# Calcium Channel Blocker Toxicity in Dogs and Cats

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**KEYWORDS**

- Calcium channel blocker • Verapamil • Diltiazem
- Dihydropyridine

Calcium channel blockers (CCBs) are a commonly used group of drugs in both human medicine since the 1960s and in veterinary medicine since the 1980s.[1,2] They are defined by their ability to block the slow, or long-lasting (L-type), calcium channel, which is found primarily in cardiac and arterial smooth muscle tissue and to a much lesser extent in other tissues as well.[3] They have been commonly used for the treatment of hypertension, cardiac disease including hypertrophic cardiomyopathy (and in human medicine, angina and congestive heart failure), and cardiac arrhythmias, and they have also been suggested for other uses such as premature labor in humans and acute renal failure in companion animals.[1,3,4]

Several classes of CCB currently exist; of these, the most widely used are the phenylalkylamine verapamil (Calan; Verelan; Verelan PM; Isoptin; Isoptin SR; Covera-HS), the benzothiazepine diltiazem (Cardizem; Dilacor; Tiazac), and the dihydropyridines amlodipine (Norvasc), felodipine (Plendil), isradipine (Dynacirc), nicardipine (Cardine; Cardine SR), nifedipine (Adalat; Procardia; Afeditab; Nifediac), nimodipine (Nimotop), nitrendipine (not available in the United States), and nisoldipine (Sular). The only example of the diphenylpiperazine class, mibefradil (Posicor), was withdrawn from the market in 1998, and the only example of the diarylaminopropylamine class, bepridil (Vascor), was withdrawn in 2003.[5,6] Each class has a different affinity for the L-type calcium channels found in arterial smooth muscle and cardiac tissue.

While there is no published data on the frequency of CCB toxicity in veterinary medicine, the ASPCA Animal Poison Control Center (APCC) has consulted on 3701 cases of CCB exposure between 2000 and 2010 (ASPCA APCC Database, unpublished data, 2011). Overdose from CCBs can result in severe, life-threatening effects on cardiac conduction and blood pressure. In addition, there may also be effects on the digestive tract, pulmonary function, the nervous system, and pancreas. Treatment may involve gastrointestinal decontamination (induction of emesis and administration of activated charcoal), stabilizing the cardiovascular system through blood pressure

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and cardiac rhythm regulation, and supportive care as needed to address other clinical signs.

## PATHOPHYSIOLOGY

Calcium channels play a significant role in a number of cellular functions, particularly in the sinoatrial (SA) and atrioventricular (AV) nodes, myocardium, and arterial smooth muscle myocytes. In the normal physiologic state, there is a large concentration gradient of calcium across the cellular membrane, with high extracellular and low intracellular calcium concentrations.[1,3,4] Since calcium is unable to diffuse freely across the cellular membrane, this large concentration gradient is maintained by limiting calcium influx into the cell through specific calcium channels, sequestration of free intracellular calcium in the sarcoplasmic reticulum of myocytes, and maintaining an adenosine triphosphate (ATP)-driven calcium export pump.[1,3,4] When activated, the various calcium channels will allow an intracellular influx of calcium, triggering a variety of responses depending on the tissue involved.[1,3,4,7]

There are a number of calcium channel types, including receptor-operated, stretch-operated, second messenger operated, and voltage-sensitive calcium channels.[1,3] The voltage-sensitive calcium channels are of most importance to calcium channel blocker toxicity and are so-called because they open in response to a change in the cell membrane potential.[1,3,4,7] The voltage-sensitive calcium channels include long-lasting (L-type), transient or fast (T-type), Purkinje (P-type), Q-type, R-type, and neuronal (N-type) calcium channels.[1,3,7] The L-type calcium channels are found primarily in the heart, vascular smooth muscle, skeletal muscle, and, to a lesser extent, pancreas, lung, brain, and other tissues.[3,7] T-type calcium channels are found in cardiac nodal and conducting cells, smooth muscle, skeletal muscle, and neuronal tissue.[1,3] P-type, Q-type, and R-type calcium channels are found in Purkinje cells of the cerebellum and cerebellar granule cells.[1] N-type calcium channels are found in neurons throughout the brain.[1] Within the L-type calcium channel, there are at least 4 subclasses.[7] The various CCBs currently available act on the $\alpha_{1c}$ subunit of the L-type voltage-sensitive calcium channel.[7] The different classes of the CCBs have affinity for the various isoforms of the L-type calcium channel, which may account for the variability in their cardiovascular effects.[3,7]

