

PEER-REVIEWED

Bufo species toxicosis: Big toad, big problem

Paul A. Eubig, DVM

It is common for companion animals to mouth toads. Oral exposure to larger toad species such as marine and Colorado River toads can be life-threatening. Fortunately, mouthing other toad species found throughout the United States usually results in nothing more than signs of oral irritation, including profuse ptyalism, gagging, and pawing at the mouth.

True toads, from the genus *Bufo*, are represented by 18 species in the continental United States.¹ Only two species—*Bufo marinus* and *Bufo alvarius*—have been reported to cause serious signs after oral exposure.^{2,3}

Bufo marinus, also known as the cane, marine, or giant toad, is found in the southern tips of Florida and Texas and in Hawaii. *Bufo marinus* was introduced from Puerto Rico into Hawaii in 1932 in an effort to control an insect threat to the sugar cane industry.⁴ Adults range from 4 to 9.5 in long. The toad's size and its extremely large, raised parotid poison glands extending caudally over the shoulders aid in its identification (Figure 1).

The Colorado River toad, *B. alvarius*, is found in the southern half of Arizona, southeastern California, and southwestern New Mexico. Also known as the Sonoran Desert toad, this species ranges from 3 to 7 in long and has comparatively smooth skin.¹ Besides its parotid poison glands, this species has an additional pair of poison glands on the forelimbs and several pairs on the hindlimbs.⁵

All toads from the genus *Bufo*



1. A marine toad, *Bufo marinus*. Note the prominent parotid poison glands (arrows) over the shoulders.

produce poisonous glandular secretions. The biochemical classes of the components in the secretions are similar, although individual components vary among species.⁶ *Bufo marinus*, followed by *B. alvarius*, has the largest parotid poison glands and the largest volume of secretions from the glands.⁷

Toxins and their mechanisms of action

Parotid glands in toads are not salivary glands. They are aggregations of skin glands that have several small orifices that empty on the skin's surface.⁷ The secretions' primary toxins are bufogenins, such as marinobufa-

gin, and bufotoxins, such as marinobufotoxin.⁸ Bufogenins are similar to cardiac glycosides. These compounds inhibit Na^+ , K^+ -ATPase activity in the myocardial cell membrane, similar to digitalis.⁹ This effect leads to an increase in intracellular sodium and, by stimulating sodium-calcium exchange, ultimately increases calcium concentrations in the myocardial cells, resulting in arrhythmias. Bufogenins also block sodium channels,⁹ similar to local anesthetics. Bufotoxins are conjugates of a bufogenin with suberyl arginine.⁶ Their mechanism is thought to be similar to that of the bufogenins.

Secondary toxins produced by parotid glands include the bufotenines serotonin and 5-hydroxytryptophan as well as catecholamines.¹⁰ Bufotenines can potentially cause signs such as seizures, depression, tremors, hyperesthesia, hyperthermia, vomiting, and diarrhea if absorbed in sufficient quantities.¹¹ Catecholamines may cause signs such as tachycardia, hypertension, anxiety, and respiratory difficulty. However, dogs that were experimentally given *Bufo* species toxins orally did not experience an elevation in blood pressure.⁴ Generally, the oral mucosa prevents marked absorption of most compounds. The role of serotonin is questionable because of its rapid degradation in the gastrointestinal tract.⁴ Other bufotenines such as 5-hydroxytryptophan are better-absorbed through the gastrointestinal tract¹¹ and may play a more important role. Catecholamines are also inactivated by the intestine and the liver, but endogenous cate-

CAMILIA LIESKE, DVM

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BRIEF SUMMARY

Before using Baytril Tablets, please consult the product insert, a summary of which follows:

CAUTION:

Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.
Federal law prohibits the extralabel use of this drug in food-producing animals.

INDICATIONS:

Baytril® (brand of enrofloxacin) Antibacterial Tablets are indicated for the management of diseases associated with bacteria susceptible to enrofloxacin. Baytril Antibacterial Tablets are indicated for use in dogs and cats.

CONTRAINDICATIONS:

Enrofloxacin is contraindicated in dogs and cats known to be hypersensitive to quinolones.

