Amlodipine

Amlodipine is a drug commonly used to treat hypertension in dogs and cats, especially hypertension secondary to acute or chronic kidney disease.

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Overview

Amlodipine, a dihydropyridine, is an L-type calcium channel blocker that acts predominantly on arterial vasculature.

- Serious adverse effects on the cardiovascular system can occur in the event of an overdose (see **Overdose & Toxicity**, page 22).
- Other less serious effects can develop with routine use.

The drug is commonly used to treat primary or secondary hypertension, although primary hypertension in dogs and cats is rare.[1]

- Acute or chronic kidney disease, hyperthyroidism, hyperadrenocorticism, diabetes mellitus, primary hyperaldosteronism, pheochromocytoma, and iatrogenic drug use (eg, steroids, erythropoietin) are associated with secondary hypertension in dogs and cats.[1,2]
- In both dogs and cats, amlodipine has been shown to be efficacious in lowering systemic blood pressure.[2-6]

In cats, both chewable tablets and transdermal gel have been shown to be efficacious, although lower blood pressure measurements and greater reduction in plasma drug concentrations have been achieved using the gel.[2,7]

In dogs, the pharmacokinetic profile has been studied and is ideal, with a high volume of distribution (25 L/kg) and low elimination rate resulting in a long half-life of approximately 30 hours.[8]

Adverse Events

Cats only

- Adverse effects are not commonly reported but may include lethargy, inappetence, mild hypokalemia,[8] azotemia, hypotension (resulting in hypoperfusion and reflex tachycardia), and weight loss.[9]
  - —Mild hypokalemia (3.76 ± 0.62 mmol/L) was found in a study of 30 cats treated with amlodipine for systemic hypertension, with renal disease being the most common cause for hypertension.[10]
    - The mechanism is unknown but may be associated with mild natriuretic and diuretic effects of amlodipine.[8,10]
  - —Hypotension can cause hypoperfusion and activation of baroreceptors, resulting in reflex tachycardia as a compensatory reaction.[9]

Dogs only

- Gingival hyperplasia (GH) is infrequently (7/82 dogs, 8.5%) reported with chronic use of amlodipine in dogs with degenerative valve disease.[11]
  - —Signs began to resolve within 2 weeks and were completely resolved within 6 months of amlodipine discontinuation.
  - —Of the 7 dogs with GH, 2 were severely affected and 3 moderately affected.
    - Hydralazine was initiated to replace amlodipine for treatment of hypertension in dogs with GH; dogs responded appropriately and GH was resolved.
  - —The mechanism for GH as caused by amlodipine has not been elucidated in dogs.

Amlodipine is commonly used to treat primary or secondary hypertension, although primary hypertension in dogs and cats is rare.[1]

—In humans, the mechanism for GH has been speculated to be multifactorial (age; genetic predisposition; pharmacokinetic variables; noninflammatory changes, inflammatory changes, and drug-induced changes in gingival connective tissues).[12-14]
  - Noninflammatory mechanisms involve decreased folic acid uptake causing abnormal collagenase activity and inhibition of aldosterone synthesis causing increased ACTH release, leading to up-regulation of keratinocyte growth factor.[12-14]
  - Inflammation may develop from direct effects of the drug on dental plaque or gingival fluid; in addition, gingival fibroblasts are stimulated by inhibition of intracellular calcium uptake.[12-14]

- Peripheral edema has been reported in 2 dogs receiving a dose of 0.19 to 0.51 mg/kg once a day.[15]
  —In one dog, the edema resolved with amlodipine discontinuation; the other dog was euthanized because of severe diffuse edema.
  —The mechanism for development of peripheral edema remains unknown.[15]