In the heart, the L-type voltage-sensitive calcium channel plays a key role in conduction of the cardiac rhythm. The pacemaker cells of the SA node and AV node have L-type calcium channels that allow a slow intracellular flow of calcium.[3,4,7] In those cells, the slow calcium influx results in spontaneous depolarization during phase 4 of the action potential.[3,4] Propagation of the electrical impulse through the AV node, Purkinje fibers, and cardiac myocytes is also maintained by the calcium influx through L-type calcium channels, which open during phase 2 depolarization.[3,4] CCBs prevent this calcium influx in the nodal and myocardial cells, resulting in a slower sinus rate in the SA node and reduced AV conduction.[3,4]

The calcium influx through L-type calcium channels is also important in contraction of the myocardium and smooth muscle by facilitating the excitation-contraction coupling. In the cardiac myocytes during phase 2 depolarization, the small calcium influx stimulates the sodium-calcium exchange pump to further increase intracellular calcium and also causes release of calcium from the sarcoplasmic reticulum (known as calcium-induced calcium release, or CICR).[1,3,4] The excess intracellular calcium binds to troponin-C, leading to a conformation change in the troponin–tropomyosin complex that exposes the actin filament, allowing actin-myosin binding. This results in contraction of the myocyte.[1,3,4] For vascular smooth muscle, the excess intracellular calcium binds to calmodulin rather than troponin-C.[1,3,4] This results in phosphorylation of

myosin, which allows the myosin-actin interaction, leading to contraction.[1,3,4] CCBs prevent the calcium influx into cardiomyocytes and vascular smooth muscle, resulting in reduced cytosolic calcium and reduced CICR from the sarcoplasmic reticulum, leading to reduced cardiac inotropy and vascular tone.[1,3,4] For vascular beds with high resting tone (coronary and arterial smooth muscle), significant vasodilation will occur with reduced vascular tone.[3,4] For vascular beds with low resting tone (gastrointestinal and venous smooth muscle), little vasodilation occurs.[3,4]

The L-type calcium channels are also important systemically. In the pancreas, the L-type calcium channels influence insulin release from the pancreatic $\beta$ cells. CCBs block the L-type calcium channels in these cells, resulting in reduced insulin release and hyperglycemia.[1] At the cellular level, the calcium influx through L-type calcium channels results in increased mitochondrial uptake of calcium, affecting intracellular ATP levels.[1,3] CCBs lower mitochondrial calcium levels, resulting in reduced pyruvate dehydrogenase activity, leading to lactate accumulation.[1,3] Platelet aggregation may also be inhibited to some extent with CCBs.[3] Endothelin-mediated vasoconstriction is also dependent on L-type calcium channels. Acute renal failure secondary to endothelin-mediated vasoconstriction may be attenuated by CCBs.[3]

## PHARMACOLOGY

Of the 5 classes of CCB that have been developed, only 3 are currently on the US market. The CCBs mibefradil, a diphenylpiperazine, and bepridil, a diarylaminopropylamine, antagonized both the L-type and T-type calcium channel; however, they were withdrawn from the US market in 1998 and 2003, respectively, because of numerous severe drug interactions.[5,6] The remaining classes of CCB vary in the extent to which they affect the L-type calcium channels within vascular and cardiac tissues.

### *Phenylalkylamines*

The representative drug of the phenylalkylamine class of CCB is verapamil. Verapamil is a nonspecific L-type CCB in that it has effects on both vascular and cardiac tissue, resulting in vasodilation, negative inotropy, and SA and AV node suppression.[3,4]

The pharmacokinetics for verapamil have been studied in dogs and humans (**Table 1**); however, little information regarding cats has been published. Verapamil is rapidly absorbed but has low bioavailability because of extensive first-pass metabolism; bioavailability is lower in the dog (10%–23%) compared to 20% to 35% in healthy humans and approximately 50% in human liver patients.[8,9] In humans, 60% to 80% of the absorbed verapamil is metabolized in the liver via cytochrome P-450 to active and inactive metabolites, with norverapamil being the major metabolite.[9] Norverapamil has a cardiovascular potency 20% that of verapamil.[9] In dogs, verapamil is also metabolized to several active and inactive metabolites.[8] In humans, verapamil reaches the cerebrospinal fluid poorly, crosses the placenta, and passes into the milk.[9] Elimination of verapamil varies between dogs and humans, with biliary excretion as the primary route in dogs and renal excretion as the primary route of elimination of verapamil in humans.[8,9] With intravenous (IV) dose-escalation studies in humans, drug clearance becomes nonlinear due to saturation of hepatic metabolism.[9] The onset of pharmacologic action and time to peak plasma concentration depend on the route of administration and formulation, with IV dosing fastest (1–5 minutes) and oral controlled-onset extended-release (COER) preparations longest at 11 hours in humans.[9]