Dogs: Based on the studies discussed under the section on Animal Safety Summary, the use of enrofloxacin is contraindicated in small and medium breeds of dogs during the rapid growth phase (between 2 and 8 months of age). The safe use of enrofloxacin has not been established in large and giant breeds during the rapid growth phase. Large breeds may be in this phase for up to one year of age and the giant breeds for up to 18 months. In clinical field trials utilizing a daily oral dose of 5.0 mg/kg, there were no reports of lameness or joint problems in any breed. However, controlled studies with histological examination of the articular cartilage have not been conducted in the large or giant breeds.

ADVERSE REACTIONS:

Dogs: Two of the 270 (0.7%) dogs treated with Baytril® (brand of enrofloxacin) Tablets at 5.0 mg/kg per day in the clinical field studies exhibited side effects, which were apparently drug related. These two cases of vomiting were self-limiting.

Post Approval Experience: The following adverse experiences, although rare, are based on voluntary post-approval adverse drug experience reporting. The categories of reactions are listed in decreasing order of frequency by body system.

Gastrointestinal: Anorexia, diarrhea, vomiting, elevated liver enzymes

Neurologic: ataxia, seizures

Behavioral: Depression, lethargy, nervousness

Cats: No drug-related side effects were reported in 124 cats treated with Baytril® (brand of enrofloxacin) Tablets at 5.0 mg/kg per day for 10 days, in clinical field studies.

Post Approval Experience: The following adverse experiences, although rare, are based on voluntary post-approval adverse drug experience reporting. The categories of reactions are listed in decreasing order of frequency by body system.

Ocular: Mydriasis, retinal degeneration, (retinal atrophy, attenuated retinal vessels, and hyperreflective tapeta have been reported), loss of vision. Mydriasis may be a condition of impending or existing retinal changes.

Gastrointestinal: vomiting, anorexia, elevated liver enzymes, diarrhea

Neurologic: ataxia, seizures

Behavioral: Depression, lethargy, vocalization, aggression

To report adverse reactions or a suspected adverse reaction call 1-800-633-8405.

ANIMAL SAFETY SUMMARY:

Dogs: Adult dogs receiving enrofloxacin orally at a daily dosage rate of 52 mg/kg for 13 weeks had only isolated incidences of vomiting and inappetence. Adult dogs receiving the tablet formulation for 30 consecutive days at a daily treatment of 25 mg/kg did not exhibit significant clinical signs nor were there effects upon the clinical chemistry, hematological or histological parameters. Daily doses of 125 mg/kg for up to 11 days induced vomiting, inappetence, depression, difficult locomotion and death while adult dogs receiving 50 mg/kg/day for 14 days had clinical signs of vomiting and inappetence.

Adult dogs dosed intramuscularly for three treatments at 12.5 mg/kg, followed by 57 oral treatments at 12.5 mg/kg, all at 12 hour intervals, did not exhibit either significant clinical signs or effects upon the clinical chemistry, hematological or histological parameters.

Oral treatment of 15 to 28 week old growing puppies with daily dosage rates of 25 mg/kg has induced abnormal carriage of the carpal joint and weakness in the hindquarters. Significant improvement of clinical signs is observed following drug withdrawal. Microscopic studies have identified lesions of the articular cartilage following 30 day treatments at either 5, 15 or 25 mg/kg in this age group. Clinical signs of difficult ambulation or associated cartilage lesions have not been observed in 29 to 34 week old puppies following daily treatments of 25 mg/kg for 30 consecutive days nor in 2 week old puppies with the same treatment schedule.

Tests indicated no effect on circulating microfilariae or adult heartworms (*Dirofilaria immitis*) when dogs were treated at a daily dosage rate of 15 mg/kg for 30 days. No effect on cholinesterase values was observed.

No adverse effects were observed on reproductive parameters when male dogs received 10 consecutive daily treatments of 15 mg/kg/day at 3 intervals (90, 45 and 14 days) prior to breeding or when female dogs received 10 consecutive daily treatments of 15 mg/kg/day at 4 intervals (between 30 and 0 days prior to breeding, early pregnancy (between 10th and 30th days), late pregnancy (between 40th and 60th days), and during lactation (the first 28 days).

