Pentoxifylline, a trisubstitute xanthine derivative, is a hemo-rheologic agent used to treat diseases and conditions in which improved circulation is beneficial.

**PHARMACOLOGY**

The mechanism of action for pentoxifylline is not completely understood, but it does increase erythrocyte flexibility by inhibiting erythrocyte phosphodiesterase. It also decreases the viscosity of blood by reducing plasma fibrinogen and increasing fibrinolytic activity. It is thought that pentoxifylline reduces the negative endotoxic effects of cytokine mediators through phosphodiesterase inhibition.\(^1^\text{–}^3\)

Pentoxifylline is also rapidly absorbed in dogs, reaching peak plasma levels within an hour after oral administration and having a bioavailability of 15% to 32%. Metabolite I has been detected in dogs but does not appear to be one of their major metabolites. Therefore, pentoxifylline has a short elimination half-life (1 hour or less) in dogs. In a clinical study of the pharmacokinetics of pentoxifylline in dogs, decreased concentrations were seen after repetitive doses.\(^4\)

One possible explanation for this is that repetitive treatment causes an induction of liver enzymes (responsible for the first-pass effect seen with pentoxifylline). Another possibility is a decrease in absorption of pentoxifylline. The latter possibility would be hard to explain, however, as diet was not changed during the study and other drugs were not given in conjunction with pentoxifylline.\(^4\)

Absorption of oral pentoxifylline in horses is extremely variable. Times to peak concentration range from 30 minutes to 10 hours. Rapid elimination and a large volume of distribution characterize intravenous administration of the drug. Urinary excretion was less than 10% of the total dose.\(^5\)

**INDICATIONS**

In humans, pentoxifylline has been used to treat diseases and conditions in which microperfusion is diminished (e.g., intermittent claudication, sickle cell disease, Raynaud’s phenomenon).

Pentoxifylline has also been used in dogs to treat ulcerative dermatosis and other conditions in which improved microcirculation may be beneficial. It has been used to treat numerous other diseases in dogs, including vasculitis, dermatomyositis, systemic lupus erythematosus, atopy, contact allergy, and acral lick granuloma.\(^4\)

In a study performed in dogs, pentoxifylline was shown to decrease renal vasoconstriction and prevent the increase in renal endothelin release caused by cyclosporine.\(^6\) However, use of pentoxifylline in canine septic shock can be harmful.\(^7\) One hypothesis consistent with these data is that high pentoxifylline levels slowed endotoxin clearance, resulting in high levels of endotoxemia and increased proinflammatory-mediator release and death. Thus long-term continuous infusion of pentoxifylline (a common clinical practice) can be harmful during gram-negative septic shock.\(^7\)

In horses, pentoxifylline has been used to treat endotoxemia and navicular disease. In one study evaluating the effect of oral pentoxifylline on digital and laminar blood flow, no increases in blood flow to the digit or perfusion within the dorsal laminae were found.\(^8\) Results of this study suggest that the clinical benefits of pentoxifylline in ischemic conditions of the hoof may be caused by a mechanism other than improved perfusion.\(^8\)

**CAUTIONS**

Because pentoxifylline is a methylxanthine, it should be used with caution in patients with known sensitivity. Patients at risk for hemorrhage (recent surgery, peptic ulceration) should be examined occasionally for signs of bleeding, including hemoglobin and hematocrit levels. Pentoxifylline should not be used in patients with recent cerebral or retinal hemorrhage. Adverse effects of pentoxifylline in humans include gastrointestinal upset, cardiovascular stimulation, and
Client Counseling Information

- Pentoxifylline should be given with a small amount of food or a treat to lessen gastrointestinal upset.
- If your pet shows signs of agitation, restlessness, or a rapid heartbeat while taking pentoxifylline, contact your veterinarian immediately.
- Give your pet only the dose of pentoxifylline recommended by your veterinarian.
- Because pentoxifylline may interact with other drugs, contact your veterinarian before giving any other medications.

Central nervous system manifestations (e.g., headache, dizziness). Clinical testing of pentoxifylline in dogs revealed no adverse effects. No studies evaluating adverse effects of pentoxifylline in horses have been conducted.

Use in Pregnancy

Safe use of pentoxifylline in pregnancy has not been established. Studies performed in rats and rabbits using oral doses 24 and 11 times the maximum recommended human daily dose, respectively, revealed no fetal malformations. Increased resorption was seen in rats at a dose of 576 mg/kg (24 times the maximum recommended human daily dose). Pentoxifylline and its metabolites are excreted in human milk; due to the potential for tumorigenicity in rats, a decision to discontinue nursing or the drug should be made with regard to the importance of the drug to the mother.

Acute Toxicity

Data on acute toxicity in animals is unavailable; however, signs of pentoxifylline toxicity in humans (e.g., flushing, hypotension, convulsions, somnolence, unconsciousness, fever, agitation) are dose-related and similar to those of all methylxanthine toxicities. Symptoms are uncommon, usually occurring 4 to 5 hours after ingestion and lasting approximately 12 hours. Treatment is with gastric lavage and administration of activated charcoal. As an adjunct to symptomatic treatment, respiration support, maintenance of blood pressure, treatment of cardiac arrhythmias, and control of convulsions may be needed. Since dogs and cats are especially sensitive to methylxanthines, they may have an increased manifestation of signs in a pentoxifylline overdose.

Drug Interactions

Warfarin use with pentoxifylline may result in an increased risk of bleeding; prothrombin times should be monitored more frequently in patients on concurrent warfarin therapy. Concomitant use of other methylxanthines (theophylline) may lead to increased blood levels and toxicity of one of the methylxanthines. Patients should be monitored for signs of toxicity and doses adjusted as necessary. Patients on simultaneous antihypertensive therapy have shown small decreases in blood pressure; their systemic blood pressure should be monitored intermittently and doses of the antihypertensive agent reduced if indicated.

Dosage and Administration

For dogs, the dose of pentoxifylline as adjunctive therapy for ulcerative dermatosis is 400 mg PO sid (or every other day if vomiting is a problem). For adjunctive treatment of dermatomyositis, the dose is 10 mg/kg PO sid or every other day. Two to 3 months of therapy may be needed to see improvement. For adjunctive treatment of ear margin seborrhea, the recommended dose of pentoxifylline is 400 mg/day PO unless the dog weighs less than 10 kg (in which case 200 mg/day is administered). A recent study revealed that food had no effect on plasma pentoxifylline concentrations or bioavailability in dogs.

In horses, a dose of 8.5 mg/kg PO bid is recommended for reducing the cytokine effects in endotoxemia. For the treatment of navicular disease, 6 g/day PO for 6 weeks should be used.

It is important to note that most veterinary use of pentoxifylline occurs after crushing or other manipulation of the sustained-release dosage form (i.e., Trental® [Hoechst Marion Roussel, Kansas City, MO]). As crushing alters the bioavailability of extended-release dosage forms in veterinary patients, the extended-release effect is not appreciated in veterinary patients.

Patients should be monitored for efficacy of treatment. Because pentoxifylline is a methylxanthine, dogs and cats in particular should be monitored for such adverse reactions as central nervous system or cardiovascular stimulation.

Preparations

Trental® is available in 400-mg tablets. Pentoxifylline is available generically as 400-mg tablets by various manufacturers. As the majority of veterinary patients receive a compounded product, pricing varies.

Storage and Handling

Tablets should be stored in tightly closed containers at 59°F to 86°F (15°C to 30°C). They should be protected from light and kept out of the reach of children and pets.

References


