Therapeutic Contraindications in Exotic Pets

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KEYWORDS

• Ivermectin • Fipronil • Benzimidazoles • Glucocorticoids
• Antibiotic-associated dysbiosis • Ibuprofen • Ketoprofen

KEY POINTS

- Veterinarians who treat exotic pets are often forced to prescribe drugs to a particular species without any knowledge of the pharmacokinetics or safety of that drug in that species; a drug may cause no problems in certain species but lead to death in another, sometimes closely related species.
- Ivermectin, even at low doses, has led to flaccid paralysis and death in many chelonians, and this drug should not be used in any of these species.
- When applied topically to rabbits, fipronil can lead to seizures and death and is not recommended for use in this species.
- Benzimidazoles can negatively affect rapidly growing cells, leading to pancytopenia in many species.
- β-Lactam and macrolide antibiotics often lead to a fatal dysbiosis if given orally to hind-gut fermenters, such as rabbits, guinea pigs, and chinchillas.

INTRODUCTION

Many of the drugs used in exotic pets have never been pharmacologically evaluated in the species of interest, and doses are sometimes extrapolated from nonrelated animal species. In addition, many of these drugs have no safety data in anything other than common domestic species. A drug may cause no problems in certain species but lead to death in other—sometimes closely related—species. Widespread death of Old World *Gyps* vultures after ingestion of cattle carcasses treated with diclofenac is an example of this phenomenon, because no apparent toxicity is seen in certain

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other vulture species when treated directly with various nonsteroidal anti-inflammatory drugs (NSAIDs).[1,2] The purpose of this review is to provide a brief overview of drugs that have documented contraindications in certain exotic pet species but could be administered in other species without apparent complications. Specific toxins (ie, lead), drugs that have known complications in all species (ie, renal toxicity of aminoglycosides), and drugs that are contraindicated for regulatory reasons are not discussed, because they are outside the scope of this review.

ANTIPARASITIC MEDICATIONS

Ivermectin

Ivermectin is a macrocyclic lactone that targets the ivermectin-sensitive glutamate-gated chloride channel receptors, only found in invertebrates, and the γ-aminobutyric acid (GABA) receptors.[3] In many species of animals, it does not cross the blood-brain barrier; however, in certain species, neurologic signs can occur after ivermectin administration, even at recommended doses. Ivermectin toxicity in chelonian species was first described in 1983 by Teare and Bush[4] Five red-footed tortoises (*Chelonoidis carbonarius*) received a single intramuscular (IM) injection of ivermectin (0.4 mg/kg) and developed paresis or flaccid paralysis. Additional studies in the red-footed tortoise showed that paresis occurred with dosages as low as 0.05 mg/kg. These investigators found several other species of chelonians were considered susceptible to ivermectin toxicosis at dosages of 0.1 mg/kg or less. The leopard tortoise (*Stigmochelys pardalis*) seemed the most susceptible of the species tested, and they consistently developed paresis with a dosage of as low as 0.025 mg/kg and death with dosages as low as 0.3 mg/kg. Based on these and other published data, the use of ivermectin in any chelonian species is not recommended. Treatment of ivermectin toxicity is largely supportive, and respiratory support must be maintained for at least the duration of action of ivermectin at the neurotransmitter site (7 days).[5] Anecdotal reports of full recoveries after 4 weeks to 6 weeks of supportive care have been reported in tortoises.[6] Aside from reported toxicities in tortoises, ivermectin toxicosis has also been suspected in a chameleon (*Chamaeleo senegalensis*), which received a single dose of 0.2 mg/kg IM of ivermectin. This animal's clinical signs resolved within a week with supportive care.[7] In addition, there are conflicting reports of toxicity in prehensile-tailed skinks (*Corucia zebrata*)—1 reported death 24 hours after an oral dose of ivermectin at 0.2 mg/kg[8] and a second report of the same dose administered up to 6 times IM with no apparent adverse effects.[9] Nevertheless, several investigators advise against the use of ivermectin in skinks. Similarly, specific recommendations to avoid the use of ivermectin in crocodilians and indigo snakes have also been previously published.[10]

