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# IVERMECTIN TOXICOSIS AFTER TOPICAL ADMINISTRATION IN DOG-FACED FRUIT BATS (*CYNOPTERUS BRACHYOTIS*)

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*Abstract:* Forty dog-faced fruit bats (*Cynopterus brachyotis*) were administered 1 drop of 1% ivermectin topically as part of a routine physical exam and deworming program, and 11 developed sudden generalized paresis. Six of the bats recovered within 24–48 hr, and the remaining 5 were presented recumbent and weak to the University of Florida Veterinary Medical Teaching Hospital. Ivermectin toxicosis was suspected, and the admitted bats died or were euthanatized within 3–5 days of the development of clinical signs despite supportive care. Three of the dead bats had renal tubular necrosis.

*Key words:* Bats, *Cynopterus brachyotis*, ivermectin, toxicosis, renal, tubular necrosis.

## INTRODUCTION

Ivermectin, an endo- and ectoparasiticide, potentiates the action of gamma amino butyric acid (GABA), an inhibitory neurotransmitter, increasing its release and binding at postsynaptic receptors,[3,16] and this decreases nerve conduction. In mammals GABA receptors are restricted to the central nervous system (CNS), which is not easily penetrated by large compounds such as ivermectin, making ivermectin safe for use in mammals. In contrast, these receptors regulate peripheral muscle activity in many invertebrates,[3,16,17] making ivermectin an effective parasiticide.

Safe and effective ivermectin dog dosages range from 0.006 mg/kg, p.o., for heartworm prevention to 0.2 mg/kg, s.c. or i.m., for the treatment of mites and nematodes.[19] Collie breeds, which may show toxic effects at dosages as low as 0.1 mg/kg, are exceptions.[19] Their susceptibility appears to be associated with a more permeable blood–brain barrier.[18,19] The recommended dosage for cattle, horses, sheep, and birds is 0.2 mg/kg, p.o., s.c., or i.m., for susceptible parasites.[19]

High canine oral dosages (e.g., >2 mg/kg) may cause mydriasis, ataxia, tremors, depression, emesis, and stupor.[16,20] Clinical toxicoses have been reported in horses, cattle, and swine at oral dosages of 2, 4, and 30 mg/kg, respectively.[3,20] The oral $LD_{50}$s in rhesus monkeys, mice, rats, and dogs are 24, 25, 50, 80 and 24 mg/kg, respectively.[2,3] Although ivermectin toxicosis is well recognized clinically, its pathogenesis is not well understood.

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A description of ivermectin toxicosis in a captive collection of dog-faced fruit bats (*Cynopterus brachyotis*) associated with topical administration follows.

## CASE REPORT

Five adult male dog-faced fruit bats, each weighing 30–40 g, were evaluated at the University of Florida Veterinary Medical Teaching Hospital (UFVMTH) because of the sudden onset of generalized paralysis. They had been housed indoors with other fruit bats in free-flight enclosures at a private facility and maintained on a diet of fresh fruit, vitamin, mineral, and protein supplements.

The day before admission of the first four bats, they, and 35 others, had been administered a topical 1% glycerol formal and propylene glycol ivermectin solution for use in cattle (Ivercide® 10 mg/ml, Phoenix Pharmaceutical, Inc., St. Joseph, Missouri 64503, USA), during an annual physical examination and preventative care program. Each bat was administered 1 drop from a 0.5-ml insulin syringe (Terumo Medical Corporation, Elkton, Maryland 21921, USA) on the skin of the chest or the patagium. The following morning, 11 of the bats had fallen from their perches and were lying either on the ground or in their food bowl, unable to move. Six bats recovered within 24–48 hr. Two days later another animal was found in a food bowl.

Of the five bats admitted, individuals A through D breathed spontaneously but could not eat or perch, and they had minimal movements in all parts of the body. They were placed in an incubator at 25°C and tube fed every 2 hr with 0.4 ml of a carbohydrate liquid supplement (Carbo-Fuel®, Twin Laboratories, Inc., Ronkonkoma, New York 11779, USA). One bat consumed fluid on its own. Bat A was given flumazenil (Romazicon® Hoff-

man-LaRoche, Basel, Switzerland; 0.02 mg, s.c.) to attempt reversal of benzodiazepene-regulated CNS depression. Three bats died, and one was euthanatized 1 day after admission, and Bat E, evaluated 5 days after the ivermectin treatment because of severe weakness, died spontaneously 7 days after topical ivermectin treatment. All bats were necropsied.

Bats A, B, and C revealed histologic signs of mild to moderate acute tubular necrosis with evidence of tubular epithelial regeneration. Bat C had a proliferative glomerulonephritis, with marked cortical tubular distension and tubular proteinosis along with severe hemorrhagic gastroenteritis and intralesional fungal organisms. Bat E had suppurative bronchopneumonia.

## DISCUSSION

Based on clinical signs, the paralysis or paresis of these bats was most likely caused by ivermectin administration. Other possible causes include spinal cord injury, polyneuropathy, polymyopathy, metabolic abnormalities, and other toxicants.[15] These were ruled out because of the acute onset of the clinical signs in combination with multiple animal involvement and the history of recent topical ivermectin therapy.

