Treatment of Toad Venom Poisoning With Digoxin-Specific Fab Fragments*

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Toxicity from toad venom poisoning is similar to digoxin toxicity and carries a high mortality rate. We report on six previously healthy men who developed vomiting and bradycardia after ingesting a purported topical aphrodisiac. Each patient had positive apparent digoxin levels and the first four patients died of cardiac dysrhythmias. The last two patients recovered following treatment with digoxin Fab fragments. We analyzed samples of the purported aphrodisiac and found that it was identical to Chan Su, a Chinese medication made from toad venom. To our knowledge, this is the first reported use of digoxin Fab fragments to treat toad venom poisoning.

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Key words: bufodienolides; cardenolides; cardiac glycosides; digoxin; digoxin Fab fragments; toad venom

Abbreviations: ED=emergency department; EDLIS=endogenous digoxin-like immunoreactive substances; FDA=Food and Drug Administration; GC/MS=gas chromatography/mass spectrometry; TLC=thin layer chromatography

When threatened, many toads will secrete a protective venom from their parotid glands. The most toxic components of this venom are steroids similar in structure to digoxin. Dried toad venom is used in China as a traditional medicine known as Chan Su and is a major component of Kyushin, a popular traditional medication used in other Asian countries. Four cases of poisoning from the venom of the Chinese toad Bufo bufo garnarizans, two of which were fatal, were reported from Taiwan. Human poisonings from toad venom have also been reported in the United States. The venoms of the Colorado River toad (Bufo alvarius) and that of the cane toad (Bufo marinus) are similar to that of the Chinese toad. Severe toxic reaction or death has occurred after mouthing toads and following ingestion of an entire toad, or toad eggs. There are also many reports in the popular press about the practice of "toad licking" to get "high" and fatalities have been attributed to this practice.

The cardiacactive compounds in toad venom are bufadienolides and therefore differ from digoxin, and most other plant-derived cardiac glycosides, which are cardenolides. While both bufadienolides and cardenolides are based on a steroid nucleus, the cardenolides have a five-member lactone ring whereas the bufadienolides have a six-member lactone ring (Fig 1). Also, unlike the cardiac glycosides found in plants, the cardioactive compounds in toad venom are known as ag-

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Cardenolide

Bufadienolide

Figure 1. Cardioactive steroids: cardenolides and bufadienolides differ in their lactone rings. Cardioactive compounds have sugars substituted at the R position, whereas cardiac genins (or aglycones) have a hydrogen molecule. Digoxin is a cardiac glycoside of the cardenolide class. The cardioactive steroids in toad venom are cardiac genins of the bufadienolide class.

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lycones or cardiac genins because they do not have attached sugars. To simplify this terminology, we will use the term cardioactive steroids to refer to both the cardiac glycosides and the cardiac genins.

We have recently been involved in the treatment of a series of patients with severe toxic reactions following the ingestion of a product marketed in New York City as a topical aphrodisiac. Analysis of this product by thin layer chromatography (TLC) and by gas chromatography/mass spectrometry (GC/MS) showed it to be identical to Chan Su. All patients were previously healthy young men who developed vomiting and bradycardia. Each patient had a clinical course that was reminiscent of digoxin toxicity, and all had positive apparent digoxin levels by digoxin immunoassays. The first four patients died of cardiac dysrhythmias despite resuscitative attempts. The last two of these patients were successfully treated with digoxin Fab fragments (Digibind). To our knowledge, this is the first time that digoxin Fab fragments have been used to treat poisoning from toad venom in any form.