**Table 1**
**Pharmacokinetics of the different classes of CCB**

| Class | Phenylalklamine | Benzothiazepine | Dihydropyridine | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Representative Drug** | **Verapamil** | **Diltiazem** | **Amlodipine** | **Felodipine** | **Nifedipine** | **Nicardipine** | **Nisoldipine** | **Isradipine** |
| Absorption | *Dog:* 90%<br>*Human:* 90% | *Dog:* rapid<br>*Human:* 98% | 60%–65% | 10%–25% | 30%–60% (IR)<br>30%–50% (ER) | 35% | 87% | 15%–24% |
| % Bioavailability | *Dog:* 10–23<br>*Human:* 20–35 | *Dog:* 17–24<br>*Cat*[a]: 71 (IR)<br>36 (ER) | *Dog:* 90<br>*Human:* 64–90 | 13–20 (ER) | 30–60 (IR)<br>30–50 (ER) | 35 | 4–8 | 14–24 |
| Time to Cmax (h) (oral) | 1–2 (IR)<br>7–11 (ER)[b] | *Dog:* 0.5<br>*Cat*[a]: 0.75 (IR)<br>5.7 (ER)<br>*Human:* 2–4 (IR)<br>4–18 (ER)[b] | *Dog:* 6<br>*Human:* 6–12 | 2–6 (ER) | 0.2–0.75 (IR)<br>6 (ER) | 0.5–2 (IR)<br>1–4 (ER) | 1–1.5 (IR)<br>4–13 (ER) | 1.5 (IR)<br>7–18 (ER) |
| Time to onset (h) (oral) | 0.5–1.5 (IR)<br>4–5 (ER) | 0.25–1 (IR) | | 1 (IR)<br>5 (ER) | 0.2 (IR)<br>0.5–1 (ER) | 0.2 | 1–3 (IR) | 1 (IR)<br>2 (ER) |
| Effect of food | None | None | None | Increases rate of absorption | Variable | Reduced absorption | Slows absorption | ? |
| Metabolism Site | Liver | Liver | *Dog:* liver<br>*Human:* liver | Liver | Liver, gut wall | Liver | Liver, gut wall | Liver |
| Active metabolites? | *Dog:* yes<br>*Human:* yes | Yes | Yes | No | No | No | Yes | No |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Excretion | *Dog:* mostly bile<br>*Human:* kidney 70%<br>Bile/feces 9%–16% | Bile/feces 65%<br>Kidney 35% | *Dog:* feces 45%<br>kidney 45% as metabolites<br>*Human:* kidney 70% as metabolites, 10% unchanged bile/feces 20%–25% | Kidney 70%–80%<br>Bile/feces <15% | Kidney 60%<br>Bile/feces 35% | Kidney 60%<br>Bile/feces 35% | Kidney 60%–80%<br>Bile/feces 6%–12% | Kidney 60%–65%<br>Bile/feces 30% |
| Elimination T½ (h) | *Dog:* 1.8–3.8<br>*Human:* 8–12 | *Dog:* 2–4<br>*Cat*[a]: 1.8 (IR) 6.8 (XR)<br>*Human:* 3–6.6 (IR)<br>4–10 (ER) | 30–60 | 11–16 (IR)<br>27–33 (ER) | 2–5 | 8.6 | 9–17 | 8 |

*Note:* There may be significant variability in pharmacokinetic data between species, and many of the listed medications have only been extensively studied in humans.

*Abbreviations:* $C_{max}$, peak plasma concentration; ER, non–immediate-release preparation (including extended-release, sustained-release, controlled-release, long-acting, and controlled-onset extended-release); IR, conventional immediate-release preparation; T½, half-life

[a] Cardizem IR and Cardizem CD have been studied in cats.[12]

[b] The time to peak plasma concentration (oral route) varies with the different extended-release preparations. The time listed is the range including all extended-release, sustained-release, controlled-release, long-acting, and controlled-onset extended-release preparations.