Cats: Cats in age ranges of 3 to 4 months and 7 to 10 months received daily treatments of 25 mg/kg for 30 consecutive days with no adverse effects upon the clinical chemistry, hematological or histological parameters. In cats 7-10 months of age treated daily for 30 consecutive days, 2 of 4 receiving 5 mg/kg, 3 of 4 receiving 15 mg/kg, 2 of 4 receiving 25 mg/kg and 1 of 4 non-treated controls experienced occasional vomiting. Five to 7 month old cats had no side effects with daily treatments of 15 mg/kg for 30 days, but 2 of 4 animals had articular cartilage lesions when administered 25 mg/kg/day for 30 days.

Doses of 125 mg/kg for 5 consecutive days to adult cats induced vomiting, depression, incoordination and death while those receiving 50 mg/kg for 8 days had clinical signs of vomiting, inappetence, incoordination and convulsions, but they returned to normal.

Enrofloxacin was administered to thirty-two (8 per group), six- to eight-month-old cats at doses of 0, 5, 20, and 50 mg/kg of body weight once a day for 21 consecutive days. There were no adverse effects observed in cats that received 5 mg/kg body weight of enrofloxacin. The administration of enrofloxacin at 20 mg/kg body weight or greater caused salivation, vomiting, and depression. Additionally, dosing at 20 mg/kg body weight or greater resulted in mild to severe fundic lesions on ophthalmologic examination (change in color of the fundus, central or generalized retinal degeneration), abnormal electroretinograms (including blindness), and diffuse light microscopic changes in the retina.

DRUG INTERACTIONS:

Compounds that contain metal cations (e.g., aluminum, calcium, iron, magnesium) may reduce the absorption of some quinolone-class drugs from the intestinal tract. Concomitant therapy with other drugs that are metabolized in the liver may reduce the clearance rates of the quinolone and the other drug.

Dogs: Enrofloxacin has been administered to dogs at a daily dose rate of 10 mg/kg concurrently with a wide variety of other health products including anthelmintics (praziquantel, febantel), insecticides (pyrethroids), heartworm preventatives (diethylcarbamazine) and other antibiotics (ampicillin, gentamicin sulfate, penicillin, clindamycin). No incompatibilities with other drugs are known at this time.

Cats: Enrofloxacin was administered at a daily dosage rate of 5 mg/kg concurrently with anthelmintics (praziquantel, febantel), an insecticide (propoxur) and another antibiotic (ampicillin). No incompatibilities with other drugs are known at this time.

WARNINGS:

For Use in Animals Only. In Rare Instances, Use of this Product in Cats has been associated with Retinal Toxicity. Do not exceed 5 mg/kg of body weight per day in cats. Safety in Breeding or Pregnant Cats has not been Established. Keep Out of Reach of Children.

Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposure. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of severe photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight.

For a copy of the Material Safety Data Sheet, call 1-800-633-8405.

PRECAUTION:

Quinolone-class drugs should be used with caution in animals with known or suspected Central Nervous System (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation which may lead to convulsive seizures.

Quinolone-class drugs have been associated with cartilage erosions in weight-bearing joints and other forms of arthropathy in immature animals of various species.

The use of fluoroquinolones in cats has been reported to adversely affect the retina. Such products should be used with caution in cats.

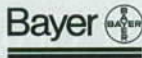
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cholinergic release may instead serve to potentiate the toxicosis.⁴ The clinical signs are likely caused by a combination of factors rather than by just one type of compound.

