenergic blockade,⁴ is used in people and dog models but is more expensive and less readily available for many practitioners.^{4,17}

To control bradyarrhythmias, atropine sulfate (0.02 to 0.04 mg/kg intravenously) or isoproterenol hydrochloride (0.4 mg in 250 ml of 5% dextrose solution, slow drip to effect) may correct these signs.¹⁵ The tachyarrhythmias seen with the dihydropyridines usually resolve when the hypotension is corrected. Frequent auscultation is important in severely affected cases to detect evidence of pulmonary edema. Evidence of non-cardiogenic pulmonary edema has been reported after an amlodipine overdose (36 mg/kg) in a dog (ASPCA APCC Database; Unpublished data, 2000) and has occurred in people after verapamil hydrochloride overdose.¹⁸

Control seizures with diazepam (0.5 to 1 mg/kg intravenously) or pentobarbital sodium (3 to 15 mg/kg intravenously slowly to effect).¹⁵ Control hyperglycemia with insulin if it persists for more than a few hours. Insulin increases contractility during myocardial ischemia in vitro (*i.e.* it has positive inotropic effects) as well as controls hyperglycemia.¹⁹

Conclusion

Because of the effects of calcium channel blockers on the myocardium and peripheral vasculature, it is not uncommon for hypotension to persist despite correction of arrhythmias. Treatment and monitoring should continue until all signs have resolved. The prognosis depends on the amount ingested and the severity of signs at presentation. Early, aggressive decontamination can prevent the onset of serious signs.

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