Ivermectin toxicosis in birds has been reported sporadically. There are several toxicity studies, which examined the histologic effects of feeding high levels of avermectins to pigeons.[11,12] The purpose of those studies, however, was to examine the potential negative effects of avermectin residues in the environment rather than for use in the clinical setting. Additionally, there are anecdotal reports of ivermectin toxicity in finches.[10]

Fipronil

Fipronil is a phenylpyrazole insecticide used for the treatment of fleas, ticks, pediculosis, sarcoptic mange, and cheyletiellosis in dogs and cats.[13] Fipronil blocks GABA receptors in the central nervous system by preventing chloride ion uptake. This results in excessive central nervous system stimulation. Fipronil has a greater binding affinity

for insect GABA receptors than mammalian receptors; however, rabbits seem more sensitive to fipronil compared with other mammals. Dermal absorption is 0.07%, but oral absorption is 30% to 50% if a rabbit licks off product after topical application.[14] The narrow safety margin in rabbits makes them susceptible to the neurologic effects of this drug.

Seizures, tremors, anorexia, and lethargy are the most commonly seen clinical signs of toxicity and can develop within a few hours up to a few weeks after exposure. Other clinical signs commonly encountered include hypothermia, gastrointestinal stasis, diarrhea, emaciation, ptyalism, and sudden death. Diagnosis is generally made based on the history with corresponding clinical signs; however, other causes of seizures, such as hypoglycemia, hypocalcemia, and lead toxicity, should be ruled out.

Affected rabbits should be bathed if exposure was within 48 hours to remove any residual drug from the surface of the skin. Light sedation with midazolam may be warranted in nervous rabbits. Bathe with a mild puppy/kitten shampoo in warm water to prevent hypothermia. Wash to the level of the skin to remove all toxin.[15] Activated charcoal may be considered to limit additional absorption of the drug if ingestion is suspected. If seizures are present, midazolam (1–2 mg/kg IM or intravenous [IV]) can be administered to control seizures. Continued seizures can be treated with levetiracetam (20 mg/kg orally every 8 h).[16] Parental fluids and nutritional support should be administered to anorectic rabbits. The prognosis is guarded for rabbits that are seizing.

Benzimidazoles

Benzimidazoles are used widely as an anthelmintic for a variety of domestic species, including dogs, cats, cattle, horses, swine, and birds. In rabbits, they have also been used in treatment protocols for *Encephalitozoon cuniculi*. This class of drugs binds to β-tubulin and thus inhibits microtubule formation in parasitic intestinal cells. This in turn decreases glucose uptake and effectively starves the parasite, which results in death.[17] Their binding affinity is greater to parasitic tubulin, which interferes with the parasite cytoskeleton. Vertebrate tubulin can also be affected, especially in rapidly dividing cells, including bone marrow and the cells lining the intestinal tract. Consequently, this medication can result in radiomimetic lesions, such as depletion of the myeloid, erythroid, and megakaryocytic cell lines.[18] This pancytopenia can lead to severe immunosuppression and subsequent bacterial and/or fungal infections, which may be fatal. Additionally, gastrointestinal erosion and crypt necrosis can contribute to generalized septicemia. Benzimidazoles undergo extensive hepatic metabolism (by cytochrome P450 and others) after oral administration; therefore, if hepatic disease is present, a patient may be at greater risk for toxicosis. Toxicity associated with benzimidazole anthelmintic has been reported in avian,[19–23] reptile,[24] elasmobranch,[25] and several exotic/zoo mammalian species including rabbits and North American porcupines.[18,26]

A study was performed in 6 Hermann tortoises (*Testudo hermanni*) to evaluate hematologic parameters after administration of a standard fenbendazole treatment (two 5-day courses of fenbendazole, 2 weeks apart, at a dosage of 50 mg/kg).[24] The tortoises remained clinically healthy during the 125-day study; however, there were significant biochemical changes considered to be in response to fenbendazole administration, including an extended heteropenia with transient hypoglycemia, hyperuricemia, hyperphosphatemia, and equivocal hyperproteinemia/hyperglobulinemia.

