



## **Ibuprofen Ingestion in Ferrets: 43 Cases (January 1996 - March 2000)**

by

Jill A. Richardson, DVM; Rachel A. Balabuszko, CVT

### **ABSTRACT**

**Objective:** To summarize typical clinical signs, characterize the anticipated course of action, and give treatment recommendations for ibuprofen ingestion in ferrets.

**Design:** Retrospective study.

**Patients:** Records of 43 cases of ibuprofen ingestion in ferrets that were reported between January 1996-March 2000, to the ASPCA Animal Poison Control Center (APCC).

**Measurements and Main Results:** 27 (93.1%) ferrets that had ingested ibuprofen developed neurologic signs, such as depression, coma, ataxia, recumbency, tremors, and weakness. In addition, 16 cases (55.2 %) had one or more GI effects including anorexia, vomiting, retching or gagging, diarrhea, and melena. Polydipsia, polyuria, dysuria, renal failure, weight loss, shallow breathing, metabolic acidosis, dehydration, and hypothermia were also reported. Death was reported in 4 cases. The lowest dose associated with death was 220 mg/kg.

**Conclusion:** Data in this study indicate that clinical signs of ibuprofen toxicosis in ferrets are more severe than those expected at similar dosages in dogs. The reason for this difference is poorly understood since the pathophysiology of ibuprofen is relatively unknown in ferrets. The onset of clinical signs appeared to occur soon after ingestion and the toxic effects in ferrets typically involve the CNS, GI and renal systems. Treatment for ibuprofen toxicosis in the ferret includes stabilization, gastrointestinal decontamination, fluid diuresis, GI protection, and supportive care. (*J Vet Emerg Crit Care 2001; 11(1):53-59*).

### **KEY WORDS:**

Ibuprofen, ferret, non-steroidal anti-inflammatory drugs, NSAIDS, toxicoses.

### **INTRODUCTION**

Ferrets are extremely curious and can access areas like purses, backpacks, and counter-tops, where medications, such as ibuprofen, are stored. Ferrets can even pry caps from child-resistant bottles or chew through plastic containers. Between January 1996-March 2000, the ASPCA Animal Poison Control Center (APCC) received 43 cases concerning ibuprofen ingestion in ferrets. The objective of this article is to summarize typical clinical signs, characterize the anticipated course of action, and give treatment recommendations for ibuprofen ingestion in ferrets.

#### *Ibuprofen General Properties*

Ibuprofen (2(4-isobutylphenyl) propionic acid) is a substituted phenylalkanoic acid with nonsteroidal anti-inflammatory, antipyretic, and analgesic properties.<sup>(1)</sup> Ibuprofen is available over the counter and by prescription. Available forms include 50, 100, 200, 300, 400, 600, and 800 mg tablets and pediatric suspensions in 40 mg/mL and 100 mg/5ml strengths.<sup>(1,2)</sup> Ibuprofen can also be found as a 5% ibuprofen topical ointment and in combination with decongestants as cold or flu medications.<sup>(1)</sup>

Ibuprofen is used as an anti-inflammatory in the treatment of arthritis, as an analgesic in the treatment of acute and chronic musculoskeletal pain, and to reduce fever.<sup>(1,2)</sup> Ibuprofen is not used therapeutically in ferrets. Ibuprofen has been used in dogs at a dose of 5 mg/kg but routine use is not recommended due to the risk of gastric ulceration and perforation.<sup>(4,5)</sup>

### *Mechanism of Action and Kinetics*

The mechanism of action of ibuprofen is inhibition of prostaglandin synthesis through blocking the conversion of arachidonic acid to prostaglandins, which are mediators of inflammation. Prostaglandins are involved in renin release, local vascular tone, regional circulation, water homeostasis, and potassium balance.<sup>(5)</sup> Prostaglandins also stimulate repair of gastrointestinal epithelial cells and stimulate secretion of bicarbonate by epithelial cells.<sup>(1,5)</sup> Ibuprofen can decrease secretion of the protective mucous layer in the stomach and small intestine, and can also cause vasoconstriction in the gastric mucosa. In addition, ibuprofen can inhibit renal blood flow, glomerular filtration rate, and tubular ion transport.<sup>(1,5)</sup> Ibuprofen may affect platelet aggregation and possibly hepatic function.<sup>(5)</sup>

