BENZIMIDAZOLE TOXICOSIS IN RABBITS: 13 CASES (2003 TO 2011)

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Abstract

The objective of this study was to evaluate both clinical and histologic anomalies associated with suspected benzimidazole toxicosis in rabbits. Histopathologic records were reviewed from rabbit cases that were diagnosed with suspected benzimidazole toxicosis at 2 specialty pathology services. Medical records were also solicited from veterinarians who treated rabbits with suspected benzimidazole toxicosis. In all, 13 cases were included in this retrospective study. Histologically, presumed radiomimetic lesions of benzimidazole toxicosis were noted in 3 cases. An additional 10 cases exhibited lesions suggestive of benzimidazole toxicosis. Common clinical signs observed in the study of rabbits included inappetence, lethargy, hemorrhage, and death. One rabbit with suspected benzimidazole toxicosis survived. Benzimidazoles should be used judiciously in rabbits at published doses only after the owners are knowledgeable of the potential health risks associated with this class of drugs. The prognosis for rabbits with suspected benzimidazole toxicosis is poor, but supportive care resulted in the survival of 1 suspected case in this study.

Key words: benzimidazole; hemorrhage; immunosuppression; rabbit; radiomimetic; toxicosis

Benzimidazole-associated toxicosis has been reported in avian,[1-4] reptile,[5] elasmobranch,[6] and mammalian species,[7-9] including humans.[10] Because benzimidazoles bind to tubulin, microtubule and cellular division are affected, thus interfering with mitosis.[11] The benzimidazoles bind with greater affinity to the parasitic tubulin compared with the similar mammalian structure, which results in the inhibition of polymerization in the parasite cytoskeleton. Classic histologic findings of benzimidazole toxicosis include radiomimetic lesions in rapidly dividing cells (e.g., bone marrow and crypt epithelium of the intestinal tract necrosis).[3,7] By definition, radiomimetic substances are similar to ionizing radiation in that they exert mutagenic and carcinogenic effects, cause acute and chronic degenerative changes in the bone marrow, intestinal mucosa, and genital organs in mammals, suppress the formation of antibodies, and impair oxidative phosphorylation and protein biosynthesis. Aplastic anemia has been associated with the use of benzimidazoles in dogs, cats, and humans.[7,10]

Benzimidazole metabolism depends on the substituent present on carbon-5 of the benzimidazole nucleus and involves a wide variety of reactions.[12] Cytochrome P-450 and the microsomal flavin monooxygenases are primarily responsible for benzimidazole biotransformations.[12] After oral administration in mammals, benzimidazole anthelmintics are metabolized extensively by the liver, and the metabolites are found in plasma, tissues (e.g., liver, kidney, fat, muscle, and skin), and excreta (e.g., milk, urine, and feces).[12] Some of the benzimidazoles, including fenbendazole, are only marginally absorbed after oral administration. Rabbit (*Oryctolagus cuniculus*) metabolism of fenbendazole and albendazole has been

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examined.[13,14] Some of the factors affecting metabolism of benzimidazoles include gastric pH, administration with food, and concurrent drug administration.

Most patients diagnosed with benzimidazole toxicosis have nonspecific clinical signs including inappetence, lethargy, vomiting, fever, and ataxia. Erythroid and myeloid cell production, primarily granulocytes, may be suppressed with benzimidazoles in birds and mammals.[3,4,7,8] Severe immunosuppression with subsequent bacterial and/or fungal infection is the usual cause of death in cases of benzimidazole toxicosis.[2-5] Pancytopenia, or depletion of erythrocytes, leukocytes, and thrombocytes, is a blood abnormality that has been reported in animals affected with benzimidazole toxicosis.[10] Diagnosis of cytopenias may be achieved with either a complete blood count (CBC) or bone marrow examination. Patients that are pancytopenic have decreased numbers of all cell lines in the peripheral blood smear or by hypoplastic or hypocellular bone marrow. Patients with thrombocytopenia may have general weakness or malaise, bruising with minor trauma, or evidence of spontaneous bleeding.

Benzimidazoles are reported to have in vitro efficacy against *Encephalitozoon cuniculi*.[15] Despite frequent administration of benzimidazoles in rabbits, there are few reports of toxicosis associated with the use of these drugs.[16] Current published dosages for benzimidazoles used to treat *E. cuniculi* in rabbits are as follows: 20 mg/kg of albendazole administered orally, once a day for 30 days; 20 mg/kg of fenbendazole given orally, once a day for 30 days; and 30 mg/kg of oxibendazole given orally, once a day for 7 to 14 days, then 15 mg/kg orally, once a day for 21 days.[17,18] The purpose of this retrospective study was to review clinical and histologic findings associated with suspected benzimidazole toxicosis in rabbits. The results of this retrospective study are based on review of histopathology records from 2 specialty pathology services and solicited medical records from veterinary hospitals that treated rabbits with suspected benzimidazole toxicosis.

MATERIALS AND METHODS

Criteria for Case Selection

This retrospective study collected records of rabbit cases that had a history of treatment with a benzimidazole drug and evidence of radiomimetic lesions (e.g., crypt necrosis in the small intestine and necrosis or absence of hematopoietic cells in the bone marrow), enteritis, coagulopathy, and/or sepsis from 2 specialty pathology services. As coagulation profiles were not measured in any of the rabbit cases in this retrospective study, coagulopathy was suspected when antemortem spontaneous bleeding was recorded or if hemorrhage in the tissues or body cavities was noted on postmortem examination. Several veterinary hospitals were also solicited for medical records of rabbits fitting these criteria.

Estimation of Drug Dosage, Classification of Cases, and Records Review

Medical records were reviewed when available, and veterinarians were contacted directly to determine benzimidazole drug, dosage, and duration of therapy used. Cases were categorized as having recognized lesions[3,7] (radiomimetic lesions in the bone marrow or small intestine) or suspected secondary lesions (generalized bacteremia, thrombocytopenia, or evidence of coagulopathy). Rabbit breed, sex, and age were reported if this information was available.

RESULTS

Overall, 13 cases were included in this study and are summarized in the Table. Cases were defined as presumed when radiomimetic lesions were observed in the bone marrow or small intestine. Cases were defined as suspect if bone marrow or intestine was not available for examination but suspected secondary lesions including generalized bacteremia, thrombocytopenia, or evidence of coagulopathy were identified. A total of 3 cases had presumed radiomimetic lesions of benzimidazole toxicosis including crypt necrosis in the small intestine and necrosis or absence of hematopoietic cells in the bone marrow, and 10 cases had suspected lesions of benzimidazole toxicosis. One of the suspect cases survived.

Among the rabbits, 7 were female, 4 had their ovaries and reproductive tract removed; 4 were male, 2 of which were castrated; and 2 rabbits were of undetermined sex. The breeds for 5 cases included the following: California, Polish, Holland Lop, Dutch, and Rex.

In this study, the dosage of benzimidazole used in each case was categorized when possible. Dosages varied but were above current recommended dosages in at least 7 of the rabbits. Complete dosage information was not obtained for 3 rabbits. Albendazole was the documented benzimidazole used in 10 (77%) of 13 rabbits,