**CASE REPORTS**

**Case 1**

A 26-year-old man purchased two pieces of an aphrodisiac called “Rock Hard.” He ingested one on the evening before admission to the hospital. Shortly thereafter, he began vomiting and developed abdominal pain and weakness. On arrival in hospital the next day, he complained of feeling cold and of being unable to feel his feet. He was alert and oriented but hypotensive. His vital signs were as follows: BP, 94/60 mm Hg; heart rate, 90/min; respiratory rate, 16/min; and temperature, 36.8°C. His initial laboratory values were as follows: sodium, 135 mEq/L; potassium, 8.4 mEq/L (not hemolyzed); chloride, 102 mEq/L; bicarbonate, 18 mEq/L; BUN, 6.4 mmol/L (18 mg/dL); creatinine, 290 µmol/L (3.2 mg/dL); and glucose, 9.1 mmol/L (164 mg/dL). An arterial blood gas determination was obtained while receiving 100% O2: pH, 7.24; PCO2, 36 mm Hg; and PO2, 519 mm Hg. The patient was treated for hypotension and hyperkalemia with fluids, bicarbonate, and calcium chloride. His cardiac rhythm deteriorated from normal sinus rhythm, to slow atrial fibrillation, to progressive sinus bradycardia. Cardiac pacing was attempted with an external pacemaker followed by a transvenous pacemaker. The patient developed ventricular fibrillation and died within 7 h of admission (approximately 20 h after ingestion). Thirty minutes before cardiac arrest, the electrolytes were as follows: sodium, 138 mEq/L; potassium, 7.5 mEq/L; chloride, 119 mEq/L; bicarbonate, 11 mEq/L; BUN, 3.6 mmol/L (10.0 mg/dL); creatinine, 200 µmol/L (2.3 mg/dL); and glucose, 12.1 mmol/L (219 mg/dL). Because of unexplained hyperkalemia and dysrhythmias, a premortem digoxin level was obtained at the advice of the Poison Control Center. His apparent digoxin level by immunoassay was 3.6 nmol/L (2.79 ng/mL).

**Case 2**

A previously healthy 28-year-old man ingested an aphrodisiac that he had purchased in New York City’s China Town. He began vomiting within 1 h of ingestion and continued to vomit all night. The next morning he walked to an emergency department (ED) complaining of vomiting, diarrhea, and abdominal pain. In the hospital, he was found to be hypotensive and tachycardic. He had a seizure and then became progressively bradycardic. His initial laboratory values were as follows: sodium, 136 mEq/L; potassium, 5.9 mEq/L (hemolyzed); chloride, 103 mEq/L; bicarbonate, 21 mEq/L; BUN, 8.0 mmol/L (23 mg/dL); creatinine, 140 µmol/L (1.6 mg/dL); and glucose, 7.5 mmol/L (135 mg/dL). An arterial blood gas sample obtained while receiving supplemental O2 was a pH of 7.54, PCO2 of 12.8 mm Hg, and PO2 of 161 mm Hg. The patient died of ventricular fibrillation within 2 h of admission to the hospital. An autopsy was performed and a postmortem apparent serum digoxin level was 2.0 nmol/L (1.6 ng/mL). This case came to our attention via the medical examiner’s office (personal communication: M. Smiddy, MD; Manhattan, NY; February, 1985).

**Case 3**

A 23-year-old man ingested a topical aphrodisiac sold in a “smoke shop” as “Love Stone” on the evening before presentation. He began to vomit 30 min later, vomited for most of the night, and also had diarrhea. On presentation to the ED the following day, he was noted to be diaphoretic. His vital signs were as follows: BP, 98/60 mm Hg; heart rate, 76/min; respiratory rate, 28/min; and temperature, 33.9°C. His pupils were midrange and reactive. He was alert and not severely agitated but in respiratory distress, and his chest radiograph was consistent with noncardiogenic pulmonary edema. His initial laboratory values were as follows: sodium, 139 mEq/L; potassium, 4.3 mEq/L; chloride, 100 mEq/L; bicarbonate, 21 mEq/L; BUN, 5.0 mmol/L (14 mg/dL); creatinine, 90 µmol/L (1.0 mg/dL); and glucose, 5.8 mmol/L (104 mg/dL). An arterial blood gas sample on room air was as follows: pH, 7.44; PCO2, 23 mm Hg; and PO2, 41 mm Hg. The patient was intubated and ventilated. During intubation, his heart rate fell to 20/min. He was given 1 mg atropine and his heart rate increased to 150/min. An ECG obtained after atropine showed ventricular tachycardia with a right bundle branch block pattern possibly caused by an accelerated focus in the left fascicle. The patient went into ventricular fibrillation approximately 3 h after arrival to the ED. During resuscitation efforts, he became asystolic. At that time, we were in contact with the treating physicians and recommended administration of 400 mg of digoxin Fab fragments (10 vials of Digibind). Despite these efforts, the patient could not be resuscitated. The apparent serum digoxin level sent before cardiac arrest was 1.2 nmol/L (0.9 ng/mL).

