Toad Intoxication in the Dog by *Rhinella marina*: The Clinical Syndrome and Current Treatment Recommendations

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**ABSTRACT**

Oral exposure to the secretions of *Rhinella marina* (formerly *Bufo marinus*) can carry a high fatality rate without early and appropriate treatment. In dogs, the clinical syndrome, which is evident almost immediately, manifests in profuse ptyalism along with gastrointestinal, respiratory, and neurologic signs. Severe cardiac arrhythmias develop less frequently. This review will cover the history, toxicology, and clinical syndrome of *Rhinella marina* intoxication, and will discuss the recommended therapies for stabilization. *(J Am Anim Hosp Assoc 2016; 52:205–211. DOI 10.5326/JAAHA-MS-6365)*

**Introduction**

For centuries, toads have been known to carry toxic substances in their skin that serve as a form of chemical defense against predators.1 Of particular concern in small animal emergency medicine, especially in areas of temperate climate, are the toxic secretions from toads of the family Bufonidae. *Bufo marinus*, now renamed *Rhinella marina*, is known to secrete a protective substance that is highly toxic to dogs.2,3 While cats can be poisoned by toads, this is not a commonly encountered clinical scenario.4 Regardless of the species exposed, because the intoxication can lead to seizures and cardiac dysrhythmias, it can be fatal if severe signs develop and are not treated in a timely fashion.2,3 However, there is little information on stabilization and treatment required in severe cases of intoxication, especially from an emergency and critical care perspective. This review will cover the history, toxicology, and clinical syndrome of *R. marina* intoxication with an emphasis on recommended therapies for stabilization and treatment specific for this toxicosis.

**History of Rhinella marina**

The native range of *R. marina* extends from South and Central America, throughout Mexico, to southern Texas. *R. marina* was widely introduced throughout the Caribbean and Pacific Ocean, including Hawaii and Australia in the 1930s, in an effort to control insect pests on sugar cane and other crops.3–5 *R. marina* is also found in southern Florida, with the current population originating from an accidental release by an animal importer in Miami prior to 1955 and subsequent, intentional releases by exotic animal dealers in the early 1960s.6 The habitat of *R. marina* is not confined to lush tropical or rural areas; in southern Florida, *R. marina* appears to be thriving in many urban areas and is expected to expand its range further north.7

*R. marina* is omnivorous; its diet consists of insects, vegetation, small birds, frogs, lizards, and smaller toads.7 Due to its indiscriminate eating habits, *R. marina* is considered a highly invasive species in the areas where it was introduced.5 Because of its tropical and nocturnal nature, intoxications are commonly reported in warmer and wetter months from dusk through the early...
morning.\textsuperscript{2,3,8} A fully developed, \textit{R. marina} can reach 6–9 inches in size, which is an important distinguishing factor from its smaller, minimally-toxic counterpart, the southern toad \textit{Anaxyrus terrestris} (formerly \textit{Bufo terrestris}) that is native to southern Florida.\textsuperscript{7}

**Pathophysiology of \textit{R. marina} Toxicosis**

Toxins from \textit{R. marina} and other species in the family Bufonidae are produced and stored in the parotoid glands, which extend along the neck and parascapular region (see Figure 1). A thick, milky-white substance containing the toxic constituents is secreted from the parotoid pores on the glands. The secretions are believed to provide a form of defense against predators.\textsuperscript{9} Toxicosis occurs when animals mouth a toad, resulting in oral exposure to the glandular secretions.\textsuperscript{3,7,10,11} \textit{R. marina} produces a much greater volume of secretions than other toad species in the United States not only because it is much larger in size but also because, even in immature \textit{R. marina}, the parotoid glands are much larger than in other toad species. The greater volume of secretions is why oral exposure to \textit{R. marina} can result in life-threatening toxicosis.\textsuperscript{12} Younger, smaller dogs, especially terrier breeds, are overrepresented in previous studies, which likely reflects that smaller dogs receive a larger dose of secretions on a per kg basis when they mouth \textit{R. marina}.\textsuperscript{2,3} With the exception of the Sonoran Desert toad (\textit{Incilius alvarius}, formerly \textit{Bufo alvarius}), which also produces prodigious secretions, other species of toads in the United States do not produce enough secretions to cause more than mild, self-limiting signs, such as excessive ptyalism, gagging, or pawing at the mouth, in animals that mouth them.\textsuperscript{12,13}