Data are for humans, unless otherwise specified; *from* Refs.[3,8,9,11–21]

### *Benzothiazepines*

Diltiazem is the most commonly used drug of the benzothiazepine CCB class. Compared to verapamil, diltiazem has less significant effects on arterial vascular smooth muscle, cardiac contractility, and AV node suppression, although the SA node suppression is approximately the same between the 2 drugs.[3,4]

Diltiazem is formulated as a conventional immediate-release tablet or as a COER preparation. There are several different COER preparations available. Cardizem CD is a dual-release capsule that holds 2 types of beads containing the drug; the beads differ in the thickness of the surrounding membranes, with 40% of the beads meant to dissolve within the first 12 hours after oral administration and the remaining 60% formulated to dissolve over a second 12-hour period of time.[10] Dilacor XR is an extended-release capsule that contains several 60-mg tablets contained in a matrix core that swells and slowly releases the drug over a 24-hour period of time in humans.[11] The individual tablets are generally removed from the capsule and sectioned in order to dose small animals.[11]

The pharmacokinetics for diltiazem have been studied in cats, dogs, and humans (see **Table 1**).[3,8,12–15] In dogs and humans, systemic bioavailability is low due to a high first-pass effect; however, in cats bioavailability is much higher.[3,12,13] This difference is hypothesized to be related to a reduced hepatic first-pass effect in the cat.[12] Diltiazem is widely distributed through most tissues.[13] It can cross the placenta and can be found in milk as well, with one report suggesting that concentrations in human breast milk may approximate serum levels.[13] Diltiazem is metabolized in the liver through both deacetylation and demethylation in dogs and primarily through deacetylation in humans.[3,13,14] Deacetyldiltiazem is the major active metabolite in humans and is 25% to 50% as potent a coronary vasodilator as the parent compound.[13] Diltiazem also undergoes enterohepatic recirculation in dogs and humans, with the second plasma peak in humans occurring 3 to 4 hours after ingestion.[3] Elimination of diltiazem in dogs and humans is blood flow dependent, while in cats it is suggested to be independent of blood flow.[12] It is primarily eliminated in the feces, although renal excretion accounts for approximately one-third of elimination in humans.[13] The terminal half-life is dependent on the formulation, with immediate-release preparations eliminated faster compared to extended-release formulations.[13] The time to reach the maximal plasma concentration for oral immediate-release/conventional diltiazem is 30 minutes in dogs and 45 minutes in cats, to an average of 5.7 hours following oral administration of the extended-release capsule Cardizem CD in cats.[11,12]

### *Dihydropyridines*

There are a number of drugs that fall within the dihydropyridine CCB class, including amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nitrendipine, and nisoldipine.[7] Of these, the one most commonly involved in exposures reported to the ASPCA APCC is amlodipine, which accounted for 76% of all dihydropyridine cases from 2000 to 2010 (ASPCA APCC Database, unpublished data, 2011). The dihydropyridines are most noted for their effects on vascular smooth muscle while having relatively little effect on cardiac contractility or conduction.[3,4]

Dog and cat pharmacokinetic data are lacking for most of the drugs in the dihydropyridine class of CCB (with the exception of amlodipine in dogs); however, there is a significant amount of pharmacokinetic data in humans (see **Table 1**).[15–21] In general, the absorption, bioavailability, volume of distribution, and terminal elimination half-life of the dihydropyridines vary between drugs. Amlodipine has the highest

**Table 2**
**Therapeutic doses of selected CCB commonly used in veterinary medicine**

| | Verapamil | Diltiazem | Amlodipine |
|---|---|---|---|
| Dog | IV: 0.05 mg/kg to a maximum cumulative dose of 0.15 mg/kg<br>PO: 0.5–5.0 mg/kg q8h | IV: 0.05–0.35 mg/kg to a maximum cumulative dose of 0.75 mg/kg<br>PO: 0.5–2.0 mg/kg | PO: 0.05–0.4 mg/kg q12h |
| Cat | IV: 0.025 mg/kg to a maximum cumulative dose of 0.15–0.2 mg/kg<br>PO: 0.5–1.0 mg/kg q8h | IV: 0.125–0.35 mg/kg to a maximum cumulative dose of 0.75 mg/kg<br>PO: 0.5–1.5 mg/kg q8h up to 10 mg/kg daily | PO: 0.625–1.25 mg daily |
| Human (pediatric) | PO: 3–5 mg/kg daily in 3 divided doses | PO: 1.5–2 mg/kg daily in 3–4 divided doses to a maximum cumulative dose of 3.5 mg/kg daily | PO: 0.1 mg/kg q12–24h to a maximum of 0.6 mg/kg/day or 20 mg/day |

*Data from* Refs.[9,13,16,22–24]

bioavailability and volume of distribution.[15,16] All of the dihydropyridines are highly protein bound, extensively metabolized by the liver, and eliminated primarily through the kidneys.[15–21] The onset of action and time to peak plasma concentrations depend on the formulation, with immediate-release preparations being the shortest and COER preparations being the longest.[15–21]