Benzimidazole toxicosis or suspected toxicosis has been reported in 2 vulture species,[19] 2 stork species,[19,22] columbiformes,[20,21] and pelicans.[23] Nonspecific clinical signs are typically seen within 48 hours of drug administration, and clinicopathologic findings include heteropenia to agranulocytosis and sometimes anemia. Additionally,

feather abnormities have been noted in birds treated with fenbendazole during active molt. The resulting bone marrow dysplasia, primarily of the myeloid series, can result in peracute bacteriemia and sepsis.[23,27]

Various benzimidazoles are also used in the treatment of *E cuniculi* in rabbits. A retrospective study compiled 13 cases of benzimidazole toxicosis in rabbits.[19] Rabbits presented for signs of anorexia, lethargy, diarrhea, pale mucous membranes, epistaxis, petechial to ecchymotic hemorrhage, abdominal hemorrhage, gastrointestinal stasis, fever, and acute death.[18] If considering the use of a benzimidazole for the treatment of *E cuniculi*, it is highly advisable to have pretreatment serology, biochemical profiles, and complete blood cell count performed. Serologic testing for *E cuniculi* could help determine if a rabbit is strongly seropositive and likely to have an active *E cuniculi* infection. A biochemical profile is used to screen for hepatic disease, because decreased hepatic function may predispose a rabbit to toxicosis. Complete blood cell counts should be performed prior to treatment as well as weekly throughout treatment to assess for anemia, thrombocytopenia, and/or leukopenia.

Immediate cessation of benzimidazoles is recommended if signs of lethargy or significant decreases in the complete blood cell count are noted. Sucralfate and acid reducers, such as famotidine and omeprazole, can be used to treat and prevent gastrointestinal ulceration. If septicemia is suspected, antibiotics and fluid therapy are recommended. Blood transfusions should be performed in patients with severe anemia and may need to be repeated until the bone marrow is functional. Medications to support anemia, such as iron dextran and vitamin B_{12}, may be beneficial. Based on these studies and several anecdotal reports of toxicity in these various species, clinicians should carefully consider the risk of mortality of an individual from a parasitic infection compared with the risk of septicemia after damage to hematopoietic and gastrointestinal systems from fenbendazole therapy. Despite reported side effects, fenbendazole has been used safely in many species kept as pets and in zoos.

ANTI-INFLAMMATORY MEDICATIONS

Glucocorticoids

Glucocorticoids are used in veterinary and human medicine for a variety of maladies but most commonly for their anti-inflammatory, immunosuppressive, and antineoplastic effects and as replacement therapy in patients with adrenal insufficiency and associated endogenous glucocorticoid deficiency.[13] Glucocorticoids exert their anti-inflammatory effects by inhibiting both the cyclooxygenase-mediated and lipoxygenase-mediated arachidonic acid inflammatory pathways.[28] The mechanisms of their immunosuppressive effects are less well understood but seems related to effects on leukocyte kinetics, phagocytic immunity, cell-mediated immunity, and humoral immunity.[28] Glucocorticoids also increase the secretion of gastric acid, pepsin, and trypsin as well as decrease mucosal cell proliferation, thus increasing the risk for gastrointestinal ulceration in susceptible species.[13]

Birds and certain mammalian species, such as mouse, rat, and rabbit, are considered steroid-sensitive species, whereas dogs, ferrets, and guinea pigs are considered steroid-resistant species.[28,29] When exposed to exogenous glucocorticoids, steroid-sensitive species exhibit an immediate and profound lymphopenia due to lymphocytolysis induced by activation of a resident endonuclease.[28] Lymphocytes of steroid-resistant species, in contrast, do not succumb to the same lytic effects and, instead, their circulating lymphocytes redistribute to the lymph nodes, spleen, and bone marrow. This is not to say, however, that steroid-resistant species are

not susceptible to the adverse effects of steroid administration, especially with high doses and/or chronic use.