While the secretions from the parotoid glands are comprised of similar classes of chemical constituents between all species of Bufonidae, there are species differences between the individual compounds within each chemical class. The main classes of constituents of toxicologic importance are bufadienolides, catecholamines, and indolealkylamines.\textsuperscript{1,12,14} Other relatively non-toxic constituents include sterols, such as cholesterol and 7-dehydrocholesterol or provitamin D, and proteins, which likely are degradation products from cells lining the glands.\textsuperscript{1,15}
Bufadienolides

Bufadienolides, or bufagins, are structurally similar to cardiac glycosides and comprise at least 8% of the content of the dried secretions in \textit{R. marina}, with marinobufagenin (also called marinobufagin) being the most common.\textsuperscript{16,17} The chemically-related bufotoxins are also found in the secretions but are less potent than bufadienolides.\textsuperscript{1,12} Despite being relatively lipophilic, bufadienolides are reported to be poorly absorbed from the gastrointestinal (GI) tract of dogs and cats.\textsuperscript{1,18} What is absorbed across the GI mucosa peaks in the circulation within 30 min, and is then fairly quickly eliminated, with half-lives of 2–4 hr being reported in a rodent model, the only species in which the toxicokinetics of bufadienolides have been reported.\textsuperscript{19} Bufadienolides cross the blood-brain barrier and can inhibit their own P-glycoprotein-mediated efflux, which the authors speculate serves to concentrate these compounds in tissues including the central nervous system (CNS).\textsuperscript{20,21}

One question that has not been well addressed by prior studies is the extent to which absorption of bufadienolides occurs across the oral mucous membranes, which is arguably the region of the GI tract where exposure to toxicants in toad secretions is the greatest. Sublingual or buccal absorption bypasses metabolism in the rest of the GI tract and first-pass hepatic metabolism, resulting in greater systemic exposure to unmetabolized bufadienolides.\textsuperscript{22} While absorption from the oral cavity of the cardiac glycoside, ouabain, has been shown to occur in a canine \textit{ex vivo} model and in humans, to the authors’ knowledge there are no studies that provide evidence of oral absorption of other cardiac glycosides or bufadienolides.\textsuperscript{22,23} It has been theorized that vomiting of the swallowed secretions prevents significant GI absorption of the toxic constituents of the secretions.\textsuperscript{24} However, if absorption through the oral mucous membranes is the primary route of exposure, profuse salivation and vomiting seen with \textit{R. marina} exposure may be important in reducing the absorption of toad secretions. Even if bufadienolides are poorly absorbed, the evidence is that bufadienolides have a significant role in \textit{R. marina} toxicosis because of their high degree of potency, with lethal doses measured in the decigrams/kg range.\textsuperscript{1}

Bufadienolides exert similar effects to cardiac glycosides by inhibiting the sodium, potassium-adenosine triphosphatase (Na\textsuperscript{+}, K\textsuperscript{+}-ATPase) pump.\textsuperscript{25} Pump inhibition results in intracellular sodium and calcium accumulation and potassium depletion, manifesting as increased excitability of cardiac Purkinje fibers and neurons.\textsuperscript{13,26,27} Bufadienolides also affect voltage-gated sodium, potassium, and calcium channels, further destabilizing excitable membranes.\textsuperscript{27} These changes ultimately lead to arrhythmias and CNS stimulation.\textsuperscript{1,28} Additionally, transcellular shifting of potassium out of the cell from inhibition of the Na\textsuperscript{+}, K\textsuperscript{+}-ATPase pump, possibly in combination with acidemia, may result in hyperkalemia.\textsuperscript{29,30} It should be noted that the clinical signs seen with \textit{R. marina} toxicosis in dogs differ from what is seen with cardiac glycoside toxicosis in dogs and other species, with cardiac effects being more prominent when cardiac glycosides are the sole source of toxicity.\textsuperscript{28,31,32}