The exact pharmacokinetics of ibuprofen in the ferret is unknown. Following ingestion in humans, 80% of ibuprofen is absorbed from the gut and peak serum concentrations are reached in 1-2 hours.<sup>(2,6)</sup> Ibuprofen is highly protein-bound (about 90–99%) and undergoes enterohepatic recirculation.<sup>(2,7)</sup> Acute renal insufficiency, liver disease, and hypoalbuminemia can decrease plasma protein binding and increase volumes of distribution.<sup>(5)</sup> Although plasma half-life is between 2 and 4 hours in humans and dogs, the excretion of ibuprofen is usually complete within 24 hours.<sup>(2,7)</sup> Ibuprofen is biotransformed in the liver to metabolites that are excreted in the urine.<sup>(5)</sup> Ibuprofen is excreted 50-60% as metabolites and approximately 10% as unchanged drug primarily via glomerular filtration and tubular secretion, and the remainder of the drug is eliminated in feces both as metabolites and the unabsorbed drug.<sup>(2)</sup>

### *Clinical Effects*

Vomiting, diarrhea, nausea, anorexia, gastric ulceration, and abdominal pain can be seen with acute ingestion of ibuprofen in the dog at doses between 50-125 mg/kg. At doses greater than 175 mg/kg, renal damage can be seen in addition to the gastrointestinal signs. Doses greater than 400 mg/kg may result in CNS effects such as seizure, ataxia, and coma.<sup>(10)</sup> Cats are considered to be at least twice as sensitive as dogs to ibuprofen toxicosis because they have a limited glucuronyl-conjugating capacity.<sup>(10,11,12)</sup>

In humans, the onset of gastrointestinal upset is generally within the first 2-6 hours after ingestion, with the onset of gastrointestinal hemorrhage and ulceration occurring 12 hours to 4 days post ingestion.<sup>(2)</sup> The onset of renal failure in humans often occurs within the first 12 hours after massive exposure to any NSAID, but may be delayed until 3-5 days after exposure.<sup>(2)</sup> Onset of signs and symptoms is not well documented for dogs. In a review of 35 cases of canine ibuprofen ingestion, 7 dogs vomited shortly after exposure and 6 developed vomiting or hematemesis within 20 to 24 hours after exposure.<sup>(2)</sup> Severe hemorrhagic gastroenteritis developed 48 hours after exposure in one case.<sup>(2)</sup>

### *Diagnosis*

The diagnosis of ibuprofen toxicosis is primarily based upon exposure history and the development of associated signs. Ibuprofen analysis has been performed in the ferret on serum, urine, or hepatic tissues via gas chromatography and mass spectrophotometry.<sup>(11)</sup>

## **MATERIALS AND METHODS**

Information compiled from the APCC database was analyzed. Upon receiving a case, the APCC collected information such as species, breed, age, sex, weight, number of animals at risk, number of animals affected, estimated dosage of product ingested and time of ingestion. The case record also contained information about the

onset, severity, and duration of clinical signs. The APCC veterinarian assesses each case of ibuprofen ingestion as an exposure, toxicosis, suspected toxicosis, possible toxicosis, or doubtful, based upon clinical signs and exposure history. A case that is assessed as "exposure only" is one in which no clinical signs were seen from the ingestion. If the clinical history and clinical signs were not consistent with an expected reaction to ibuprofen, or if another cause for the clinical signs was discovered, the case was assessed as "doubtful". A case is assessed as a "toxicosis" if clinical signs and exposure history are consistent with an expected reaction to ibuprofen. The case is assessed as a "suspected toxicosis" if the clinical signs are consistent with an expected reaction but some data is lacking. A case is assessed as a "possible toxicosis" when either the clinical signs or the time of ingestion are not completely characteristic of ibuprofen toxicosis.

## **RESULTS**

Out of 43 cases of ibuprofen ingestion in ferrets received by the APCC, 9 (20.1%) were assessed as exposure only, 1 (2.3%) was assessed as doubtful, 5 (11.6%) were considered as a toxicosis, 20 (46.5%) were considered suspect, and 8 (18.6%) were considered as possible toxicosis. The assessments were not confirmed by analytical methods. All cases involved the accidental exposure of ferrets to ibuprofen tablets except one that involved inappropriate administration by the owner. One case involved exposure of two ferrets. Age of the involved ferrets ranged from 9 weeks to 4 years. There were 19 (43.2%) females and 18 (41.8%) males and the sex of 7 ferrets was not known. Estimated ingested dosages ranged from 18.4 mg/kg to 15,500 mg/kg. Of the 33 cases of toxicosis, suspected or possible toxicosis, only 29 cases were evaluated since four of these cases involved exposure to multiple agents.

27 (93.1%) ferrets that had ingested ibuprofen developed neurologic signs, such as depression (75.8%), coma (27.5%), ataxia (24.1%), recumbency (13.7%), tremors (6.8%) and weakness (6.8%). In addition, 16 cases (55.2%) exhibited one or more GI effects including anorexia (17.2%), vomiting (17.2%), retching or gagging (17.2%), diarrhea (10.3%), and melena (3.4%). Signs involving the urinary system, such as polydipsia, polyuria, dysuria, and renal failure were reported in 4 cases (13.7%). Weight loss, shallow breathing, metabolic acidosis, dehydration, and hypothermia were also reported. Death was reported in 4 cases (13.7%). The lowest dose associated with death was 220 mg/kg. Since severe effects can be seen at such a low dose, any dose of ibuprofen in the ferret is potentially toxic.

