

**Gigi Davidson, BS, RPh, DICVP**

North Carolina State University  
College of Veterinary Medicine  
Raleigh, North Carolina

Just as Hamlet agonized over his *raison d'être*, veterinary clinicians agonize over whether or not to use benzoic acid derivatives in cats. Phenolic benzene rings are found in many therapeutic entities, from preservatives to anesthetics to antibiotics. One of the most confounding uses of benzoic acid derivatives is represented by the use of metronidazole benzoate. Metronidazole is a mainstay of veterinary drug therapy. It is bactericidal, amebicidal, and trichomonacidal and also exhibits antiprotozoal activity. Metronidazole has uniform therapeutic value across all animal species. It is widely used to treat anaerobic infections and infections from *Giardia* and trichomonads. The dosage range for cats is usually 10 to 30 mg/kg orally once to twice daily. Metronidazole is approved in the United States only as the hydrochloride salt. Despite its universal therapeutic value, the taste of metronidazole hydrochloride is uniformly detestable to all animal species. Humans report a bitter, unpleasant, metallic taste after administration. Although cats are not able to verbalize their objections, they do demonstrate violent salivation and head shaking after the administration of metronidazole hydrochloride.

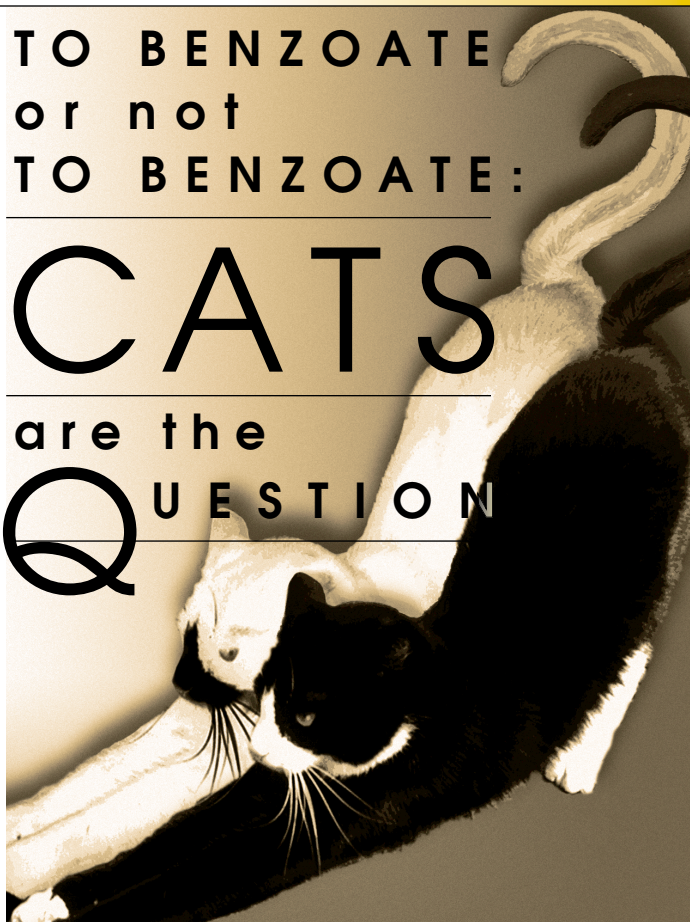
### METRONIDAZOLE BENZOATE: RISKS VERSUS BENEFITS

Not all esters of metronidazole, however, are equally bitter. Metronidazole benzoate, also known as benzoyl metronidazole, has been available as an approved drug in Europe and Mexico for many years and has been used widely in many veterinary species because of its greater palatability. The molecular weight of metronidazole benzoate is approximately 275.3, and the molecular weight of metronidazole hydrochloride is 171.2. Because of the larger benzoate molecule, a factor of 1.6 must be multiplied to convert doses of metronidazole hydrochloride to metronidazole benzoate. Cats and birds have accepted the benzoate ester much more willingly than they accept metronidazole hydrochloride and do not seem to be stressed by its administration.

Although metronidazole hydrochloride is excreted as approximately 50% unchanged in the urine, metronidazole benzoate must be conjugated with glucuronide to facilitate elimination, as must all benzene moieties. Cats, unfortunately, are metabolically deficient in the ability to conjugate with glucuronide. Normally, benzyl alcohol is rapidly oxidized to benzoic acid. In most species, benzoic acid is then metabolized to hippuric acid and benzyl glucuronide (and in some species to ornithuric acid). In the cat, only hippuric acid is formed, because that species lacks adequate glucuronic acid conjugation capacity. This results in a decreased rate of metabolism and in cumulative toxic effects of the benzene moiety. For this reason, benzoates have caused many fatal toxicities in cats, and many clinicians have been afraid to prescribe metronidazole benzoate for cats. The toxicity manifests as ataxia, hyperesthesia, fasciculations, blindness, aggression, coma, convulsions, respiratory failure, and (ultimately) death.