Catecholamines

Catecholamines found in the secretions of \textit{R. marina} include epinephrine, comprising at least 5% of the content of dried secretions, and much smaller amounts of norepinephrine and dopamine.\textsuperscript{1} GI absorption of catecholamines is minimal due to the presence of inactivating enzymes in the GI mucosa. However, epinephrine is well absorbed sublingually, with an initial peak in the plasma occurring as early as 10 min post-administration.\textsuperscript{33}

While catecholamines alone can be arrhythmogenic, their ability to cause arrhythmias increases when combined with other arrhythmogenic compounds.\textsuperscript{28} Otani et al. reported that the cardiac glycoside, ouabain, and epinephrine together better reproduced the cardio-respiratory effects of IV administration of \textit{R. marina} toxins than either substance alone.\textsuperscript{8} Additionally, the bufadienolide, bufalin, has been shown to increase the release and decrease the reuptake of norepinephrine, elevating synaptic norepinephrine concentrations, in a canine saphenous vein model.\textsuperscript{34} These findings suggest that catecholamines and bufadienolides may act synergistically to produce the clinical effects of \textit{R. marina} toad toxicosis.

Indolealkylamines

Indolealkylamines are compounds derived from serotonin. Dehydrobufotenine is the most common indolealkylamine found in \textit{R. marina} secretions.\textsuperscript{14,35} Daly et al. reported large amounts of dehydrobufotenine in the parotoid glands but did not quantify the amount.\textsuperscript{36} Serotonin has also been isolated from \textit{R. marina} secretions, but only in small amounts that comprise 0.1% of the content of dried secretions.\textsuperscript{9} Because many indolealkylamines are polar compounds, they are limited in their ability to cross biologic membranes within the physiologic pH range.\textsuperscript{37} This suggests that dehydrobufotenine is even more limited in the ability to traverse membranes because it is an ionized quaternary ammonium compound.

Although it is questionable whether indolealkylamines are absorbed to an extent sufficient to contribute to the toxicity of \textit{R. marina} secretions, many of the clinical effects of \textit{R. marina} toxicosis resemble those of serotonin excess. Serotonin intoxication or serotonin syndrome typically manifests in vomiting, mydriasis,
tachycardia, tremors, and seizures in dogs.38–41 Because the extents of neurologic and cardiovascular signs of *R. marina* toxicosis in dogs do not strictly resemble what is seen with cardiac glycoside toxicosis, there may be other mechanisms by which serotonergic compounds play a role in *R. marina* toxicosis. For example, cardiac glycosides have been shown to increase the release of endogenous serotonin in the CNS.42

**Clinical Signs**

Many owners report seeing their dog mouth a *R. marina* toad or a witness a toad in close proximity to their dog. Severe ptyalism and hyperemic mucous membranes develop almost immediately after oral contact with a *R. marina* toad.43 Within 30–60 min, vomiting, hyperactivity, mydriasis, nystagmus, and, in the most severe cases, status epilepticus and cardiac dysrhythmias may occur.2,3,43,44 Profuse ptyalism and hyperemic mucous membranes are the most common signs following oral exposure to *R. marina*.3 Vomiting occurs frequently in the acute phase, but is usually not persistent. Neurologic effects are also common clinical manifestations of *R. marina* intoxication, being reported in more than half of the dogs in a retrospective clinical report.2 Neurologic signs can vary in both length and severity.10,11 Initially, mydriasis, altered mentation, or abnormal gait may be present. Signs may progress to extensor rigidity, opisthotonos, seizures, and coma in the most severe of cases.2,3 Hyperthermia and non-cardiogenic pulmonary edema also have been reported in cases of *R. marina* intoxication in dogs.2,24,43 Mild hyperkalemia has been reported in an experimental study of oral exposure to *R. marina* secretions in dogs but has not been documented in clinical cases.4 Dogs that are exhibiting advanced signs, such as seizures or coma, after *R. marina* exposure are often acidotic, either from respiratory acidosis due to poor ventilation in comatose patients or metabolic acidosis in patients that are tremoring or seizuring.43