⚠ **Both dogs and cats**

- When amlodipine is used alone as sole treatment of hypertension, the renin-angiotensin-aldosterone system (RAAS) can become activated, presumably as a result of excessive vasodilation.[1,9,16]
  —In healthy dogs, amlodipine at 0.57 mg/kg PO twice a day for 6 days resulted in 3-fold increase in urinary aldosterone concentration.[17]
  —In cats (60.9% azotemic, 39.1% nonazotemic), amlodipine at 0.625 mg/cat PO once a day resulted in significant increase in plasma renin concentration but not in plasma aldosterone concentration.[18]
- Angiotensin-converting enzyme (ACE) inhibitors can partially antagonize RAAS activation in hypertensive patients; however, routine combined use remains controversial.[1,9,16]
  —Combined use of calcium channel blockers (CCBs) and ACE inhibitors is controversial because of concerns for systemic hypotension and worsening renal function.
    - ACE inhibitors preferentially dilate the efferent arteriole and decrease glomerular hydrostatic pressure, thus theoretically decreasing the glomerular filtration rate.
  —Advantages of combined use of amlodipine with an ACE inhibitor include blunting the RAAS system, which achieves a decrease in systemic blood pressure.
    - In normal adult dogs, combined use of high-dose amlodipine (0.57 mg/kg PO twice a day) and enalapril (0.57 mg/kg PO twice a day) has been shown to mildly increase blood urea nitrogen.[17]
  —In hypertensive humans, combined low-dose use of

ACE = angiotensin-converting enzyme, ACTH = adrenocorticotropic hormone,
CCB = calcium channel blocker, GH = gingival hyperplasia, RAAS = renin-angiotensin-aldosterone system

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amlodipine and an ACE inhibitor has been shown to be more renoprotective than occurs when either drug is used alone.[19]

- Amlodipine undergoes slow, extensive hepatic metabolism and should be used with caution in patients with hepatic insufficiency or compromised hepatic blood flow.[9]
- Amlodipine has mild effects on cardiac contractility and automaticity.[9,16]
  - —Amlodipine is a (mild) negative inotrope.[16]
  - —Amlodipine causes mild sinoatrial node and atrioventricular depression (negative chronotropic effects).[16]
  - —Use cautiously in patients with heart failure or in cardiogenic shock.[9]

Overdose & Toxicity

⚠ A toxic dose is the dose expected to produce toxic effects, resulting in morbidity or possibly mortality of the patient.

- The toxic dose of amlodipine has not been reported in dogs or cats and may depend on species or comorbidities.
  - —Because there are no published reports or studies, information is extrapolated from human literature.
  - —An overdose is considered a dose higher than generally recommended, which may or may not result in morbidity.
  - Dogs: 0.1-0.5 mg/kg PO once a day; start at low end of dosing range (recommended, *Plumb's Veterinary Drug Handbook*, 8th ed)
  - Cats: 0.625-1.25 mg/cat once a day (recommended, *Plumb's Veterinary Drug Handbook*, 8th ed)
  - Clinically in acute kidney injury/dialysis patients: 0.1-0.3 mg/kg PO once or twice a day (unpublished data, University of Florida)
- The half-life of amlodipine in dogs is 30 hours[20] but is unknown in cats.
- Because toxic effects may be prolonged, the patient should be monitored for an adequate duration (1-10 days).[21,22]

⚠ Clinical signs for and diagnosis of amlodipine overdose or toxicity

- Signs of an overdose may include
  - —Lethargy, weakness, altered mental status, or tachycardia attributed to systemic hypotension[4,9,23,24]
  - —Vomiting[9]
  - —Constipation[23]
  - —Bradycardia presumably resulting from sinoatrial (SA) node suppression at high doses, which is uncommon at currently recommended therapeutic doses.[16,21,25]
- In humans, ingestion of toxic doses resulted in death due to cardiovascular collapse, causing acute kidney injury, noncardiogenic pulmonary edema, hypoxic ischemic encephalopathy, and refractory hypotension (this has not been reported in dogs or cats).[21,22,25-28]
- Diagnosis is based on history, clinical signs, physical examination, and supportive diagnostic findings (eg, low arterial blood pressure, tachycardia, bradycardia).