The use of metronidazole benzoate in cats represents a true

# TO BENZOATE or not TO BENZOATE: CATS are the QUESTION



juxtaposition of therapeutic risk versus benefit. Metronidazole is a valuable tool in antimicrobial and antiprotozoal therapy, but the resultant stress of having the hydrochloride salt administered can be as harmful as the infection to the animal. Similarly, the resultant toxicity of benzoic acid from the benzoate ester may be more dangerous than the microbial infection. The question asked is then "How much benzoate is safe to use in cats?" To date, safety studies of metronidazole benzoate in cats have not been performed. Therefore, the veterinary clinician must evaluate available literature regarding the use and toxicity of other benzoates in cats. Again, little information is available. The World Health Organization recommends a maximal intake of 5 mg/kg/day of benzoate in humans,<sup>1</sup> but humans have a much greater capacity for conjugation with glucuronide than do cats. In 1923, Ellinger<sup>2</sup> reported the toxic dose of benzoate in cats as being 2 g/kg orally as a single dose. Clinical toxicities and experimental studies<sup>3-7</sup> suggest that toxic doses are considerably lower than that. When benzoic acid was routinely added to food as a preservative in the 1970s, many episodes of toxicity were reported in humans and animals. Feeding benzoic acid concentrations of 0.2% to 2% of the diet has resulted in many clinical poisonings in cats. One report<sup>3</sup> described a cattery in London in which 70 cats were poisoned by food preserved with benzoic acid, and 40% of those cats died as a result of benzoate poisoning. It was this unfortunate event that prompted Bedford and Clarke<sup>4</sup> to induce benzoate toxicity experimentally in cats by introducing varying concentrations in food. By administering

benzoic acid in concentrations from 0.25% to 1% of the diet, those investigators showed that the maximum permissible single oral dose of benzoic acid in the cat was 450 mg/kg. The highest level that could be safely fed daily was 200 mg/kg. Those studies also demonstrated that benzoic acid accumulates with chronic dosing. Doses at > 200 mg/kg daily produced symptoms of cumulative toxic effects (hyperesthesia, depression, and apprehension) within 48 to 72 hours, and sometimes caused death. Therefore, the longer the duration of therapy, the greater the possibility of toxicity. By extrapolating the numbers of Bedford and Clarke to metronidazole benzoate (40% benzoic acid), it can be inferred that doses of 500 mg/kg/day of metronidazole benzoate would be toxic to cats. Because the normal dosage range for metronidazole benzoate in cats is 16 to 48 mg/kg (1.6 x metronidazole hydrochloride dose) q 12 to 24 hours, it is not likely that this drug will cause toxicity in cats with normal hepatic and renal func-

tion. It is important to keep in mind, however, that the studies of Bedford and Clarke were conducted in young, healthy laboratory cats. Any debilitated cat with impaired hepatic or renal function could suffer a fatal toxicity at a much lower dose of benzoate if the drug is administered long-term and is allowed to accumulate. For this reason, metronidazole benzoate should be discontinued immediately in any cat showing signs of behavior change or disturbance of the central nervous system.

### OTHER SOURCES OF BENZOATE-RELATED TOXICITY

Metronidazole benzoate is not the only therapeutic moiety packing a phenolic benzene ring. Preservatives in the form of benzyl alcohol or methyl- or propyl- parabenzonic acid may also pose possible toxicities in cats. Cases of benzyl alcohol poisoning in cats after the administration of fluids preserved with 1.5% benzyl alcohol have been

reported.<sup>5</sup> There are no documented cases in cats of toxicity induced by parabenzonic acid-preserved diluents, but because those agents do contain phenolic benzene rings, they would be suspect. Documented fatalities in cats after exposure to benzyl benzoate, a miticide and flea killer, have also been reported.<sup>6</sup>

Benzocaine is another possible benzoate-containing product used in cats. Many toxicities have been reported in cats that have received this local anesthetic, and its use should be avoided in cats.<sup>7</sup> Benzoic-acid-containing topical medications are even more toxic to cats as a result of grooming.

### CONCLUSION

In summary, until further safety studies are conducted on the effect of benzoic acid derivatives in cats, veterinary caregivers should minimize the amount of benzene-containing agents used in that species. In the case of metronidazole, however, the benzoate ester offers a less stressful, more palatable dosage form for short-term therapy. Because stress can be as detrimental as any infectious disease, increasing the palatability of medication can improve the acceptance of therapy, decrease the length of treatment, and improve therapeutic outcome. Veterinarians should be reassured that metronidazole, when indicated for short-term use in hepatocompetent cats, is a relatively safe choice.

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Address correspondence to: Gigi Davidson, BS, RPh, DICVP, Director of Pharmacy, North Carolina State University, College of Veterinary Medicine, 4700 Hillsborough Street, Raleigh, NC 27606. ■

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