In 13 (44.8%) cases, clinical signs developed within 4 hours. In 6 cases (20.6%), signs developed within 5-8 hours. The longest onset of clinical signs was reported at 48 hours post-exposure. In 9 cases, the time of onset of clinical signs was not known.

## **DISCUSSION**

According to data collected in this study, clinical signs of ibuprofen toxicosis in ferrets are more severe than those expected at similar dosages in dogs. The reason for this species difference is poorly understood since pathophysiology of ibuprofen is relatively unknown in ferrets. The onset of clinical signs occurred soon after ingestion in most cases. The one case in which clinical signs were seen 48 hours post ingestion was assessed as a possible toxicosis because a delay in onset of clinical signs would not be expected. The toxic effects of ibuprofen in ferrets typically involve the CNS (93.1%), GI (55.2%) and renal (13.7%) systems. Similar effects were seen in a recent case report of a ferret that had ingested an unknown amount of ibuprofen.<sup>(11)</sup> Since even one tablet of a regular strength ibuprofen (200 mg) could be fatal to an average-sized ferret (1.5-2 lbs.), the ingestion of ibuprofen has an unfavorable prognosis unless the animal is decontaminated early and given aggressive treatment.

## **TREATMENT**

The primary goal of treatment is to prevent or treat gastric ulceration, renal failure, CNS effects and possible hepatic effects; however stabilizing the ferret is the first priority. Prognosis is good if the ferret is treated promptly and appropriately, while delay in treatment can decrease survival potential.

### *Stabilization*

A comatose ferret should be given oxygen therapy and monitored for bradycardia, hypotension, shock, and respiratory depression. A patent airway should be established and artificial respiration can be given with a 2.5-3.5 mm endotracheal tube.<sup>(12)</sup> The cardiovascular system should be monitored closely and any abnormality should be corrected.<sup>(13)</sup> Corticosteroid therapy for shock may increase the likelihood of GI ulcerations.<sup>(21)</sup>

Seizures may occur with large doses of ibuprofen and can be controlled with diazepam (1-2 mg/kg IM or IV) or other anticonvulsants.<sup>(14)</sup> The ferret's core body temperature should also be monitored. The normal body temperature of the ferret is reported to be 37.8-40° C (100-104° ), with an average being 38.3° C (101.0° F).<sup>(13,15)</sup>

### *Preventing Absorption*

Ferrets do have the ability to vomit and emesis may be induced in the asymptomatic ferret unless a contraindication exists (i.e., presence of severe CNS depression, recent abdominal surgery, or pre-existing health problems.) Gastric lavage is not considered to be as effective as emesis, but could be attempted if emesis is not an option.<sup>(16)</sup> Establishing the time of exposure is important because the ferret has a short gastrointestinal transit time (3-4 hours in the adult) and emesis will be useful only if induced within 1-2 hours after the exposure.<sup>(16)</sup> Three percent (3%) hydrogen peroxide solution has been shown to be an effective emetic for ferrets and can be given orally at a dose of 1ml/lb. In cases when emesis is contraindicated but emptying of stomach contents is essential, gastric lavage under general anesthesia using a cuffed endotracheal tube should be considered.

Activated charcoal adsorbs ibuprofen and can be given via a stomach tube or a dosing syringe at a dose of 1-2 g/kg.<sup>(2,16)</sup> Activated charcoal should be repeated, since ibuprofen undergoes enterohepatic recirculation.<sup>(2)</sup> A cathartic, such as sorbitol, should be used in combination with activated charcoal unless the ferret is dehydrated or has diarrhea.<sup>(16)</sup>

### *Supportive Care*

The approach to the diagnosis and treatment of renal disease in ferrets is the same as for other companion animal species.<sup>(17)</sup> Diuresis for 24-36 hours is recommended to prevent acute renal failure. The placement of a 22-24 gauge peripheral catheter in the lateral saphenous, the cephalic, or the jugular vein may be necessary for parenteral fluids.<sup>(13,18)</sup> When this is not an option, an intraosseous catheter can be placed in the tibia crest (preferably), humerus, or femur using a 20-22 gauge, 1.5 inch spinal needle.<sup>(13,18)</sup> Catheter placement is performed with the ferret under anesthesia. Isoflurane using an induction chamber or a face mask provides the safest means of anesthesia in the ferret.<sup>(13,19)</sup> An infusion pump should be used to prevent overhydration, and the ferret should be monitored for wet lung sounds or the development of a heart murmur, which could indicate overhydration.<sup>(13)</sup>