## CLINICAL SIGNS

The minimum oral toxic dose of each CCB has not been established in humans or animals. Signs of toxicity have been noted at therapeutic doses of verapamil, diltiazem, amlodipine, and nifedipine in some dog and cat cases (**Table 2**) (ASPCA APCC Database, unpublished data, 2011).[22–24] The diltiazem oral dose resulting in death of 50% of exposed patients ($LD_{50}$) in dogs has been reported as somewhere beyond 50 mg/kg but has not been reliably established.[23]

While the various classes of CCBs have distinct differences in their specificity for either the vascular smooth muscle or heart at therapeutic doses, in overdoses the tissue specificity may be lost.[3,4,25–27] Typically, the clinical signs seen are the result of an exaggeration of the normal pharmacologic activity of CCBs.[3,4,25–27] With verapamil and diltiazem toxicity, clinical signs include sinus bradycardia and/or bradyarrhythmias (all degrees of heart block, QT interval prolongation, or junctional rhythms) due to slowed cardiac conduction and also hypotension due to vasodilation and reduced cardiac inotropy (ASPCA APCC Database, unpublished data, 2011).[25–28] Sinus tachycardia likely due to carotid sinus reflex stimulation is possible as well.[25–28] With the dihydropyridines, common clinical signs include profound hypotension due to vasodilation and reflex sinus tachycardia (ASPCA APCC Database, unpublished data, 2011).[25–27]

Additional clinical signs associated with all CCBs include digestive upset, hypothermia (presumably due to hypotension), central nervous system depression due to hypotension and/or bradycardia, noncardiogenic pulmonary edema, hyperglycemia due to inhibition of insulin release, hypokalemia, metabolic acidosis due to tissue hypoperfusion and increased lactate production, and, rarely, stimulatory signs such as seizures, agitation, or tremors (ASPCA APCC Database, unpublished data,

2011).[1,25–27,29] The exact mechanism of pulmonary edema is unknown; however, several mechanisms have been proposed. The development of pulmonary edema is thought to be secondary to aggressive fluid therapy combined with either increased pulmonary capillary permeability, drug-induced changes to alveolar membrane permeability, or selective precapillary vasodilation from CCBs.[30,31]

## DIAGNOSIS

The diagnosis of CCB toxicity in veterinary patients is largely based on clinical signs consistent with CCB toxicity and the history of a possible exposure. Serum drug levels for CCBs are not routinely evaluated on presentation because the tests are not widely available and drug levels for specific agents do not necessarily correspond with the degree of clinical signs seen.[1,29] Signs of toxicity can occur at therapeutic drug levels in humans.[1,29] When tests are available, they could be used to confirm an exposure.[1]

The clinical presentation of a patient with hypotension and bradycardia or tachycardia can be consistent with other etiologies as well. Differential diagnoses may include toxicity from digoxin, cardiac glycoside containing plants, $\beta$-adrenergic antagonists, $\alpha_2$-adrenergic agonists, organophosphates, type 1a antiarrhythmic agents such as procainamide or quinidine, bufadienolides, and nontoxic causes such as myocardial infarction or other cardiac disease.[32]

## TREATMENT

Treatment for CCB toxicity focuses on the reducing the absorption of the drug, providing supportive care based on the clinical signs seen, and augmenting myocardial function. There is no specific antidote for treatment of CCB toxicity due to the number of mechanisms contributing to clinical signs; however, there are a number of therapies available that can counteract some of the CCB effects.

### *Decontamination*

For the asymptomatic patient with a recent exposure of less than 2 hours, gastric decontamination is recommended.[26] This may be accomplished by inducing emesis, gastric lavage and/or administration of activated charcoal (Toxiban; UAA Gel). In the symptomatic patient, gastric decontamination should only be attempted once the patient's condition is stable. Inducing emesis is contraindicated for a symptomatic patient; however, gastric lavage or activated charcoal administered via a stomach tube could be considered, particularly with large ingestions or ingestion of sustained-release preparations.[25]

