

# Mortality Associated with Fenbendazole Administration in Pigeons (*Columba livia*)

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A group of 12 domestic pigeons (*Columba livia domestica*) was treated for capillariasis by use of fenbendazole at 30 mg/kg orally once daily for 5 d. After treatment, 8 of the 12 pigeons exhibited signs of anorexia, lethargy, and dehydration; these birds died within 2 d after the onset of clinical signs. A total of 6 birds were necropsied, and all had unremarkable gross findings. Microscopic examination of tissues revealed acute hemorrhagic enteritis, diffuse lymphoplasmacytic enteritis, small intestinal crypt necrosis, periportal lymphoplasmacytic hepatitis, bile duct hyperplasia, and renal tubular necrosis. Erythrocytes in blood samples collected from surviving birds demonstrated polychromasia compatible with a regenerative anemia. The clinical and histopathologic findings in these pigeons were consistent with recent reports of fenbendazole toxicity in domestic pigeons and other columbiform birds.

**Abbreviation:** UCLA, University of California at Los Angeles

Benzimidazoles have frequently been used for the treatment of ascarid, capillarial, fluke, and giardial infections in birds.<sup>1,10</sup> Fenbendazole is used frequently in birds, including poultry and pet and game birds, in which the drug is considered to be safe at doses as high as 100 mg/kg.<sup>4,5,14</sup> In 1983, Lawrence and coworkers<sup>5</sup> treated 230 birds of 6 orders and 38 different species with a single dose of 100 mg fenbendazole per kg body weight. In some cases, in addition to the initial treatment, fenbendazole at a dose rate of 30 mg/kg was given daily for 7 d. That study reported no deaths or side effects occurring in the studied population of birds, but none of the species tested were from the family *Columbidae*. Although generally considered safe in many avian species, the use of fenbendazole is contraindicated in molting birds or young birds in the pin-feather state because of the drug's tendency to induce abnormal feather formation.<sup>2</sup> More recently, the benzimidazole group of antiparasitic drugs has been suspected of causing toxicity in some avian species, including pigeons<sup>3,9</sup> and storks.<sup>13</sup> In this report we describe 8 cases of mortality in pigeons associated with the administration of fenbendazole at a moderate dose of 30 mg/kg.

## Case Report

A mixed group of 12 White Carneaux and Racing Homer pigeons (*Columba livia domestica*) were purchased from a commercial vendor (Double T Farm, Glenwood, IA) for use in a spacial cognitive study approved by the University of California at Los Angeles (UCLA) Institutional Animal Care and Use Committee. The birds were housed indoors in stainless steel cages and fed a standard commercial pigeon diet (Pigeon Pellets, Leach Grain and Milling, Downey, CA), seeds (Feed and Seed, Southwest Farms Old Fashioned Feeds, Rancho Cucamonga,

CA), and grit (Red Pigeon Grit, Leach Grain and Milling); water was provided ad libitum. As part of the routine health surveillance, feces were examined for parasites by the formol-ether concentration technique. In addition to parasitologic examination, the UCLA pigeon health monitoring program included fecal testing for *Salmonella* spp. by culture (IDEXX, Sacramento, CA) and for *Chlamydophila psittaci* by polymerase chain reaction assay (University of Georgia, Athens, GA) upon arrival and quarterly thereafter. Fecal samples were negative for *Salmonella* spp. and *C. psittaci* but revealed infection with coccidia, ascarids, and *Capillaria* spp. The ascarid and capillaria infections were treated with piperazine (Wazine 34, Fleming Laboratories, Charlotte, NC) at a dosage of 2 g/l in the drinking water for 3 d. The following week the coccidial infection was treated with sulfadimethoxine (Albon, Pfizer, Exton, PA) at a dosage of 50 mg/kg body weight orally once daily for 3 d.

The capillarial infection was not eliminated by the piperazine treatment, and 1 mo afterwards, fenbendazole (Panacur, Intervet, Millsboro, DE) was administered orally at a dosage of 30 mg/kg once daily for 5 d. On the last day of treatment, 2 birds were observed to have decreased appetite, and on the following day 2 additional birds were affected similarly. In addition, the investigator reported weight loss, loss of appetite, and signs of dehydration as well as behavioral signs including listlessness, loss of activity, stooped posture, and shivering among the treated pigeons. The first birds clinically affected were found dead on days 3 and 4 after treatment. By day 6 after treatment, a total of 8 birds had died despite institution of fluid therapy. The other 4 birds remained clinically healthy and continued to eat normally. Blood samples were collected from the cephalic vein of the clinically unaffected pigeons, and smears were prepared and stained with Wright-Giemsa for cytologic examination.