Treatment Measures

⚠ For acute oral overdose (within 2 hours), induction of emesis followed by oral administration of activated charcoal should be considered, as there is no reliable antagonist.

- Because of risks for aspiration, this should not be attempted in dogs or cats presenting with clinical signs of overdose (eg, hypotension, weakness, lethargy).[24]

⚠ For patients with mild signs of toxicity, basic treatment includes amlodipine discontinuation, symptomatic treatment, and supportive care.

⚠ For patients with severe signs of toxicity (eg, refractory hypotension, noncardiogenic pulmonary edema, acute kidney injury, altered mental status, bradycardia), the following pharmacologic options may be considered, although none has been proven to be superior.[24]

- IV lipid 20% emulsions[29]

—1.5-4 mL/kg IV bolus over 1 minute, followed by CRI 0.25 mL/kg/min over 30-60 minutes[30]

- Calcium gluconate 10%[24,31]
  - —0.5-1.5 mL/kg IV slowly (ECG monitoring during administration[31])
- Atropine, if patient bradycardic
  - —0.02-0.04 mg/kg IV[24,31]
- Vasopressors (norepinephrine, vasopressin, dobutamine, dopamine, epinephrine) titrated to effect[24,30]; none has been shown to be superior.
  - —Norepinephrine, 0.05-2 µg/kg/min IV[24]
  - —Vasopressin, 0.5-5 milliunits/kg/min IV in dogs; unknown dose in cats[24]
  - —Dobutamine, 2-20 µg/kg/min IV in dogs; 1-5 µg/kg/min IV in cats (use with caution at doses >5 µg/kg/min due to potential for seizures)[24]
  - —Dopamine, 5-20 µg/kg/min IV[24]
  - —Epinephrine, 0.005-1 µg/kg/min IV [24]
- Glucagon
  - —0.15 mg/kg IV bolus, followed by CRI 0.05-0.10 mg/kg/hr titrated to effect[24]
- Insulin and dextrose administration (ie, hyperinsulinemia/euglycemia therapy)[24,30,31]
  - —CCBs inhibit pancreatic β cells, interfering with insulin release.[30]
  - —Central venous catheter required for hyperosmolar dextrose administration[30]
  - —Initial bolus dosing for CCB toxicity
    - Clinically, the author has used 0.5-1 mL/kg (250-500 mg/kg) 50% dextrose diluted to an osmolality to administer through a peripheral vein (600 mOsm/L) or diluted to 20% solution to give via a central venous catheter if patient not severely hyperglycemic (ie, >400 mg/dL)[24,31] (anecdotal, as adapted from the literature)
    - 0.5-1 unit/kg regular insulin IV cited for humans[31]; 1 unit/kg recently cited for small animal critical care.[24]
  - —Maintenance infusion for CCB toxicity
    - 500-1000 mg/kg/hr IV infusion of 20% dextrose to maintain euglycemia[30,31] (anecdotal dose as adapted from the literature)
    - 0.5 unit/kg/hr IV regular insulin infusion) until toxicity resolves[24] (anecdotal dose as adapted; adjust to maintain euglycemia when treating CCB toxicity)
  - —Monitoring[30,31]
    - Blood glucose every 30 minutes for 4 hours, then hourly
    - Potassium monitored hourly and replaced as needed to maintain normokalemia
  - —Discontinuation
    - No evidence for weaning protocol[31]
    - Titration of infusion until hemodynamic stability recommended[31]
- Extracorporeal therapy as a means to rapidly remove the drug from circulation can be considered if the dose ingested is potentially lethal (although this is currently unknown in dogs and cats).[32,33]
  - —Continuous venovenous hemodiafiltration with charcoal hemoperfusion[32]
  - —Plasmapheresis[33]

ACE = angiotensin-converting enzyme, CCB = calcium channel blocker, CRI = constant-rate infusion, ECG = electrocardiogram, SA = sinoatrial

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