Clinical signs and differential diagnoses

Signs of *Bufo* species toxicosis manifest immediately and can progress to advanced signs in less than 15 minutes. The most common noncardiac signs in dogs resulting from *B. marinus* exposure include neurologic abnormalities (seizures, stupor, ataxia, and nystagmus), ptialism (usually profuse), hyperemic mucous membranes, recumbency or collapse, tachypnea, and vomiting.² Hyperthermia or hypothermia may also develop. The most common electrocardiographic findings in dogs following *B. marinus* exposure were sinus arrhythmia, sinus tachycardia, and normal sinus rhythm. However, 10 of 94 dogs evaluated required treatment for bradycardia, while only two dogs required measures to slow tachycardia.² A variety of arrhythmias can develop. Experimentally, dogs that were given *B. marinus* toxin orally consistently experienced progressive negative ventricular deflection followed by ventricular fibrillation.⁴ Hyperkalemia is often seen after oral exposure in dogs⁴ and people,¹² but hypokalemia has also been reported.³

The severity of signs likely depends on the volume of the secretions released by the toad and the patient's size. Exposure to larger toads, such as *B. marinus* or *B. alvarius*, is more likely to produce

more severe signs, especially in smaller animals. For example, smaller dogs were hospitalized longer in one case series.² However, exposure to any *Bufo* species can potentially produce advanced signs, especially if a patient is small, geriatric, or in poor health.

Consider other possible causes of these clinical signs if an exposure was not witnessed. Inquire about recent pesticide use, because organophosphorus, carbamate, pyrethroid, metaldehyde, or chlorinated hydrocarbon exposure can cause similar signs. Also ask about medications in the home. Toxicosis from ingestion of a sympathomimetic such as pseudoephedrine or amphetamine, a methylxanthine such as theophylline, a β -blocker, a β -agonist, or one of many antidepressants can have a similar presentation. Exposure to common outdoor plants such as *Rhododendron* species, *Nerium oleander* (oleander), and *Digitalis purpurea* (foxglove) can also manifest with similar signs. Oral signs such as ptialism can be induced by oral exposure to agents such as freshly applied topical flea products, caustic cleaning products, liquid potpourri, and plants such as *Dieffenbachia* and *Philodendron* species that contain insoluble calcium oxalate. Finally, other medical conditions such as seizure disorders, vehicular trauma, and heat stroke can have a similar presentation.

Treatment

Oral lavage is recommended for all exposures. The most effective way to

decrease oral absorption of secretions is to have the owner lavage the mouth with running water from a tap or a hose pointed in a rostral direction through the oral cavity. This is indicated only if exposure is likely and the patient is exhibiting either no signs or mild signs such as gagging or ptyalism. If the patient is exhibiting advanced signs such as depression or tachypnea, oral lavage should be performed at the veterinary facility. If possible, intubate the patient before oral lavage to decrease the risk of iatrogenic aspiration. If the patient is from an area where *B. marinus* or *B. alvarius* is found, immediate evaluation is recommended after oral lavage, regardless of the patient's size. In other areas of the country, advise the owner of the small likelihood of serious exposure, and tell the owner to watch for the clinical signs. Evaluate the patient immediately if any serious signs emerge.

The ingestion of a whole toad is potentially more life-threatening than the mouthing of a toad. If a toad is ingested, emesis is indicated unless signs other than ptyalism are present. Other means of decontamination in this situation can include endoscopic retrieval, surgical removal, or multiple doses of activated charcoal with a cathartic.

Activated charcoal may help adsorb *Bufo* species toxins, but its efficacy for this use has not been evaluated. Nevertheless, activated charcoal is recommended if advanced signs are developing. If any abnormality in cardiac rate or rhythm is auscultated or if severe neurologic signs develop, monitor an electrocardiogram continuously.² Evaluate serum electrolyte activity and monitor serial potassium concentrations if hyperkalemia or hypokalemia is detected. Correct any electrolyte imbalances as needed.