Emesis can be accomplished in the asymptomatic patient using a few different methods. For dogs, apomorphine (Apokyn) or hydrogen peroxide 3% can be used as emetics, while in cats xylazine (AnaSed; X-Ject; Xyla-Ject; Sedazine; TranquiVed) can be used.[33–35] Dopaminergic receptors in the chemoreceptor trigger zone are stimulated by apomorphine, resulting in emesis in the dog.[33] The apomorphine dose recommended in dogs is 0.03 to 0.04 mg/kg IV, intramuscularly (IM) or in the subconjunctival sac.[33,34] If given in the subconjunctival sac, the sac can be flushed with saline once emesis has occurred.[33] Common adverse effects associated with apomorphine use include sedation and when given IV or IM protracted vomiting.[34] In dogs, hydrogen peroxide 3% can also be given an alternative to apomorphine. Hydrogen peroxide 3% causes local irritation in the stomach to stimulate emesis, and is used at a dose of 1 to 2 mL/kg PO up to a maximum of 50 mL/patient.[33] In cats, xylazine (1.1 mg/kg IM or subcutaneously [SQ]) causes emesis through stimulation of

the $\alpha_2$-adrenergic receptors in the emetic center.[35] Common adverse effects associated with xylazine include sedation, hypotension, bradycardia, and respiratory depression, although these effects can be reversed with atipamazole (0.2 mg/kg IV) or yohimbine (0.1 mg/kg IV).[33,35] For patients where emesis is contraindicated, gastric lavage performed under anesthesia may be considered.[33]

Activated charcoal can also be used for gastrointestinal decontamination. It is effective for both immediate and extended-release preparations of CCBs.[36] In a human study evaluating the effectiveness of activated charcoal for verapamil exposures, activated charcoal was effective in reducing the absorption of immediate-release verapamil when administered immediately following ingestion but not 2 hours after ingestion.[36] Activated charcoal was effective in reducing absorption of sustained-release verapamil 4 hours after ingestion (the longest time evaluated in the study).[36] Activated charcoal is used in dogs and cats at a dose of 1 to 3 g/kg PO with a cathartic such as sorbitol.[33,37] Activated charcoal can be repeated every 4 to 6 hours for 2 to 4 doses if a high dose of a sustained-release preparation is ingested.[33,37] Adverse effects associated with activated charcoal include aspiration pneumonia or hypernatremia.[37] If the patient is symptomatic, airway protection is critical and the risk versus the benefits of activated charcoal should be considered. For the ingestion of sustained-release preparations, a warm water enema at a rate of 2.5 to 5 mL/kg could also be considered to facilitate evacuation of the intestinal contents.

Extracorporeal decontamination (hemodialysis) is not expected to be of benefit in CCB toxicity. CCBs are highly protein bound, which minimizes the benefit of hemodialysis.[1]

### *Monitoring*

When there has been a possible exposure to a CCB, close monitoring of the cardiovascular system, respiratory system, nervous system, and blood chemistries should be implemented for 12 to 24 hours or longer following exposure.[25] The blood pressure, heart rate, and cardiac rhythm should be monitored frequently. An electrocardiogram (ECG) should be used to monitor the cardiac rhythm. Respiratory system monitoring can involve auscultation, pulse oximetry, or arterial blood gas. The nervous system should also be monitored for depression or seizures. The serum glucose, acid-base status, and electrolytes should be monitored for the development of hyperglycemia, lactic acidosis, hypokalemia, hypophosphatemia, or hypomagnesemia.

As noted previously, plasma CCB levels can be performed to determine if an exposure has occurred; however, monitoring CCB levels is not expected to be beneficial during the course of treatment since reference ranges have not been established in animals and since clinical signs can occur at therapeutic doses of CCBs.[1,22–25,29]

### *Supportive Care*

In the symptomatic patient, stabilization and supportive care should be provided. Fluid therapy using a balanced isotonic crystalloid fluid should be administered for cardiovascular support and to help maintain hydration. Persistent hypotension despite crystalloid therapy should be treated with a colloid-containing fluid such as hetastarch (Hespan). Hetastarch is used in dogs at an initial dose of 5 mL/kg IV bolus over 15 to 30 minutes followed by an IV continuous rate infusion (CRI) of 12 mL/kg/d, and in cats, 10 mL/kg/d IV CRI.[25,26,38] Aggressive fluid therapy should be used with care to minimize fluid overload and the development of pulmonary edema.[25,26,30,31]

An antiemetic such as maropitant (Cerenia) (1 mg/kg SQ q24h), metoclopramide (Reglan) (0.1–0.5 mg/kg SQ or IM or 0.01–0.02 mg/kg/hr IV CRI), ondansetron (Zofran) (0.1–1 mg/kg IV q12–24h), or dolasetron (Anzimet) (0.5–1 mg/kg IV q24h) may be used to manage any vomiting.[39–42] If seizures develop, diazepam (Valium; Diastat) (0.5–1 mg/kg IV) or a barbiturate such as pentobarbital (Nembutal) (3–15 mg/kg IV) or phenobarbital (Tubex; Carpujects; Luminal Sodium) (2–20 mg/kg IV) may be used.[43–45] Potassium should be supplemented in the fluids when the serum potassium is below 2.5 mEq/L. If pulmonary edema develops, oxygen support should be provided.