Clinical recommendations for corticosteroid administration to steroid-sensitive species (including birds) include using lower doses than in steroid-resistant species and ideally using a short treatment time of no more than 5 consecutive days.[30] The most common uses of glucocorticoids in exotic animal medicine include palliative treatment of systemic neoplasia, treatment of ocular disease, or postoperative cataract therapy. In 1 exotic animal formulary, there are several references for use of glucocorticoids for treatment of shock conditions in a variety of avian species.[10] The use of glucocorticoids in certain emergencies (acute lung injury, acute spinal cord injury, anaphylaxis, and so forth) of domestic mammalian species is controversial. Based on information from human medicine, however, the routine use of glucocorticoids for treatment of traumatic brain injury is not recommended.[31]

Systemic administration of steroids as an adjunct to chemotherapy for treatment of hematopoietic neoplasia in several avian species have been previously described.[32–35] Prednisone has also been used as a sole palliative treatment after radiation for periorbital lymphoma in a blue-and-gold macaw (*Ara ararauna*).[36] Prednisolone has been used in conjunction with radiation therapy for the treatment of lymphocytic thymomas in rabbits.[37] In the clinic of 1 author (Chen), prednisolone has also been used solely as a palliative measure. In these rabbits, clinical signs improved and radiographic evidence of a significant decrease in the size of their thymomas was noted after receiving oral prednisolone alone. Adverse effects, including mild to moderate pododermatitis and mild upper respiratory infections, did develop in some but not all rabbits (Sue Chen, DVM, unpublished data, 2017).

Topical therapy with prednisolone acetate for uveitis secondary to multicentric lymphoma has been associated with transient improvement in ocular disease in a macaw.[38] To reduce the risks of systemic side effects of the corticosteroid, the clinicians used a 0.12% prednisolone acetate ophthalmic medication for that patient rather than the more commonly prescribed 1% solution. According to a recent review of cataract management in avian species in zoologic collections, a majority (72%) of birds that underwent cataract surgery received a topical antibiotic-steroid ophthalmic solution postoperatively. In addition, some birds also received preoperative and intraoperative topical steroid ophthalmic solutions.[39] Bilateral phacoemulsification and intraocular lens implantation were performed in a great horned owl, and an antibiotic-steroid ophthalmic solution was applied topically at a tapering frequency for 5 weeks postoperatively.[40] An immunosuppressive dose of prednisolone was prescribed for 40 days in a case of presumed immune-mediated hemolytic anemia in a conure.[41] After discontinuation of the medication, the clinical signs returned and the patient died; however, the association between dosage discontinuation and return of clinical signs may or may not have been directly correlated.

In rabbits, most adverse effects are secondary to the immunosuppressive effects of steroids, such as mucopurulent ocular and nasal discharge associated with an upper respiratory infection. Pododermatitis, progressing to hock abscesses, may be due to a combination of immunosuppression and thinning of the skin that occur with administration of long-term glucocorticoids. The investigators have seen a case of severe otitis externa and pinna abscessation in a rabbit after a short course of topical otic medication containing a steroid (**Fig. 1**). In birds, there is limited peer-reviewed literature to document the adverse effects of steroids, which reportedly include immunosuppression and secondary bacterial and fungal infections, delayed wound healing, diabetes mellitus, hepatic disease, and gastrointestinal ulceration.[42] Involution of the cloacal bursa, thymus, and spleen with resulting suppression of both

