Ponazuril

Mark A. Mitchell, DVM, MS, PhD

Protozoa from the phylum apicomplexa are associated with significant animal losses in both pet and production systems. These organisms can infect a wide range of vertebrate hosts, although many are host specific. The apicomplexans of greatest interest to exotic pet practitioners are *Isospora* spp, *Eimeria* spp., *Toxoplasma gondii*, and *Cryptosporidium* spp. Historically, these organisms have been very difficult to eliminate. One of the primary reasons for our lack of treatment success is related to the compounds used to treat the infections. The traditional treatment choices for apicomplexans are the sulfonamides. These drugs affect folic acid synthesis, and can be -cidal or -static depending on dose and species. For many of the coccidians, these compounds are considered coccidiostatic. To increase our success against these organisms, it is likely that different, possibly coccidiocidal, compounds will need to be explored.

Ponazuril is a triazine coccidiocidal drug that is related to toltrazuril.[1] Triazine antiprotozoals are considered to be active against the plastid body of the parasite. Plastids originated as a site for photosynthesis in plants. Although they have lost this function in apicomplexans, the plastid remains an essential organelle to those parasites that have them. It is important to note that the plastid has been lost in some apicomplexans, such as *Cryptosporidium* spp. With this is mind, recent research does suggest that the enzyme/enzyme pathways that serve as the inhibitory target of ponazuril may vary between species.[2] For example, even though *Neospora caninum* develops via endodyogeny and *Sarcocystis neurona* develops by endopolygeny, ponazuril effectively halts development in both cases.[2]

Ponazuril was originally developed to treat *S. neurona* infections in horses. This parasite is the causative agent of equine protozoal myeloencephalitis (EPM), which is the most commonly diagnosed neurologic disease of horses.[3] Many in the equine industry consider EPM to be the most important infectious disease facing captive horses.[4] With over 9 million horses in the United States, veterinary pharmaceutical companies identified the development of a treatment for EPM as a priority.

Marquis (Bayer Animal Health, Shawnee Mission, KS USA) is a commercial ponazuril product that is marketed specifically for the treatment of *S. neurona* in horses, and is the first drug approved for the treatment of EPM by the United States Food and Drug Administration. The product is marketed as a paste (15% w/w ponazuril). The dosing regimen recommended for horses is 5 mg/kg once a day for 28 days. When ponazuril is given at the recommended dose (5 mg/kg), peak serum and central spinal fluid levels are achieved in approximately 18 and 15 days, respectively.[1] The elimination half-life for this drug is 4.5 days in the horse.[1]

When *S. neurona* infects aberrant hosts, such as the horse, it remains in its asexual stage. This stage in the life cycle appears to have a high predilection for the central nervous system. Fortunately, ponazuril can cross the blood-brain barrier. Although not evaluated in exotic species, this could also be of benefit when treating certain protozoal diseases that infect the central nervous system.

Ponazuril is not approved for use in animals intended for food, and thus should not be used in domestic or exotic species being culled for human consumption.

Horses being treated with ponazuril are administered doses over a 28-day period. Side effects associated with this treatment appear to be limited to the development of allergic responses, including blisters

From the University of Illinois, College of Veterinary Medicine, Department of Veterinary Clinical Medicine, Urbana, IL USA.

Address correspondence to: Mark A. Mitchell, DVM, MS, PhD, University of Illinois, College of Veterinary Medicine, Department of Veterinary Clinical Medicine, 1008 W. Hazelwood Dr, Urbana, IL 61802. E-mail: mmitch@uiuc.edu

1557-5063/08/1703-$30.00

doi:10.1053/j.jepm.2008.05.013

on the nose and mouth and wheals on the skin, and mild gastrointestinal changes (e.g., mild colic).[5] Studies evaluating higher dosages (30 mg/kg) in horses reported changes in the gastrointestinal (e.g., loose feces, colic) and reproductive tracts (e.g., edema of the uterine epithelium).[5] In rats and dogs, long-term, high-dose subchronic toxicity studies have also been performed. Rats offered 250 parts per million (ppm), 1000 ppm, or 4000 ppm ponazuril daily over a 14-week period were found to have decreased weight gain and various hematologic changes.[5] All groups showed a reduction in body weight; therefore, an additional study was undertaken to determine the no-observed-effect-level (NOEL) (150 ppm). In dogs, a similar study was carried out with dosing regimens between 200 and 5000 ppm over 13 weeks.[5] The side effects observed in the dogs were similar to those found with the rats, and included decreased weight gain and food consumption. The NOEL for dogs was 200 ppm.