### *Specific Therapies*

Most conventional therapies specific for CCB toxicity aim to increase transmembrane calcium flow by increasing extracellular calcium concentrations (calcium gluconate or calcium chloride) or increasing intracellular cyclic-adenosine monophosphate (cAMP) concentrations (glucagon [GlucoGen] or inamrinone [Inocor]), increase cardiac inotropy and chronotropy (sympathomimetics, temporary pacemaker), increase peripheral vascular tone (sympathomimetics), and increase glucose or free fatty acid utilization (insulin-glucose, lipid emulsion (Liposyn). Atropine sulfate (0.02 mg/kg) IV can be used for persistent bradycardia. Repeat atropine if and as needed.

#### *Calcium*

After attempting cardiovascular stabilization, calcium is commonly administered for persistent hypotension and/or bradycardia.[1,25,26] The increased extracellular calcium available to cells may increase the intracellular calcium influx.[1,25,26] Increased calcium may also increase calcium release from the sarcoplasmic reticulum, enhancing contractility.[1,25,26] Calcium gluconate or calcium chloride may be used, although calcium chloride will provide a higher concentration of calcium ion per milliliter compared to calcium gluconate (13.6 mEq vs 4.5 mEq in 10 mL of a 10% solution).[26] Calcium gluconate 10% can be used at a dose of 0.5 to 1.5 mL/kg IV slowly over 5 minutes while monitoring the ECG closely or as a CRI of 0.05 mL/kg/h.[46] Calcium chloride 10% is used at a dose of 0.1 to 0.5 mL/kg IV slowly over 5 minutes or as a CRI of 0.01 mL/kg/h.[46] If bradycardia develops or worsens during use, discontinue the calcium supplementation.[46] Adverse effects include hypercalcemia and local tissue irritation or necrosis if given extravascularly.[46]

#### *Glucagon*

Glucagon is a cardiac inotrope and chronotrope.[1,26] In addition to stimulating hepatic glycogenolysis, thus increasing blood glucose, it also acts on cardiac G protein–coupled receptors, stimulating an increase in intracellular cAMP and thus increasing the myocardial calcium influx.[1,26] The increased intracellular calcium results in increased contractility and enhances impulse generation.[1,26] Glucagon may benefit patients with either hypotension or bradycardia, although it is expensive and may not be readily available. In case reports describing its use for verapamil toxicity in dogs, it was only transiently effective.[28,47] It can be used at an initial dose of 50 nanograms/kilogram body weight (ng/kg) IV bolus followed by a CRI of 10 to 15 ng/kg/min up to 40 ng/kg/min.[48]

#### *Inamrinone*

As a phosphodiesterase III inhibitor, inamrinone prevents degradation of cAMP in vascular and cardiac muscle, resulting in increased intracellular cAMP.[1,25,29] Increased cAMP leads to an increase in the myocardial calcium influx, resulting in improved

contractility and increased impulse generation.[1,25,29] It can cause peripheral vasodilation, thus worsening hypotension if present.[29] It can be used at an initial dose of 1 to 3 mg/kg IV bolus followed by 10 to 100 μg/kg/min IV CRI.[49]

***Sympathomimetics***

Refractory hypotension or bradycardia may respond to sympathomimetic drugs, although no one agent has been proved to be consistently effective.[26] Dopamine hydrochloride (Inotropin) (10–20 mcg/kg/min IV), dobutamine hydrochloride (Dobutrex) (2–20 μg/kg/min IV), isoproterenol (Isuprel) (0.04–0.08 μg/kg/min IV), epinephrine (Adrenalin) (0.05–0.4 μg/kg/min IV), or phenylephrine hydrochloride (Neo-Synephrine) (0.5–3 μg/kg/min IV) may be used.[1,26,50–54]