The volume of ivermectin solution administered to each bat was approximately 0.0054 ml, so the dosage of ivermectin applied was 1.4–1.8 mg/kg. Topical $LD_{50}$ for rats and rabbits is >400 mg/kg.[3] Percutaneous ivermectin is used in canaries, finches, and budgerigars.[22] Reported topical dosages for psittacines and pigeons are 200 μg/kg, using 1% ivermectin and one drop of 0.8% ivermectin, respectively.[22] One drop of "the bovine formulation of ivermectin" is commonly applied to the skin of small birds.[4] Some bovine formulations of ivermectin, such as Ivercide® used in this case and Ivomec® (Merial, Iselin, New Jersey 08830, USA), are 1% solutions.[19]

Topical application of ivermectin in rats, rabbits, and monkeys has shown poor dermal absorption of these compounds because of their large size.[3] Absorption of topically placed ivermectin in emulsifiable concentrate and in an alcohol suspension typically resulted in <1% absorption of the applied dose.[3] In goats the peak plasma level of ivermectin after topical application (Ivomec 1% pour-on for cattle in glycerol formal and propylene glycol solution) was considerably lower compared with oral administration.[24] Absorption of ivermectin in propylene glycol solution in sheep is about 50% when orally administered.[9] Additionally, there is greater plasma availability and persistence of ivermectin in aqueous micelle or propylene glycol solution after s.c. administration when compared with oral dosing in horses and sheep.[11,12] However, great variation exists between individuals of the same species with respect to topical absorption of compounds.[25]

If 0.5% of the topically applied ivermectin had been absorbed,[3] each bat would have received approximately 9–12 μg/kg (0.009–0.012 mg/kg). This is comparable to safe therapeutic dosages in other mammal[19] and bat species.[10]

Although the estimated ivermectin dosage appears to have been within safe limits for other mammals, there are several possible reasons why 11 bats showed clinical signs of toxicity. Toxicity may have resulted from other formulation components and not from ivermectin, although this is unlikely. More than one drop may have been administered to each of these bats, the drug may have been ingested during auto- and allogrooming, this species may be particularly sensitive to ivermectin, or drug absorption through the patagium may have been greater. Some of the animals received the topical dose on the skin of the ventral thorax, whereas others received it on the patagium, a thin membranous part of the wing with a generous blood supply.[14] Absorption may have been increased because of the thin barrier between the drug and the underlying vasculature. Unfortunately, the site of administration for each animal was not recorded.

It is possible that these bats' toxicoses related to a deficiency of p-glycoprotein, a protein transporter that excretes ivermectin out of tissue cells.[8,23] In humans this protein is present in the intestines, kidneys, and liver and is highly expressed in the brain, presumably to protect these organs from certain compounds.[23] Mice with a defect in this p-glycoprotein are up to 100-fold more sensitive to orally administered ivermectin,[8,23] and brain levels of ivermectin are up to fourfold higher in defective mice than in normal mice.[23] As described in mice, defects in p-glycoprotein transporters may explain the increased sensitivity seen in collies and possibly in this bat species.[23]

Avermectins potentiate benzodiazepine receptor binding,[3] so flumazenil, a benzodiazipine receptor antagonist, was given to one bat to reverse benzodiazepine-mediated CNS depression but with no visible effect.

The acute tubular necrosis observed in three of the bats is consistent with toxic or ischemic insult[5,12] from hypotension (associated with hemorrhage, dehydration, or vasodilation), vasoconstriction, or thromboembolism. Aminoglycosides, some

heavy metals, ethylene glycol, and many plants are nephrotoxic.[12] Although it was difficult to assess the bats at presentation for hypotension, there was no evidence of hemorrhage, and hydration was probably maintained orally with the fluid diet. Bat C, however, may have become dehydrated after the onset of gastroenteritis. The affected bats had not received either drug therapy or access to toxic plants or chemicals.

Renal damage has not been previously attributed to ivermectin, except in humans with onchocerciasis, in which glomerular and tubular kidney dysfunction after ivermectin treatment was probably related to microfilarial load.[1,7] In teleost fish ivermectin is readily taken up by the tubular epithelial cells and transported into the kidney proximal tubules, which are functionally identical to mammalian renal proximal tubules, by a p-glycoprotein transporter.[6] Additionally, pig kidney cells bathed in ivermectin solutions of concentrations of 40 μg/ml died within 24 hr.[21]

In conclusion, it is not clear why these bats showed ivermectin toxicity and why three of them suffered renal tubular necrosis. This species may be particularly sensitive to ivermectin, and the renal damage may have been related to administration of this compound. A 1% ivermectin solution should not, therefore, be applied topically to dog-faced fruit bats the way it was applied to the individuals reported here. Further dilution of the 1% solution may allow more accurate dosing from an insulin syringe. A dosage lower than 1.4–1.8 mg/kg and an application site not accessible for autogrooming should be considered if topical administration is required.

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