Arrhythmias have been reported with *R. marina* toxicosis in dogs (20% incidence in one clinical case series), but occur less frequently than neurologic signs and often do not require treatment.2,3 Reported arrhythmias include bradycardia, sinus tachycardia, first and second degree atrioventricular block, ventricular tachycardia, and ventricular fibrillation.2,4,11 Alterations in blood pressure have rarely been reported for *R. marina* toxicosis in dogs.4,43

If exposure was not witnessed, differential diagnoses for conditions or toxicant exposures that produce similar clinical signs include hyperthermia or heat stroke, hypocalcemia, hypoglycemia, primary seizure disease, serotonin syndrome, and exposure to organophosphate or carbamate insecticides.45 If acute, severe ptyalism is the only sign, differential diagnoses include exposure to caustic substances, oral foreign bodies, and esophageal foreign bodies.46

**Treatment**

In areas where *R. marina* is endemic, dogs that have been witnessed to mouth a toad should always be evaluated, regardless of the dog’s size, due to the potential for serious, life-threatening effects from the toxins. Most cases of exposure require some form treatment, even if the clinical signs are mild.2,3,11 Upon initial presentation, triage for life-threatening conditions such as shock and treat critical conditions, before proceeding with less critical therapeutic measures.

**Decontamination**

Oral lavage is the most important step in decontamination. Because it is vital to remove the toad’s secretions from the oral cavity as soon as possible to limit continued absorption of the toxins, this should be performed by the owners at home if the patient is conscious and the exposure has just been witnessed.2 The owner should be directed to lavage the mouth with water from a garden hose. The spray should be directed from the commissure of the mouth in a rostral direction and the patient’s head should be facing down in order to avoid iatrogenic aspiration. If the patient is seizuring, oral lavage should be performed by the veterinarian using water-soaked gauze and airway protection as needed.

Although the efficacy of administering activated charcoal for *R. marina* toxicosis has not been evaluated, it has been shown to reduce absorption of bufadienolides in an *in vivo* rodent model.47 However, administration of activated charcoal is not recommended in the typical exposure scenario because it is questionable whether a significant amount of secretions traverse distal to the oral cavity, and because administering activated charcoal to patients that are vomiting or displaying CNS signs is contraindicated. Activated charcoal may be more important if other forms of toad secretions, such as traditional Chinese medications, which contain dried secretions, or if whole toads are ingested. In the latter case, endoscopic or surgical removal, or multiple doses of activated charcoal, has been recommended.13,48 Cholestyramine can be used to treat cardiac glycoside toxicosis but has been shown to be inferior to activated charcoal in preventing absorption of digoxin, suggesting that it may be less efficacious than activated charcoal in treating *R. marina* toxicosis.49

**Anti-emetic Therapy**

Ptyalism and hyperemia of the oral membranes seen with oral exposure to *R. marina* are attributed to local irritant effects of the toxins. Atropine should not be utilized to reduce oral secretions, since hyposalivation can potentially decrease the dilution of toxins remaining in the oral cavity, and atropine may potentiate cardiac dysrhythmias.3 Possible causes of vomiting from *R. marina* exposure to *R. marina* secretions in dogs but has not been documented in clinical cases.4
exposure include direct stimulation of the GI tract, which afferently projects to the medullary emesis center, and stimulation of the chemoreceptor trigger zone via blood-borne toxins.\textsuperscript{1,3} Dolasetron and ondansetron are centrally-acting anti-emetics that are antagonists of 5-HT\textsubscript{3} serotonin receptor subtypes. These medications may provide additional efficacy if some of the emetic effects are mediated via the indolealkylamine constituents of \textit{R. marina} secretions. Maropitant may be beneficial due to its action as a NK-1 receptor antagonist both centrally and locally in the GI tract.\textsuperscript{50} The effectiveness of specific anti-emetics has not been evaluated for treating \textit{R. marina} toxicosis.