**Case 4**

A 40-year-old man presented to an ED with bradycardia, vomiting, and diaphoresis. He said that he had taken cocaine, alcohol, and ingested a topical aphrodisiac called “Stone” on the previous evening. His heart rate varied from 50 to 60 beats/min and he was hypotensive, cold, and clammy. He had middrainage reductive pupils and normal bowel sounds. He was alert and oriented. The initial ECG showed slow atrial fibrillation. (Fig 2, top). He was given 1 mg of atropine and his heart rate increased to 110/min. He complained of chest discomfort and was given sublingual nitroglycerin. Shortly after this, he developed pulseless ventricular tachycardia. He was defibrillated but went into asystole and could not be resuscitated. He died 30 min after entering the ED. Presentation laboratory work was remarkable for hyperkalemia (7.3 mEq/L hemolyzed) and a positive apparent digoxin level of 4.0 nmol/L (3.08 ng/mL). The New York City Poison Control Center was notified after the patient had died.

**Case 5**

This patient was a 17-year-old man who ingested a “black cube” sold as a topical aphrodisiac on the evening before presentation. Shortly after this, he began to vomit and continued to vomit all night. When he presented to the hospital the next evening, he was still vomiting and was in sinus bradycardia at 48/min. His hospital admission electrolyte values were as follows: sodium, 136 mEq/L; potassium, 4.1 mEq/L; chloride, 102 mEq/L; bicarbonate, 23...
mEq/L; BUN, 4.6 mmol/L (13 mg/dL); and creatinine, 130 μmol/L (1.5 mg/dL). The apparent serum digoxin level was 5.0 nmol/L (3.9 ng/mL). Thirty-six hours after ingestion and 12 h after presentation to hospital, the patient had persistent vomiting and remained bradycardic. At that time, he was treated empirically with 10 vials of digoxin Fab fragments (Digibind) on our advice. Approximately 1 h later, his vomiting resolved and his heart rate increased to a maximum of 70/min and then decreased to the 60s where it remained. This patient had an uneventful recovery. Apparent serum digoxin levels measured by an assay (Abbott TDx; Abbott Laboratories; Abbott Park, Ill) (with a manual protein precipitation step) were 4.0 nmol/L (3.1 ng/mL) at 6 h after Digibind treatment and fell to 1.2 nmol/L (0.9 ng/mL) by 30 h after Digibind.

CASE 6

The patient was a previously healthy 34-year-old man who ingested a topical aphrodisiac sold as “Rock Hard” in a suicide attempt. Initially, his only symptoms were perioral and tongue numbness. Starting about 3 h after ingestion, he felt nauseated and began to vomit every 5 min. He also experienced a sensation of numbness in his chest. Five hours after the ingestion, the patient was brought to an ED. His hospital admission vital signs were as follows: BP, 130/76 mm Hg; heart rate, 62/min; respiratory rate, 20/min; and temperature, 36.7°C. The patient was vomiting and in moderate distress but findings from his physical examination were unremarkable. His electrolytes were as follows: sodium, 132 mEq/L; potassium, 4.7 mEq/L; chloride, 96 mEq/L; bicarbonate, 25 mEq/L; BUN, 2.8 mmol/L (8 mg/dL); creatinine, 110 μmol/L (1.3 mg/dL); and glucose, 13.6 mmol/L (245 mg/dL). During the first hour in the ED, his pulse slowed to the 50s and his ECG showed PR prolongation (360 to 440 ms) with occasional dropped beats (Fig 2, center). Six hours after the ingestion, blood was sent for a digoxin level and the patient was empirically given 10 vials of digoxin Fab fragments (Digibind) by IV push. The patient’s condition appeared to improve immediately following this therapy but he soon vomited and became bradycardic again with dropped beats seen on the rhythm strip. Based on this, the treating physician pushed a second 10 vials of Digibind less than 1 h after the first. Shortly after this, the patient stopped vomiting and remained in normal sinus rhythm. An ECG taken 45 min after the second dose of Digibind showed normal sinus rhythm with a rate of 84/min and a PR interval of 228 ms. Twelve hours after ingestion (5 h after Digibind), the patient remained in normal sinus rhythm and his PR interval was 200 ms (Fig 2, bottom). The patient was given activated charcoal and observed for 2 days in a monitored setting but remained well with no further vomiting or bradycardia. Serum obtained immediately before and 2 h after administration of digoxin Fab fragments was analyzed by us with a digoxin immunassay (Cedia; BM-Concord; Concord, Calif). The apparent digoxin level before treatment was 2.3 nmol/L (1.8 ng/mL). When “free digoxin” was measured by equilibrium dialysis, the apparent pretreatment level after a 1 to 1 dilution was 1.7 nmol/L (1.3 ng/mL) and the posttreatment level was 1.3 nmol/L (1.0 ng/mL).

