Toxicology Brief: Phenylpropanolamine toxicosis in dogs and cats

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VETERINARY MEDICINE

Phenylpropanolamine (PPA) is a sympathomimetic drug used in dogs and cats primarily to treat urinary incontinence secondary to urethral sphincter hypotonia. It is labeled for use in dogs and is available as a solution in 25- and 50-mg/ml concentrations (Proin Drops—PRN Pharmacal); in chewable 25-, 50-, and 75-mg tablets (Proin—PRN Pharmacal, Propalin—Vétoquinol, Uricon—Neogen Corporation, Uriflex-PT—Butler Schein Animal Health); and as a 75-mg timed-release capsule (Cystolamine—Veterinary Product Laboratories).1 PPA is classified as a list 1 chemical (can be used to manufacture methamphetamine) in the United States. Restrictions regarding its sale may vary among states, and in some states it may be a controlled substance.1

Historically in people, PPA was used as a decongestant and anorectic. It was removed from both over-the-counter and prescription use in the United States in 2000 because of data that suggested PPA increases the risk of hemorrhagic stroke in people.2 It has since also been removed from the market in Canada.

PHARMACOKINETICS AND MECHANISM OF ACTION

PPA is readily absorbed orally, with an oral bioavailability of approximately 98% in dogs.3 In people, the onset of action is rapid, occurring within 15 to 30 minutes. It is widely distributed into multiple tissues and fluids, including the central nervous system (CNS). Approximately 80% to 90% of the drug is excreted unchanged in the urine within 24 hours of dosing.1 The serum half-life in dogs is approximately three to four hours.3 Clinical effects may persist well beyond what is expected based on the half-life.4

The recommended dosage for the immediate-release forms in dogs is 1 to 2 mg/kg given orally b.i.d.5 The dose using the time-release 75-mg capsules is one-half capsule given orally once a day for dogs weighing < 40 lb (18.2 kg), 1 capsule given orally once a day for dogs weighing 40 to 100 lb (18.2 to 45.5 kg), and 1.5 capsules given orally once a day for dogs weighing >100 lb (45.5 kg).6

The exact mechanism of PPA's action has not been determined. It is thought that it directly stimulates alpha-adrenergic receptors and indirectly stimulates both alpha-adrenergic and beta-adrenergic receptors by causing the release of norepinephrine.1 It acts primarily on peripheral alpha receptors, with a weak effect on beta receptors.7 Other pharmacologic effects of PPA include vasoconstriction, mild CNS stimulation, decreased nasal congestion, and decreased appetite. It also increases urethral sphincter tone.1

TOXICITY

Adverse effects can potentially be seen at therapeutic doses and include restlessness, urine retention, anorexia, tachycardia, and hypertension. Stroke-like clinical signs have been reported rarely in dogs at therapeutic doses of PPA.1

The most common clinical finding of PPA toxicosis is hypertension secondary to peripheral vasoconstriction. A reflex bradycardia can be seen.4 Other clinical manifestations of toxicosis may

include piloerection, vomiting, tachypnea, anxiety or agitation, hyperthermia, tachycardia, tremors, and potential seizures.1

In one case report, a 5-year-old dog developed tachypnea, tachycardia, and ataxia after ingesting about 48 mg/kg of PPA.8 Diagnostic test results (electrocardiography, echocardiography, creatine kinase activity, and cardiac troponin concentration) revealed areas of focal myocardial necrosis and multiform ventricular tachycardia consistent with myocardial damage from infarction or direct catecholamine-induced myocardial toxicity. During hospitalization, the dog developed ventricular tachycardia that was successfully treated with lidocaine. Enalapril and atenolol were also administered and continued after discharge. The owners were instructed on discharge to restrict the dog's activity. All abnormalities resolved within six months.8

ASPCA APCC DATA

From 2003 to 2011, the ASPCA Animal Poison Control Center (APCC) database contains 823 cases of PPA exposures; 97% of the cases involved dogs, 3% cats, and < 1% birds.4

Only single-exposure cases were included. One cat receiving 2.8 mg/kg of PPA developed no signs.4 Another cat that ingested 9.1 mg/kg presented with vomiting and mild hypertension, and a third cat that ingested 13.8 mg/kg developed moderate hypertension and tachypnea.4

In dogs, doses of 2.8 and 6.8 mg/kg resulted in mild hypertension and bradycardia.4 Ingestion of > 15 mg/kg often resulted in significant cardiovascular signs.4 At 16.6 mg/kg, a dog developed agitation, moderate hypertension, and ventricular tachycardia.4 Ingestion of a similar dose at 16.7 mg/kg resulted in severe hypertension that responded to administration of acepromazine.4 After ingestion of 43 mg/kg, one dog developed anxiety, severe hypertension, and bradycardia.4 Both acepromazine and nitroprusside were administered to control the hypertension. Final outcomes were not obtained in these cases.