**Anticonvulsant Therapy**

The benzodiazepines diazepam or midazolam can be used to control seizure activity.\textsuperscript{2,3,43} In cases that are refractory to initial therapy with a benzodiazepine, a continuous propofol drip in combination with a benzodiazepine allows for intubation.\textsuperscript{51} In cases the authors have managed, a combination constant-rate infusion of propofol and midazolam reduced seizures and anxiety associated with \textit{R. marina} intoxication until the clinical signs abated, which typically occurred in 4–12 hr. Instituting long-term, anti-epileptic medications (e.g., phenobarbital, potassium bromide, levetiracetam) is not necessary as the seizures are due to an acute intoxication and completely resolve in most patients. If hyperthermia develops from tremors or seizure activity, standard cooling measures should be instituted.\textsuperscript{51}

**Respiratory Therapy**

Significant respiratory or ventilatory compromise may be present requiring oxygen supplementation or positive pressure ventilation, respectively.\textsuperscript{43} Flow-by or nasal oxygen, or an oxygen chamber, should be provided as a conservative measure in the more stable patients.\textsuperscript{52,53} Patients should be monitored for the development of non-cardiogenic pulmonary edema and, when pre-existing occult heart disease is present, judicious use of fluid therapy and monitoring for cardiogenic pulmonary edema is important.\textsuperscript{43}

**Treating Electrolyte and Acid-Base Imbalances**

Monitoring acid-base and electrolyte abnormalities will allow for early recognition and correction of any potentially life-threatening abnormalities, as well as assist in the diagnosis of occult shock. Abnormalities, such as hyperkalemia and metabolic or respiratory acidosis, are best treated using standard therapeutic modalities for these conditions.\textsuperscript{43}

**Cardiovascular Therapy**

No specific drugs are inherently more efficacious for anti-arrhythmic therapy due to \textit{R. marina} toxicosis so the choice of an anti-arrhythmic should be based upon the type of arrhythmia.\textsuperscript{43} Magnesium levels should be evaluated and corrected as needed. Parenteral magnesium may be beneficial, particularly in the management of ventricular arrhythmias, because hypomagnesemia potentiates the effects of cardiac glycosides.\textsuperscript{54} Magnesium is required for normal functioning of the Na\textsuperscript{+}, K\textsuperscript{+}-ATPase pump, so it is vital for maintaining the normal resting membrane potential of excitable membranes.\textsuperscript{55} Magnesium also modulates the binding of cardiac glycosides to the Na\textsuperscript{+}, K\textsuperscript{+}-ATPase pump, so its presence serves to antagonize the effects of cardiac glycosides on pump functioning.\textsuperscript{54,56} Magnesium sulfate (0.15 to 0.3 mEq/kg IV over 10 min) can be used to correct hypomagnesemia.\textsuperscript{43} Ionized magnesium or, at minimum, total magnesium should be monitored to guide therapy. If monitoring is not available, magnesium sulfate should be used cautiously, especially in patients with known decreased renal function. Ionized calcium should also be monitored if magnesium sulfate is used, as chelation of calcium by sulfate anion can occur.\textsuperscript{57}

**Adjunctive Therapies**

Treatment with digoxin-specific antigen-binding fragments (digoxin Fab) has been used in humans experiencing cardiac effects or severe hyperkalemia due to ingestion of toad secretions. Outcomes were excellent when treatment was initiated early in the intoxication.\textsuperscript{29,48} Although this treatment modality has not been reported for the treatment of \textit{R. marina} exposure in small animal clinical cases, the use of digoxin Fab to treat severe arrhythmias or hyperkalemia due to bufadienolide exposure has been suggested for companion animals.\textsuperscript{2,13} If digoxin Fab is instituted, serum potassium should be monitored closely over the first several hr of therapy since hypokalemia can develop due to fluid therapy enhancing renal potassium excretion during the hyperkalemic state in combination with potassium being transported back into cells as functioning of the Na\textsuperscript{+}, K\textsuperscript{+}-ATPase pumps is restored.\textsuperscript{58} Also, magnesium sulfate has been shown to potentiate the effect of digoxin Fab on improving Na\textsuperscript{+}, K\textsuperscript{+}-ATPase pump functioning that was impaired by marinobufagenin, so extra caution is warranted if both digoxin Fab and magnesium sulfate are administered.\textsuperscript{56}