Of the 8 dead pigeons, 6 were available for necropsy. Upon gross examination, only dehydration and a loss of pectoral muscle mass were noted. Although the birds reportedly had a decreased appetite, the crops of all birds contained food. Tissues taken for microscopic analysis were fixed in 10% neutral buffered formalin, embedded in paraffin by use of routine methods, and stained with hematoxylin and eosin.

Histologically, all of the birds had acute small intestinal crypt

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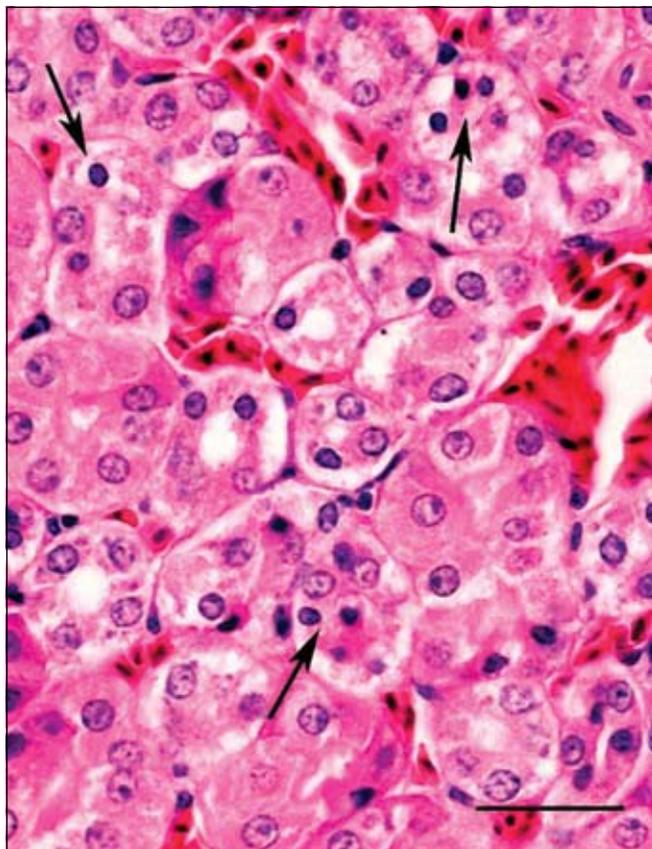


**Figure 1.** Photomicrograph of pigeon small intestine showing acute crypt necrosis (characterized by dilation of crypts, crypt loss, and necrosis of the crypt epithelial cells; arrows) and diffuse, moderate, lymphoplasmacytic infiltrate. Hematoxylin and eosin stain; magnification,  $\times 250$ ; bar, 50  $\mu\text{m}$ .

necrosis characterized by epithelial cell necrosis and dilation or loss of crypts (Figure 1). Many crypts contained necrotic cellular debris and, in some cases, contained macrophages with phagocytized cellular debris. In addition, 4 pigeons had acute, mild, multifocal, renal tubular epithelial necrosis characterized by loss of cellular detail, cytoplasmic vacuolation, and pycnotic nuclei (Figure 2). Acute, mild to moderate, segmental hemorrhagic enteritis; diffuse, moderate, chronic, lymphoplasmacytic enteritis; mild, chronic, periportal lymphoplasmacytic hepatitis with mild Kupffer cell erythrophagocytosis; and mild, chronic, bile duct hyperplasia (Figure 3) were noted in 2 pigeons, and 1 pigeon had mild, multifocal, subacute, necrotizing vasculitis and 1 pigeon had moderate, multifocal, acute, Kupffer cell necrosis. Cytologic examination of peripheral blood from the surviving birds revealed polychromasia, very few heterophils, and scattered immature thromboblots.