DECONTAMINATION

Because of the rapid onset of action, emesis, using 3% hydrogen peroxide (2 ml/kg orally with a maximum of 50 ml) or apomorphine (0.03 mg/kg intravenously; or, in the conjunctival sac, 0.25 mg/kg after dissolving the tablet in saline solution), may be attempted within the first 10 to 15 minutes of exposure in animals not exhibiting clinical signs.1 After, or in lieu of, emesis, activated charcoal (1 to 2 g/kg orally) with a cathartic such as sorbitol may be given.9 The decision to give charcoal should be based on the dose of PPA ingested, weighing the benefit of activated charcoal with the potential risks for aspiration and the development of hypernatremia.

MONITORING AND TREATMENT

Observe for CNS signs such as agitation or restlessness. Heart rate and rhythm, blood pressure, and body temperature should be monitored carefully. If marked hyperthermia is present, monitor for the development of disseminated intravascular coagulation. When hyperthermia is marked, cooling techniques should be instituted. If ventricular arrhythmias are detected, an echocardiographic examination should be considered.

Nitroprusside can be used to treat hypertension (1 to 2 µg/kg/min; increase the dose incrementally every three to five minutes, if necessary, until desirable blood pressure is achieved).1 If nitroprusside is unavailable, a low dosage of acepromazine may be given (0.02 mg/kg intravenously) and increased in small amounts to the desired effect.10 Phenothiazines are also effective for the anxiety or agitation that can be seen.

Bradycardia is usually a reflex mechanism that does not require specific intervention and is expected to resolve with correction of hypertension.

If marked supraventricular tachycardia is present, a beta-1-specific beta-blocker can be used, such as esmolol at 0.2 to 0.5 mg/kg given intravenously over one to two minutes or 25 to 200 µg/kg/min as a constant-rate infusion.1 Propranolol, a nonspecific beta-blocker, should be avoided since blockade of beta-2 receptors may worsen any hypertension that is present. Ventricular arrhythmias may be treated with lidocaine or other appropriate antiarrhythmics. Intravenous fluids should be administered to maintain hydration, provide venous access, and promote adequate renal function. Fluids should be administered judiciously when hypertension is present. Other supportive measures should be instituted as needed.

Depending on the dose, clinical signs may persist up to 48 hours. Ideally, patients should be monitored in the hospital until they are not exhibiting any clinical abnormalities and are not receiving any medications for CNS or cardiovascular signs for six to eight hours. If a patient has experienced marked ventricular arrhythmias, follow-up echocardiographic and electrocardiographic examinations may be indicated. With appropriate symptomatic treatment, a full recovery is expected.

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Proin for Cats

The generic name of this medication is Phenylpropanolamine and this is generally abbreviated as PPA. This prescription medication is not approved by the U.S. FDA but it's legally prescribed as an extra label drug. The active ingredient in Proin is phenylpropanolamine, an adrenergic agent that strengthens and tightens the sphincter muscles surrounding the urethra. It prevents urine leakage or dribbling of urine.

Incontinence is more common in older spayed cats that don't produce enough estrogen, a hormone that helps keep urethral muscles in good working order. Hence, Proin is often given in conjunction with estrogen supplements such as Diethylstilbestrol.

Dosage of Proin

Proin is available in the form of chewable tablets of strengths of 25 mg, 50 mg and 75 mg. It is also available in liquid form. The dosage depends on the weight of your pet and the recommended dosage is 0.4 to 0.8 mg per pound every 12 hours. However, it's best to consult the veterinarian and administer the medication as prescribed. A missed dose can negate the effectiveness of the medication. Hence, you should administer the missed dose as soon as you remember unless it's too close to the next dose in which case, you should miss it altogether in order to avoid an overdose.

An overdose can result in any of the side effects associated with the medication. You should ensure that your pet consumes the entire dose and you should endeavor to give him the medication at the same time daily. This medication takes a few days to be effective and needs to be administered over a long period of time.

Benefits of Administering Proin:

- Proin is a supplement used to treat urinary incontinence in cats
- It maintains phenylpropanolamine levels in the blood stream.
- It eliminates problems caused by high levels of PPA in the blood such as loss of appetite, hypertension and changes in heart rate.

Side Effects of Proin

Proin is a stimulant and your pet can experience adverse effects such as hypertension, hyper excitability, restlessness, difficulty in urinating, loss of appetite and rapid heart rate.

Contraindications of Administering Proin

Proin should not be administered to cats with diabetes, hypertension, hyperthyroidism, glaucoma or heart disease. It should also not be administered if your cat has had previous allergic responses to phenylpropanolamine or related products. Pregnant and nursing cats should also not be given Proin as it might prove harmful to the fetus and the kittens.

Proin should not be given to cats for at least 2 weeks after being treated with MAO inhibitors or flea collars. The drug may interact with medications such as aspirin, tricyclic depressants and ephedrine and it should not be given in conjunction with these medications.

Storage of the Medication

The medication should be stored away from heat and direct sunlight in an airtight container. It should be kept away from children and pets.

Proin should be given exactly as prescribed to the pet it has been prescribed for. If your pet's condition worsens or doesn't improve despite treatment, you should check with the veterinarian. If your pet suffers from any of the side effects associated with the medication, it should be discontinued at once and the veterinarian should be notified at the earliest.