The dose of digoxin Fab to administer to dogs is uncertain. Digoxin Fab does not bind other cardiac glycosides as well as it does digoxin, so it is anticipated that higher doses of digoxin Fab are needed to treat \textit{R. marina} toxicosis versus digoxin toxicosis.\textsuperscript{59} In humans, 10 vials (38 mg/vial) are empirically recommended for toxicosis from ingestion of toad secretions.\textsuperscript{48} Barbier et al. report an average weight of 590 mg of secretions isolated from \textit{R. marina}, with bufadienolides comprising greater than 8% of the secretions, which suggests that there are over 46 mg of bufadienolides in the secretions
of an average R. marina.\textsuperscript{16} If one Fab vial is required to treat an overdose of 1 mg digoxin in dogs, then it is reasonable to anticipate that multiple vials of digoxin Fab would be needed for treatment of R. marina intoxicosis in dogs, although the amount required would depend on the amount of secretions absorbed.\textsuperscript{60} One drawback is that use of digoxin Fab may be cost-prohibitive in many cases.

Intravenous lipid emulsion 20\% (intralipids) has been used to treat a variety of intoxications in both human and veterinary medicine.\textsuperscript{61,62} Intralipids may be of benefit in reducing the toxicity of the more lipophilic constituents of R. marina secretions, i.e., the bufadienolides, but there are currently no reports of its use with R. marina intoxication.

Although it is not certain whether indolealkylamines from R. marina secretions play a role in toxicosis, because some of the clinical signs suggest that there may be a serotonergic component to the clinical syndrome, therapy directed at a reduction of serotonin receptor binding may prove to be beneficial. The serotonin antagonists cyproheptadine (1.1 mg/kg \textit{per os} as needed \( q 4-6 \text{ hr} \)) and chlorpromazine (0.5 mg/kg IV, intramuscular, or subcutaneous \( q 6 \text{ hr} \)) have been very beneficial in reducing the effects of serotonin toxicosis in dogs and should be considered as a potential adjunctive therapy in severe cases of R. marina toxicosis.\textsuperscript{39,41,51} If chlorpromazine is employed, its potential hypotensive effect should be weighed against possible benefits.

**Prognosis**

With early, appropriate treatment, the outcome of R. marina toxicosis is considered excellent, with a marked resolution of signs typically occurring within the first 12–24 hr, even for severely affected patients.\textsuperscript{2,3,10,11,13} Although early reports suggest a high mortality rate, more recent reports suggest at least 96\% survival with early supportive and symptomatic therapy.\textsuperscript{2,3} In one case series, the dogs that died developed seizures in addition to other neurologic abnormalities, but seizures do not necessarily indicate a poor prognosis since only 18\% of dogs that developed seizures died.\textsuperscript{2} The authors conclude that the prognosis associated with R. marina toxicosis is influenced by the amount of toxin ingested, the size of the dog, and the administration of proper, prompt and appropriate medical treatment.\textsuperscript{2,3,10,11,13}

**Conclusion**

In the United States, R. marina toads are found in southern Florida, the southern tip of Texas, and Hawaii. R. marina intoxication has a seasonal distribution, with exposures being common in warmer months and during times of high rainfall. Classic signs of intoxication are bright red mucous membranes and excessive ptyalism, vomiting, and neurologic signs. The emergence of severe neurologic signs, such as seizures and coma, and associated respiratory compromise are the most problematic signs for dogs. Early recognition of toxin exposure followed by rapid decontamination with oral lavage may greatly reduce absorption of the toxins. Administration of digoxin Fab, intralipids, or serotonin antagonists, such as cyproheptadine, may be of benefit in treating severely affected patients, but the effectiveness of each of these therapies has not been examined. The clinical course of uncomplicated R. marina intoxication is typically less than 24 hr and carries a good prognosis if exposure is recognized and patients are treated promptly.

Paul Eubig DVM, MS, PhD, DABT, was funded by the National Institute of Health Sciences K08 ES017045.

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