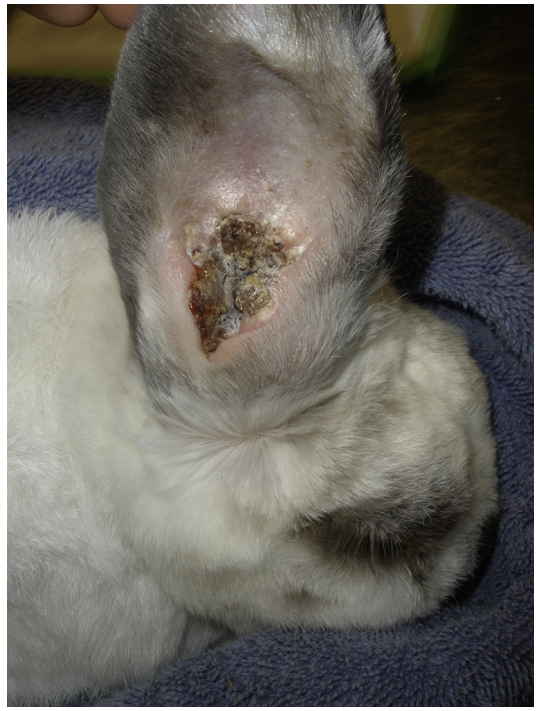

Fig. 1. This rabbit was prescribed a short course of a topical otic medication containing a steroid for mild otitis externa. After less than a week of treatment, the rabbit was evaluated by the authors for severe otitis externa and pinna abscessation. Although progression of otic disease cannot be definitively ruled out, the authors strongly suspect that the steroid greatly exacerbated the existing otitis, especially due to the short clinical progression.

cell-mediated and humoral immunity has been reported after corticosteroid use in birds.[43,44] Pigeons were found to react to exogenous glucocorticoids by early delayed feedback and were overall more sensitive to suppression of the hypothalamic-pituitary-adrenal system by glucocorticoids compared with mammals.[45] In humans, the function of respiratory macrophages is negatively impacted by exposure to systemic corticosteroids.[46] Because these immune cells provide the initial defense against *Aspergillus* infections in avian species and humans, immunocompromised patients are predisposed to fungal disease.[27] A published case series described severe mycotic airsacculitis after accidental prolonged corticosteroid treatment in 7 blue-fronted Amazon parrots. These birds also had a history of smoke inhalation and dyspnea 14 days to 20 days prior, which further complicated the suspected association between prolonged corticosteroid use and development of fungal disease.[47] Caution should also be taken with use of topical corticosteroids, because adverse effects have also been reported in some species.[30] A study in pigeons found a single ocular application of a glucocorticoid caused suppression of the pituitary-adrenocortical system, and the duration of suppression was comparable to that of a comparable single IV dose of glucocorticoids, which exceeded 24 hours in some cases.[48]

Although there are numerous studies evaluating steroid-induced immunosuppression in animal models for experimental purposes, unfortunately, there are no

pharmacokinetic, efficacy, or safety studies of the use of any steroid for treatment of any disease in any exotic companion species to date. In disease conditions where the use of steroid therapy is indicated and the benefits outweigh the negative, clinicians should closely monitor patients' white cell count by checking a complete blood cell count prior to and during treatment. A biochemical profile is also recommended to evaluate for hyperglycemia and hepatic dysfunction. Administration of antibiotics or antifungals may be necessary if a concurrent bacterial or fungal infection develops during the course of treatment. In several avian patients[34,40] that received steroids long term (ie, greater than 1 week), an antifungal medication was prescribed concurrently to help reduce the risk of systemic aspergillosis. This is clinician preference, and to the authors' knowledge, there are no studies that have evaluated the efficacy of antifungal medication(s) during treatment with topical or systemic steroid administration in birds. Antifungal medications are used in human medicine for specific, high-risk immunosuppressed patients, including those with acute myelogenous leukemia and bone marrow transplant recipients.[49] There is concern within the medical community, however, about increasing antifungal resistance due to widespread use, in particular, of voriconazole and the increasing incidence of other fungal infections in immunosuppressed populations, such as mucormycosis.[50,51]

Acid reducers, such as H_2-blockers and proton pump inhibitors, can be administered to reduce the risk of gastrointestinal ulceration. Concurrent use of other drugs and the complicated nature of the underlying disease also hamper interpretation of presumed efficacy from these published case reports. Moreover, concurrent administration of certain medications, such as NSAIDs, may exacerbate adverse reactions associated with steroid administration and are not recommended. Therefore, exotic animal and zoo clinicians must extrapolate what is known for other domestic animals and assume some degree of risk when prescribing steroids to their patients, especially if the steroid sensitivity of that species is unknown.