The ferret's BUN, creatinine, urine specific gravity, and hepatic enzymes should be monitored closely. However, the serum creatinine level alone may not accurately reflect the presence of renal failure in ferrets.<sup>(18)</sup> Baseline values and then repeated values checked at 36, 48, 72 hours post exposure are recommended. Urine output should be evaluated, and the ferret should be monitored for acidosis and electrolyte shifts. Hyperphosphatemia, hypocalcemia and reduced total carbon dioxide can be seen in ferrets with renal disease.<sup>(17)</sup> The prognosis for ferrets with acute renal failure depends on laboratory findings and response to therapy. Clinical signs of renal disease in ferrets may include depression, lethargy, inappetence, weight loss, oral ulcers, polyuria and polydipsia, melena, rear leg weakness, and dehydration.<sup>(13)</sup> The development of papillary necrosis is generally considered an irreversible condition.<sup>a(7,10)</sup>

The ferret should be placed on gastrointestinal protectants for 5-7 days post-exposure to prevent gastric ulceration. Misoprostol is a synthetic prostaglandin (PGE1) that inhibits gastric acid and has a cytoprotective effect on gastric mucosa.<sup>21</sup> Misoprostol has been used to treat GI ulceration in dogs secondary to ibuprofen ingestion and could be used in ferrets at a dose of 1-5 micrograms/kg PO q 8h.<sup>26</sup> Sucralfate at a dose of 1/8 gram q 6 h is commonly used to treat and prevent gastric ulceration in ferrets.<sup>(14,22)</sup> Sucralfate can bind to ulcers and erosions and protect them from further exposure to gastric acid, bile acids, and pepsin.<sup>(21)</sup> In addition, sucralfate is considered to be cytoprotective through stimulation of prostaglandin production.<sup>(22,23)</sup> H<sub>2</sub> receptor antagonists have been recommended for the treatment of ibuprofen-induced gastric irritation and ulceration in dogs and cats.<sup>(7)</sup> Cimetidine (5-10 mg/kg PO, SC, IM, or IV, q 8 h) or famotidine (0.25-0.5 mg/kg PO, IV, q 24 h) could be given to the ferret in addition to sucralfate

therapy.<sup>b (20,14)</sup> Metoclopramide (0.2 to 1 mg/kg q 6-8 h PO, SC) can be used to control vomiting in ferrets.<sup>(20)</sup> The animal should be monitored for clinical signs suggestive of gastritis which may include weight loss, vomiting, hypersalivation, and bruxism.<sup>(23)</sup>

#### *Ancillary Treatment*

With ibuprofen ingestion, ancillary measures, such as nutritional support, are necessary for complete recovery of the ferret. Anorectic ferrets are at risk of developing hepatic lipidosis and hypoglycemia and should be hospitalized for fluid therapy and parenteral treatment.<sup>(13)</sup> A pharyngostomy tube may be necessary to provide adequate nutrition. The technique is identical to that described for cats and utilizes an 8-10 French pediatric feeding tube.<sup>(13)</sup> Adult ferrets can be force-fed liquid soy-based or meat-based diets at 2-5ml 3 to 4 times daily.<sup>(13,17)</sup> The resting energy requirement for ferrets is 70 kcal/ day.<sup>(13)</sup> A more complete diet should be used if forced feeding continues more than 1 day.<sup>(15)</sup> Diazepam at 1 mg/kg IM or less could be used to stimulate appetite.<sup>(14)</sup>

#### **POSSIBLE DRUG INTERACTIONS**

Substances that could cause an interaction with ibuprofen include coumarin-type anticoagulants, which could increase the risk of gastrointestinal bleeding. Glucocorticoids may also increase the likelihood of GI ulcerations.<sup>5,21</sup> Other NSAIDs, such as salicylates, phenylbutazone, and indomethacin, could potentiate the gastrointestinal effects of ibuprofen.<sup>1</sup> It is unknown what effects NSAIDs would have on the CNS effects of ibuprofen in ferrets.

#### **Footnotes:**

- a. The presence of papillary necrosis can be determined by performing a wedge biopsy of a live animal or can be determined through histopathological evaluation during necropsy. However, due to the invasiveness of the wedge biopsy procedure, the authors do not recommend such sampling.
- b. The use of cimetidine with ibuprofen toxicosis appears to be controversial. Cimetidine decreases hepatic blood flow and inhibits hepatic microsomal enzymes. Pretreatment with cimetidine was found to increase both the rate and extent of absorption of ibuprofen in rats, however, the extent of decrease clearance with single-dose ibuprofen ingestion in humans is considered insignificant.<sup>(24,25)</sup>

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