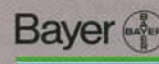
A dog exhibiting severe signs of toxicosis should receive an initial shock dose of fluids (45 to 90 ml/kg intravenously). The shock dose of fluids in cats is 25 to 60 ml/kg.¹³ Once the animal's condition stabilizes, the fluid rate may be lowered to a maintenance rate.² Measure the serum potassium concentration, and administer potassium supplementation or take steps to lower the potassium concentration as needed. Frequently monitor the body temperature of severely affected animals. Control agitation, seizures, or tremors with diazepam (0.5 to 2 mg/kg



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intravenously in dogs or 0.5 to 1 mg/kg intravenously in cats) or a barbiturate (e.g. pentobarbital sodium, 3 to 15 mg/kg slowly intravenously to effect in dogs and cats) as needed.¹⁴

Drying oral secretions with atropine is contraindicated because it can contribute to arrhythmias.¹⁵ However, a dose of atropine (0.02 to

by a constant-rate infusion of 10 to 40 µg/kg/min.¹⁶ Cats are more likely to experience side effects such as twitching and seizures from lidocaine, so be cautious with its use in this species.¹⁶

Esmolol hydrochloride has been recommended for treating prolonged sinus tachycardia as a result of *B. marinus* exposure.² A recommended

hypokalemic patient, monitor the patient's potassium concentration. Dexamethasone sodium phosphate (0.5 to 1 mg/kg intravenously) and methylprednisolone sodium succinate (15 to 30 mg/kg intravenously) have also been administered in affected dogs.² The finding of perivascular edema in the brains of dogs that were intravenously dosed with *B. marinus* secretions lends support to these recommendations.¹⁷ The above medications are acceptable for use in cats at similar doses.¹⁴

Digoxin-specific antigen-binding fragments (digoxin immune Fab) have been given in large empirical doses to people that developed signs after ingesting products containing glandular secretions from *Bufo* species toads. Digoxin immune Fab may especially be of value in treating patients that exhibit advanced arrhythmias, hyperkalemia,¹² or neurologic signs, but the use of this product may be cost-prohibitive.^{18,19}

Prognosis

Prompt treatment and supportive care initiated soon after exposure to *B. marinus* or *B. alvarius* usually result in a favorable outcome. However, fatalities can occur, especially if treatment initiation in the face of advanced signs has been delayed. Exposure to other *Bufo* species typically results in mild signs that should be self-limiting once the mouth is lavaged. Since all *Bufo* species contain similar toxins in their glandular secretions, the possibility for advanced signs always exists and should not be ignored.

Fatalities can occur, especially if treatment initiation in the face of advanced signs has been delayed.

0.04 mg/kg intravenously or intramuscularly) is appropriate in dogs and cats to treat severe bradycardia.¹⁴ Very high propranolol hydrochloride doses to treat arrhythmias have been recommended based on experimental trials,⁴ but empirical use of propranolol is not advisable because of the high incidence of bradydysrhythmias seen with toad intoxication.¹² For ventricular and supraventricular arrhythmias that are not responsive to fluids, propranolol (0.02 to 0.06 mg/kg slowly intravenously in dogs and 0.04 mg/kg slowly intravenously in cats) is indicated. Lidocaine can be used for ventricular arrhythmias, but it is ineffective for supraventricular arrhythmias. Lidocaine can be given to dogs as a slow intravenous bolus (2 to 4 mg/kg) followed by a constant-rate infusion of 25 to 100 µg/kg/min. Cats can be given a slow intravenous bolus (0.25 to 0.75 mg/kg) followed

dose of esmolol for supraventricular arrhythmias in dogs consists of a loading dose of 0.5 mg/kg slowly intravenously followed by a constant-rate infusion of 50 to 200 µg/kg/min. Esmolol's advantages include a rapid onset of action and a rapid cessation of action once the infusion is discontinued. Hypotension is a common adverse effect. Esmolol can increase serum digoxin concentrations by up to 20% if the two drugs are concomitantly administered.¹⁴ It is unknown whether esmolol would have a similar effect on the digoxin-like bufogenins and bufotoxins absorbed after oral exposure.

Using diuretics such as furosemide (1 to 2 mg/kg intravenously) and hyperosmolar agents such as mannitol (0.25 to 1 g/kg slowly intravenously over 15 to 20 minutes) has been advocated in dogs experiencing severe signs such as collapse or coma.² If you give furosemide to a

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"Toxicology Brief" was contributed by Paul A. Eubig, DVM, ASPCA Animal Poison Control Center, 1717 S. Philo Road, Suite 36, Urbana, IL 61802; (888) 4ANI-HELP.



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