***Insulin-glucose***

Hyperglycemia is commonly associated with CCB toxicity due to the inhibitory effects CCBs have on insulin release from the pancreatic β cells.[1,25,26] In cardiac myocytes stressed from hypoperfusion, there is a shift from free fatty acid to glucose utilization as the energy substrate.[1,26,47,55–57] Hypoinsulinemia and insulin resistance leading to reduced glucose delivery to cardiac tissue combined with an increase in glucose utilization by the myocardium can have negative cardiac inotropic effects.[26,47,56,57] High-dose insulin therapy with dextrose administered to maintain euglycemia (HIE) enhances glucose uptake by the myocytes to increase energy substrate utilization.[1,26,55–58] HIE also suppresses phosphodiesterase III activity, thus increasing cAMP, resulting in increased intracellular calcium influx.[1,57] In addition, HIE also enhances the intracellular potassium influx resulting in hypokalemia, which can prolong phase 2 depolarization, increasing the intracellular calcium influx.[1] The end result is increased cardiac inotropy.[1,26,29,55–57] HIE will also decrease capillary vascular resistance through increased nitric oxide synthase activity, leading to a reduction in acidosis.[57]

HIE can be used, but the ideal dose in companion animals has not been established. In a study of verapamil toxicity in anesthetized dogs, regular insulin was used at a dose of 4 U/min with 20% dextrose.[47,55] In human medicine, the dose typically used is the IV administration of 1 U/kg bolus followed by 0.1 to 1 U/kg/hr IV CRI along with 10% to 20% dextrose administration.[29,57] In many of the studies, effects were seen after 30 to 45 minutes, and it appears the most benefit was seen earlier in the course of CCB toxicity; if treatment with HIE is delayed, the benefits are reduced.[29,56] If using HIE, the serum glucose and potassium levels should be monitored closely to minimize the risk for hypoglycemia, hyperglycemia and hypokalemia.[1,26,29,56,57] When administering 10% to 20% dextrose, a central catheter should be used to minimize the risk for phlebitis.[26]

***Lipid emulsion***

Treatment with an intravenous lipid emulsion (ILE) commonly used in total parenteral nutrition has been investigated as an adjunctive therapy for various toxicities, particularly toxicity due to local anesthetics, verapamil, or diltiazem, and has been proposed as a therapy for toxicity due to other substances with high lipid solubility.[59] Although the exact mechanism by which ILE therapy works in toxicity is unknown, a few mechanisms have been suggested. One theory suggests that ILE sequesters lipophilic drug in an expanded plasma lipid phase, reducing the available free drug and promoting clearance of the compound through metabolism of drug-containing chylomicrons ("lipid sink" theory).[59,60] Another theory for ILE benefit when used in treatment of cardiotoxic drugs suggests that the increased availability of free fatty

acids provided by ILE may prevent the myocardium from switching to glucose as its preferred energy substrate.[59,61] In addition, the long chain fatty acids in ILE may also activate myocyte calcium channels, resulting in increased calcium influx.[29,59] ILE may also increase nitric oxide and $\beta$-ketoacids, which stimulate insulin release.[29]

As with HIE, the ideal dose of ILE in companion animals has not been established. The most commonly suggested dose of ILE has been 1.5 mL/kg IV slow bolus of intralipid 20% followed by 0.25 mL/kg/min for 1 hour.[59,62] This therapy may be repeated in 3 to 4 hours if the serum is not lipemic. Adverse reactions may include hyperlipidemia, fat overload syndrome (fat embolism, hepatomegaly, thrombocytopenia, hemolysis, increased clotting times, or neurologic deficits), or pancreatitis.[59]

### *Miscellaneous*

Severe heart block may require the placement of a temporary cardiac pacemaker.[28] This therapy can improve cardiac output by increasing the heart rate; however, it will not have effects on the peripheral arterial vascular tone or cardiac contractility.[28] Another treatment using 4-aminopyridine (Ampyra) has been described in experimental studies.[63,64] 4-Aminopyridine is a potassium channel blocker; blockade of potassium channels leads to an increased intracellular calcium influx. At high doses it can also increase muscle contractility.[64] In an experimental cat study using anesthetized and manually ventilated cats, 4-aminopyridine was used effectively to treat verapamil toxicity at a dose of 0.5 mg/kg IV twice, 5 minutes apart.[63] This drug can have significant side effects in animals, including seizure activity, and the dose effective for CCB toxicity has not been definitively established.[25,26,64] At this time, 4-aminopyridine should be considered an experimental treatment and could be considered if all other treatments have failed.

## SUMMARY

The prognosis of a patient exposed to a CCB depends on the amount ingested, severity of signs, and response to treatment. CCB exposure can be life threatening, with the onset of signs potentially delayed by many hours depending on the individual medication and formulation. The predominant signs include hypotension, cardiac rhythm changes, and hyperglycemia. Treatment can involve decontamination and cardiovascular stabilization with a variety of modalities. The most effective treatment regimen has not been established in companion animals.

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