## Discussion

Fenbendazole is a benzimidazole anthelmintic that is available as a white, crystalline powder, which is only slightly soluble in water. The drug is labeled for use in dogs, cattle, horses, and swine; fenbendazole has also been used in cats, sheep, goats, pet birds, and llamas,<sup>7</sup> although not approved for these species. Fenbendazole is only marginally absorbed after oral administration in mammalian species and generally does not cause any adverse effects, although the drug infrequently has been reported to cause aneuploidy as well as the loss of villus epithelium and stroma within the small intestine of mammals.<sup>6</sup> More recently Weber and colleagues<sup>12</sup> reported presumptive fenbendazole toxicosis in 4 North American porcupines. At high doses, hypersensitivity reactions secondary to antigen release

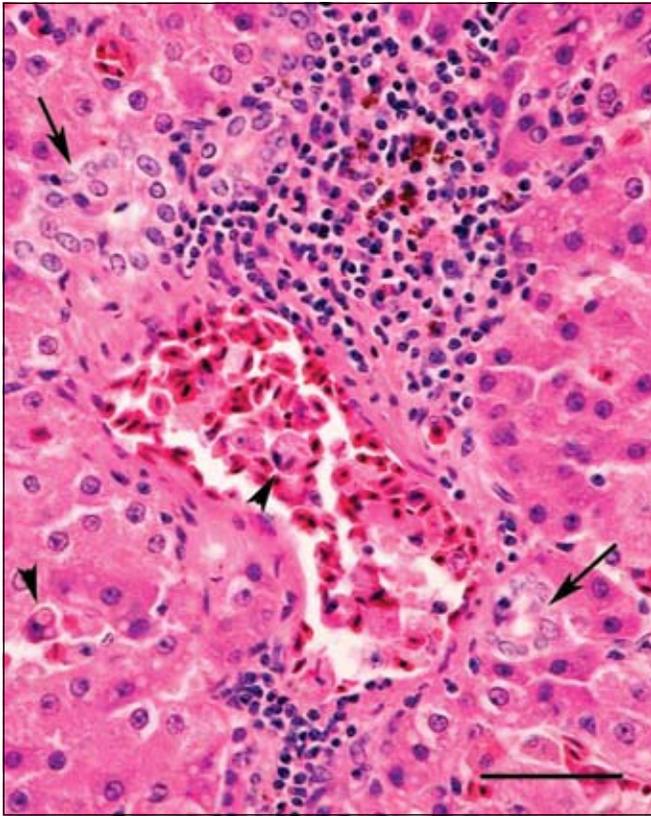


**Figure 2.** Photomicrograph of pigeon kidney with acute multifocal tubular epithelial necrosis characterized by loss of cellular detail, vacuolation, and pycnotic nuclei (arrows). Hematoxylin and eosin stain; magnification,  $\times 400$ ; bar, 30  $\mu\text{m}$ .

by dying parasites sometimes occur. For laboratory animals the dose lethal to 50% of the test population exceeds 10 g/kg when fenbendazole is administered orally;<sup>7</sup> therefore, the drug is considered to be quite safe in most mammalian species.

Benzimidazoles act primarily by binding to nematode  $\beta$ -tubulin, which prevents the dimerization of  $\beta$ -tubulin with  $\alpha$ -tubulin and subsequent polymerization into microtubules.<sup>8</sup> Microtubules are essential structural units of many nematode organelles and are necessary for numerous cellular processes, including mitosis, protein assembly, and energy metabolism. Although mammals also rely on tubulin for cellular processes, benzimidazoles have a higher affinity for nematode  $\beta$ -tubulin at the normal body temperature range of mammals,<sup>8</sup> accounting for the wide margin of safety of these drugs in mammals. Although benzimidazoles have a higher affinity for nematode  $\beta$ -tubulin than mammalian  $\beta$ -tubulin,<sup>8</sup> there are no published studies evaluating the affinity of benzimidazoles for avian  $\beta$ -tubulin.