MATERIALS AND METHODS

Analysis of Product

After the death of the first patient, a specimen of “Rock Hard” provided by the patient’s family was received. This specimen was a hard, dark brown, irregularly shaped but roughly square piece of material measuring about 1 x 1 x 0.5 cm (Fig 3). When dissolved, this substance measured strongly positive for digoxin by immunassay. Following the third case, samples of the aphrodisiac were obtained from the patient’s wife, from the “smoke shop” where the patient

**Figure 2. Rhythm strips (all from lead II). Top: rhythm strip from patient 4 showing atrial fibrillation at a rate of 50. Center: pretreatment rhythm from patient 6. There is Mobitz one atrioventricular block with a heart rate of 55. Bottom: Rhythm from patient 6 following digoxin Fab fragments (20 vials of Digibind®). The heart rate is 70, the PR interval has narrowed to 200 ms, and all beats are conducted.**
had purchased his, and from other sources in New York City. All samples had identical solvent front ratio (Rf) values on silica gel plate and identical staining with vanillin in phosphoric acid. A sample of the aphrodisiac used by the fifth patient had similar physical characteristics and was identical by TLC analysis to other samples of “Love Stone.” GC/MS analysis of these samples at the Food and Drug Administration (FDA) northeastern laboratories positively identified bufotenine (5-hydroxy-N, N-dimethyltryptamine), a hallucinogen found in a South American plant (Piptadenia peregrina) and in toad venom. Several of the cardioactive steroids found in toad venom are also potent local anesthetics.14 If the topical aphrodisiac were made from toad venom, these anesthetics might cause the desired “aphrodisiac” effect of delaying ejaculation by decreasing penile sensation. Samples of Chan Su (dried toad venom) were obtained from an importing company in New York City’s China Town. These samples had identical physical characteristics as “Love Stone.” TLC on silica gel plate using multiple solvent systems showed that “Love Stone” and Chan Su were identical and that both contained bufaline, cinobufagin, and cinobufotalin, three cardioactive steroids found in toad venom (Fig 4).

**DISCUSSION**

We communicated our findings to the FDA and they analyzed samples of Chan Su by GC/MS. They found that Chan Su and “Love Stone” were identical by GC/MS and that both contained bufotenine, and other compounds contained in toad venom, including cholesterol and the cardioactive steroids bufalin, cinobufagin, and resibufogenin (personal communication, T. Barry; FDA, Northeastern Laboratories; March, 1995).

Following these findings, the FDA banned the sale of Chan Su and of “Love Stone” and these products are no longer legally available in the United States. Further investigations by the FDA traced the source of the topical aphrodisiac to a Hong Kong company that is no longer exporting this product to the United States.15

These investigations established that the topical aphrodisiac known as “Rock Hard” or “Love Stone” is made of dried toad venom. Toad venom contains several potentially toxic compounds, including bufotenine, epinephrine, and cardioactive steroids of the bufadienolide class. Experiments involving the IV administration of bufotenine to humans show that toxic reaction from this compound is mild and differs significantly from that seen in our patients.16 Orally ingested epinephrine would also not be expected to cause the clinical findings seen in our patients. Each of our patients had vomiting and dysrhythmias, and several were hyperkalemic. Such a presentation suggests cardioactive steroid toxicity and implies that the bufadienolides are the cause of this product’s toxicity. Seizures, as seen in patient 2, are consistent with cardioactive steroid poisoning and have occurred after poisoning with toad venom,5 oleander,17 and rarely with digoxin.18