There is no right or wrong answer to the question, Should glucocorticoids be used in avian and exotic species?[52,53] Many opinions are forged after apparent success or failure of a glucocorticoid in patients with a variety of clinical syndromes. Although formation of these opinions is inevitable in the exotic and zoo animal community due to a paucity of scientific data, clinicians should critically evaluate case outcome with as much evidence-based medicine as possible. Was the positive case outcome directly related to the use of a steroid, or were there other factors involved? Was the deterioration of a case related to the use of a steroid, or was that simply the natural progression secondary to severity of the patient's disease? There is universal agreement that corticosteroids, as in all species, have well-documented side effects in exotic companion animals, and these risks should be weighed against their potential benefits for each patient.

Ibuprofen in Ferrets

Ibuprofen is a widely used NSAID used in human medicine for its analgesic, anti-inflammatory, and antipyretic effects. Despite its therapeutic effects in people, its use is not recommended in certain species due to its narrow safety margin in dogs, cats, and ferrets. Ibuprofen is consistently one of the most common toxicoses reported to the American Society for the Prevention of Cruelty to Animals (ASPCA) Animal Poison Control Center.[54] Various over-the-counter formulations exist, including 200-mg tablets/capsules, pediatric suspensions of 20 mg/mL and 40 mg/mL, and prescription-strength tablets as high as 800 mg per tablet. Because of a ferret's small size, even a single 200-mg tablet can result in a toxic dose of 100 mg/kg to 400 mg/kg in a ferret.

Ibuprofen nonselectively inhibits cyclooxygenase enzymes by blocking the conversion of arachidonic acid into various prostaglandins that mediate pain and inflammation, regulating mucus and bicarbonate synthesis, maintaining water homeostasis, stimulating repair of gastrointestinal epithelia cells, and controlling blood flow to the stomach and kidneys.[55,56] Inhibition of cyclooxyegenase-1 enzymes seems to target the prostaglandins that have a cytoprotective effect on the stomach and the regulation of gastric and renal blood flow. The conversion of arachidonic acid to thromboxane A_2 is also blocked, which can lead to impaired platelet aggregation and clot formation. As a group, NSAIDs are also recognized to have direct cytotoxic effects on the gastric mucosa, which can subsequently lead to gastrointestinal upset, ulceration, and hemorrhage, especially in cases of overdosage and/or chronic usage.[56] In dogs, doses as low as 8 mg/kg every 24 hours for 30 days have resulted in gastric ulceration, and single, acute overdoses as low as 25 mg/kg can result in vomiting.[54] Renal effects are attributed to disruption of vasodilatory prostaglandins that maintain blood flow to the kidneys, and the effects are exacerbated in patients that are dehydrated or have underlying renal or cardiovascular disease.[56] Central nervous symptoms are well documented in people and dogs with overdoses of greater than 400 mg/kg, with neurologic symptoms ranging from drowsiness to coma. Additionally, overdoses in children and dogs have resulted in seizures and episodes of apnea associated with metabolic acidosis.[54,56] The pharmacokinetics and pathophysiology of ibuprofen toxicosis in ferrets are unknown.[55]

Ferrets are especially sensitive to the toxic effects of ibuprofen. The first case of toxicosis was reported in 2000, in a 20-month-old ferret that presented for gastrointestinal signs and acute lethargy of 2 hours' duration.[57] In that case, the patient's clinical signs progressed quickly from being lethargic to being semicomatose shortly after presentation and eventually going into cardiopulmonary arrest 8 hours later despite supportive measures. In a retrospective study of 43 cases reported to the ASPCA, 93% of ferrets developed neurologic signs, including depression, ataxia, tremors, weakness, and being comatose.[55] Gastrointestinal signs, such as vomiting, anorexia, diarrhea, and melena, were noted in 55% of the ferrets. Renal dysfunction as evidenced by polyuria, polydipsia, and dysuria were noted in 13% of the cases. Other reported clinical signs included weight loss, shallow breathing, metabolic acidosis, dehydration, hypothermia, and death. In that study, the minimum lethal dose was 220 mg/kg. More than half of the ferrets developed clinical signs within 8 hours of ingestion, with many developing signs within 4 hours.[55]

Biochemical analysis should be performed to assess for renal and hepatic function. Elevated blood urea nitrogen, creatinine, and hyperphosphatemia may be noted on biochemical analysis if renal compromise is present but may be normal early in the course of disease. The urine specific gravity should also be assessed and the urine should be monitored for tubular casts, which can be seen within 18 hours of exposure.[54,55] In cases of gastrointestinal bleeding, anemia may be noted on a complete blood cell count. Metabolic acidosis may be noted on analysis of venous blood gas.[56] Toxicologic analyses for ibuprofen can be performed on serum, urine, and hepatic samples using gas chromatography and mass spectrophotometry.