Developmental toxicity studies for ponazuril have been done in rats and rabbits.[5] Rats administered ponazuril orally during gestation were found to experience maternal and developmental toxicity at 300 mg/kg. At 90 mg/kg, a NOEL was found. In gestating rabbits, 3 different doses (10 mg/kg, 30 mg/kg, and 90 mg/kg) of ponazuril were evaluated. The NOEL for developmental toxicity was found to be 90 mg/kg, whereas the NOEL for maternal toxicity was much lower (30 mg/kg).

Ponazuril has been evaluated in mice under experimental conditions.[6] The mice were used as a model to evaluate the efficacy of ponazuril against *T. gondii*. Mice administered 10 to 20 mg/kg ponazuril 1 day before experimental challenge with *T. gondii* and once a day for 10 days after challenge were found to be protected against infection. Mice treated with 10 to 20 mg/kg ponazuril 72 hours postinfection and for 10 days postchallenge were protected against fatal toxoplasmosis. When treatment was delayed up to 6 days postinfection, animals treated with a low dose (10 mg/kg) were more likely to succumb to fatal toxoplasmosis (40%) than those treated at higher doses (20-50 mg/kg; 0 mortalities). The results of the study were promising and suggested that ponazuril could be used as a method for treating *T. gondii*. The results of the study also suggest that 10 to 50 mg/kg ponazuril once daily for 10 days is apparently safe in mice.

A single pilot study has been performed to evaluate the efficacy of ponazuril in lizards. Bearded dragons given 2 doses (30 mg/kg) of ponazuril by mouth 48 hours apart were cleared of *Isospora amphiboluri*.[7] The author reported that the animals remained coccidia-free for over 1 year posttreatment.

A review of several different medical peer-reviewed search engines did not reveal any articles evaluating the efficacy or potential toxicity of ponazuril in avian patients. Similarly, other than the toxicity study described previously in rabbits, there have not been any efficacy studies done in rabbits or commonly kept rodents (e.g., guinea pigs, hamsters, and gerbils).

Ponazuril is a drug that appears to be safe and effective in a variety of vertebrate species. It is possible that this antiprotozoal may prove useful against a variety of apicomplexans found in exotic species. Future research focusing on the pharmacokinetics of the drug in different vertebrates and the efficacy of the drug against different species of protozoa is needed.

References

1. Plumb DC: Ponazuril, in Plumb DC (ed): Veterinary Drug Handbook (ed 4), Ames, IA, Blackwell Publishing, p 675, 2002
2. Mitchell SM, Zajac AM, Davis WL, et al: The effects of ponazuril on development of apicomplexans in vitro. J Eukaryot Microbiol 52(3):231-235, 2005
3. Dubey JP, Lindsay DS, Saville WEJA, et al: A review of *Sarcocystis neurona* and equine protozoal myeloencephalitis. Vet Parasitol 95:89-131, 2001
4. National Animal Health Monitoring System. Equine Protozoal Myeloencephalitis in the United States. Animal and Plant Health Inspection Service, National Animal Health Monitoring System. United States Department of Agriculture, Ft. Collins, CO, 2001
5. Marquis (ponazuril) EPM Paste, MSDS Number: R37641, Bayer Animal Healthcare LLC, Shawnee, KS, 2004
6. Mitchell SM, Zajac AM, Davis WL, et al: Efficacy of ponazuril in vitro and in preventing and treating *Toxoplasma gondii* infections in mice. J Parasitol 90(3):639-642, 2004
7. Bogoslavsky BA: The use of ponazuril to treat coccidioisis in eight inland bearded dragons (*Pogona vitticeps*). Proc Assoc Reptil Amphib Vet, New Orleans, LA, pp 8-9, 2007