Several anecdotal reports suggested that recommended doses of fenbendazole sometimes cause toxicity in pigeons. Bone marrow suppression after routine treatment with fenbendazole has recently been observed to occur in pigeons,<sup>3,9</sup> storks,<sup>13</sup> and porcupines.<sup>12</sup> According to the authors of those reports, the damage to the bone marrow and gastrointestinal tract of the affected animals was directly due to fenbendazole.<sup>3,9,12,13</sup> Epithelial cell necrosis in intestinal crypts also has been noted after administration of fenbendazole,<sup>3,9,12,13</sup> but Rivera and colleagues<sup>9</sup> suggested that concurrent coccidial infection may have led to enteritis and crypt epithelial necrosis. Coccidial infection might



**Figure 3.** Photomicrograph of pigeon liver with mild chronic periportal lymphoplasmacytic hepatitis, mild chronic bile duct hyperplasia (arrows), and erythrophagocytosis (arrow heads). Hematoxylin and eosin stain; magnification,  $\times 250$ ; bar, 50  $\mu\text{m}$ .

have caused loss of epithelial cell layer integrity, subsequently leading to increased drug absorption and systemically toxic levels of fenbendazole, even though the doses administered were within anecdotal reference ranges for domestic pigeons.<sup>10</sup>

In the cases we describe here, the pigeons were treated with fenbendazole approximately 1 mo after being treated for the coccidial infection. The coccidial treatment was efficacious, as demonstrated by lack of coccidia during the postmortem histologic examination. In addition, 4 wk would have been sufficient time for the intestinal epithelium to repair itself. Our report, as well as others,<sup>3,13</sup> describe similar enteric lesions without evidence of coccidial infection, suggesting that fenbendazole may normally be more readily absorbed from the gastrointestinal tract of birds compared with mammals. However, whether the capillarial infection in our cases contributed to increased fenbendazole absorption is unknown.

Tissue damage in our affected birds occurred primarily in the rapidly dividing cells of the intestinal crypts and the metabolically active cells of the renal cortex. The renal lesions of the pigeons that died and the regenerative anemia of the survivors suggest that at least some of the dose is absorbed systemically from the gastrointestinal tract of pigeons. In addition, the fact that abnormalities in pin feather formation have been seen in fenbendazole-treated birds supports the theory that the drug is absorbed systemically to some degree.<sup>2</sup> Interestingly, renal lesions were not described in previously published case reports involving pigeons.<sup>3,9</sup> Because we identified no other causes of renal damage in our birds, the renal tubular lesions likely were induced by the toxicity of fenbendazole or one or more of its metabolites. It also is possible that benzimidazole metabolism

in birds might differ from that in mammals, and that the metabolites may be more toxic in birds. Other causes of damage to rapidly dividing cells of the bone marrow and gastrointestinal tract (such as severe viral disease, sepsis, and immune-mediated disease) were not evident, and no new food sources were introduced to the birds before the deaths, decreasing the likelihood that a toxic agent was present in the food.

Short and colleagues<sup>11</sup> reported that when fenbendazole was administered orally to chickens, ducks, and turkeys, the majority of the drug was excreted unchanged in the feces, but the excretion pattern differed significantly among the species tested. In addition, compared with mammals, avian species had the most variation in fenbendazole excretion patterns.<sup>11</sup> This finding suggests it is likely that the absorption rates and metabolism of fenbendazole varies considerably between galliform, anseriform, and columbiform birds. Interestingly, columbiform birds comprise most of the avian cases of suspected benzimidazole toxicity,<sup>3,9</sup> suggesting that this family in particular may be susceptible to intoxication with this class of antiparasitic agents.

The UCLA pigeon health monitoring program included testing for *Salmonella* spp. and *Chlamydochloa psittaci* upon arrival and quarterly thereafter. The animals were all negative for *Salmonella* spp. and *C. psittaci* at the time the intestinal parasites were diagnosed but were not tested at necropsy. The enteric lesions and signs of bone marrow suppression observed in our cases are consistent with previous reports of fenbendazole toxicosis in pigeons,<sup>3,9</sup> storks,<sup>13</sup> and porcupines.<sup>12</sup> In addition, blood smear examination of the surviving birds showed signs consistent with regenerative anemia but not of an infectious process. In our case, the cause-and-effect relationship between the administration of the antiparasitic drug and the time of presentation of clinical signs and death strongly suggests that fenbendazole administration was the direct cause of death.

Our findings provide additional evidence that fenbendazole used at published recommended doses causes toxicity in pigeons. The birds in our report were treated with a moderate dose of fenbendazole (30 mg/kg), which resulted in a 75% mortality rate. Controlled studies are required to determine the specific mechanism of toxicity and whether fenbendazole at any dosage can safely be used as an anthelmintic in columbiform birds. In the meantime, we suggest extreme caution when fenbendazole is used for the treatment of gastrointestinal helminths in columbiform birds.

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