If ingestion of ibuprofen occurred within 2 hours of presentation to a veterinarian, consider induction of emesis if the ferret is not showing neurologic signs or vomiting.[54,55] Activated charcoal should be administered every 6 to 8 hours to prevent enterohepatic recirculation. Gastroprotectants, such as sucralfate, and acid reducers, such as famotidine and omeprazole, should be administered to treat and prevent gastric ulcers. Misoprostol, a synthetic prostaglandin E1 analog, has a cytoprotective effect on the gastric mucosa and also inhibits gastric acid secretion.[13] Although there are no

pharmacokinetic or safety studies for the use of misoprostol in ferrets, anecdotal dosage, 1 μg/kg to 5 μg/kg orally every 8 hours, has been suggested.[55] Diuresis with IV fluids is strongly recommended for a minimum of 48 hours and should be continued until renal values are back to normal. Patients that are severely anemic from gastrointestinal bleeding benefit from whole-blood transfusions. Reports of IV lipid infusion has been described in a dog with ibuprofen toxicosis,[58] but use of this therapeutic modality has not been reported in a ferret. Seizures can be controlled with diazepam, midazolam, phenobarbital, or other anticonvulsants; however, once a patient develops seizures, the prognosis is guarded.

Ketoprofen in Rats

Like ibuprofen, ketoprofen is a nonselective NSAID used for its analgesic, anti-inflammatory, and antipyretic effects in a variety of veterinary species. Ketoprofen has been used in a variety of zoo and exotic species, including ferrets, birds, reptiles, and other small mammals.[10] A prospective study by Shientag and colleagues[59] evaluated a single dose of ketoprofen (5 mg/kg) in rats, a dose previously found safe and effective for postoperative pain in this species.[60,61] Those investigators found significant mucosal damage in the intestinal tract within 24 hours of administration. The rats administered ketoprofen (with and without anesthesia) had significant drops in their packed cell volume, positive fecal occult blood tests, and varying grades of intestinal ulcers on necropsy compared with control rats. The severity of the lesions was exacerbated when ketoprofen was administered in conjunction with anesthesia.[59]

Rats with ketoprofen toxicosis have clinical signs related to ulceration of the gastrointestinal tract and include lethargy, pale mucous membranes, abdominal pain, and melena. Rats that survive the acute gastrointestinal ulceration may die 1 week to 2 weeks later possibly due to bacterial translocation and sepsis. Necropsy findings have included intestinal ulcers, diffuse bleeding into the intestinal lumen, adhesions, fibrosis, and ascites secondary to peritonitis. Treatment should center around treating and protecting the gastrointestinal mucosa by administering gastroprotectants, such as sucralfate, and acid-reducers, such as famotidine, omeprazole, and raniditine. Antibiotic therapy and supportive measures, such as parental fluids and nutritional support, may also be beneficial, especially in cases of possible sepsis. Based on the findings of Shientag and colleagues' study,[59] the standard dosing of 5 mg/kg of ketoprofen cannot be recommended for pain control in rats and additional toxicity and safety studies need to be performed.

CONTRAINDICATED ANTIBIOTICS IN HERBIVOROUS RODENTS AND RABBITS

Although any antibiotic can potentially cause disruption of the cecum's microbial flora, antibiotics that target primarily gram-positive flora can lead to fatal dysbiosis and should not be used in rabbits and rodents, such as guinea pigs, chinchillas, and hamsters. These species have a diverse gut microflora that is adversely impacted by those particular antibiotics. Antibiotics, such as penicillins, cephalosporins, clindamycin, lincomycin, erythromycin, and tylosin, have been implicated in the eradication in these species' normal gastrointestinal flora, allowing for the overgrowth of pathogenic bacteria, such as *Clostridium difficile*. Exotoxins produced by *C difficile* causes hyperactivity of the secretory neurons, which leads to secretory diarrhea, mucosal damage, and hemorrhagic typhlitis.[62] The adverse effects seem most commonly associated with oral administration of these antibiotics, but there is a peer-reviewed report of lethal hemorrhagic typhlitis in guinea pigs administered penicillin parenterally.[63] In

contrast, parental administration of penicillin and cephalosporins do not seem to affect the rabbit gastrointestinal tract in the same manner and have been used successfully for β-lactam–sensitive bacterial infections or abscesses in rabbits.[64]

Rabbits, guinea pigs, chinchillas, and hamsters may present with profuse and watery diarrhea, although they sometimes are brought in for generalized signs of gastrointestinal stasis, such as anorexia, lethargy, and diminished fecal production. A distended abdomen and perineal fecal staining are common findings. Animals may exhibit signs of abdominal pain, including a hunched posture, reluctance to move, and resistance to abdominal palpation. Varying levels of dehydration is common, and hypovolemic shock may be present in severely affected animals.

Diagnosis is usually based on clinical signs and history of recent administration of one of the offending antibiotics. A complete blood cell count and biochemical profile should be performed to evaluate for underlying metabolic and systemic disorders that may or may not be associated with the gastrointestinal tract. Radiographs may be unremarkable or have signs of ileus and gas dissension. Gram stains of the diarrhea may reveal large numbers of spore-forming bacteria as well as yeast overgrowth. The presence of toxin A, an enterotoxin, and toxin B, a cytotoxin, can be detected by enzyme immunoassay in fecal samples. Confirming the presence of cytotoxin is considered the gold standard in diagnosing enterotoxemia caused by *C difficile*,[62] although this test is not commonly performed in clinical practice.

Administration of an antibiotic should be discontinued immediately in any small herbivorous mammal presenting with diarrhea. Treatment is geared toward supportive measures to keep patients from becoming fluid and electrolyte depleted. If a patient is still bright and alert, subcutaneous fluids may be adequate to treat dehydration and electrolyte imbalances. IV fluids, however, are recommended if a patient is lethargic, hypothermic, and showing signs of hypovolemic shock. Pain medication may be beneficial for patients exhibiting signs of acute abdomen (hunched behavior, bruxism, and reluctance to move). Buprenorphine can be administered in patients with severe pain. One study found cholestyramine, an ion exchange resin that binds to clostridial iota toxins, effective in preventing deaths in rabbits challenged with acute clostridial enterotoxemia when given at 2 g in 20 mL water by mouth once daily for 18 days to 21 days.[65] Anecodotal experience with this medication, however, has been equivocal. Metronidazole (20 mg/kg orally or IV every 12 h) can be administered for clostridial overgrowth and has been reported to reduce the number of mortalities associated with enterotoxemia.[66] The re-establishment of normal colonic microbiome through fecal microbiota transplantation has an inhibitory effect against pathogenic bacteria and is now considered a standard treatment of recurrent *C difficile* infections in humans.[67] Based on this principle, anecdotal reports of transfaunation with cecotrophes from a healthy conspecific show that this treatment may be of benefit in rabbits with antibiotic-associated dysbiosis.[68]

ITRACONAZOLE IN AFRICAN GRAY PARROTS (*PSITTACUS ERITHACUS*)

Anecdotally, African gray parrots (*Psittacus erithacus timneh*) are more sensitive to itraconazole than other species, and adverse clinical signs, including anorexia, depression, and even death, have been reported.[10,69,70] Similar to the experience of many exotic animal clinicians, the authors have seen similar adverse effects in this species, even with doses as low as 2.5 mg/kg orally once daily. To the authors' knowledge, however, there are no safety studies or even published case reports of itraconazole toxicity in African gray parrots. Because of toxicity concerns, despite the paucity of published information, itraconazole should be used with caution in this

species. The pharmacokinetics of voriconazole in African gray parrots has been evaluated, and this may be a more suitable alternative for susceptible fungal diseases in this species.[71]

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