A positive digoxin level, as seen in our patients, supports the diagnosis of cardioactive steroid poison-
TLC on silica gel G plate of the ethanol extracts of Love-Stone (1 and 7) and Chan Su (2 and 6) with bufalin (3), cinobufotalin (4), and cinobufagin (5). Solvent systems: (chloroform: methanol: water by volume): (65:5:5), (65:10:10), (65:15:10), and (65:20:10) in successive order. Spray reagent: 1% vanillin in 50% phosphoric acid. Similar results were obtained using each of these four solvent systems individually.

The magnitude of the apparent digoxin level does not reflect the clinical status of the patient because there is no correlation between the toxicity of a cardioactive steroid and the degree of its cross-reactivity on digoxin immunoassays. Furthermore, the cross-reactivity of a given compound will vary from one immunoassay to another, resulting in different apparent digoxin levels. Certain patients may also have endogenous digoxin-like immunoreactive substances (EDLIS). These endogenous steroids cross-react with digoxin immunoassays to give positive apparent digoxin levels. Persons known to have EDLIS include neonates, pregnant patients, and those with renal failure, liver failure, or congestive heart failure. None of our patients had any of these conditions prior to ingesting the aphrodisiac, so EDLIS is unlikely to be the explanation for their positive digoxin levels.

Digoxin-specific Fab fragments are currently considered the treatment of choice for severe digoxin toxicity in adults and in children. Although these polyclonal antibody fragments are most suitable for the treatment of digoxin and digitoxin toxicity, they have been used successfully to treat poisoning from other cardiac glycosides, including lanatoside A, strophanthidin, oleander, and the mixture of cardiac glycosides found in foxglove extract (which in addition to digoxin also contains purpurea A, purpurea B, and gitoxin). Experimental evidence suggests that digoxin Fab fragments would also be effective treatment for poisoning by proscillaridin and scilliroside, the cardiac glycosides contained in red squill. This is important because, although plant-derived, these compounds are bufadienolides like the cardioactive steroids in toad venom. Russian investigators have re-
cently shown that antidigoxin antibodies not only bind to toad venom but that they block the ability of toad venom to inhibit the sodium-potassium adenosine triphosphatase and to increase the contractility of isolated rat atria.\(^{38}\)

The clinical courses of patients 5 and 6 also suggest that digoxin Fab fragments may be effective treatment for poisoning by this product. Patient 5 had resolution of vomiting and improvement in his heart rate after Digibind administration. Patient 6 also had improvement of symptoms and resolution of ECG abnormalities following Digibind. Furthermore, these patients are the only survivors in our series. It could be argued digoxin Fab fragments were not beneficial in patient 5 because his early course was less severe than those of the other patients. Patient 6, however, presented early after ingestion and had evidence of progressively worsening toxicity so that his response was impressive. The failure of patient 3 to improve after the administration of Digibind is not surprising because he was already asystolic when treated. In a series of patients treated with digoxin Fab fragments for severe digoxin toxicity, only half of those in cardiac arrest survived to hospital discharge and a third of the 15 patients who failed to respond to Fab therapy did so because they were already moribund.\(^{30}\)

Digoxin Fab fragments interfere with digoxin immunoassays so that posttreatment digoxin levels may be very low, very high, or intermediate and do not necessarily approximate free digoxin or total digoxin.\(^{30,40}\) The protein precipitation step in the assay (Abbott TDx) used in patient 5 is believed to remove digoxin Fab fragments without precipitating digoxin and will theoretically give a value for total digoxin.\(^{40}\) It is expected that digoxin levels measured by this assay will increase following digoxin Fab administration. This assumption is based on the fact that digoxin has a much larger volume of distribution than Fab fragments and that the protein precipitation step does not remove digoxin. Neither of these assumptions is known to be true for the steroids in toad venom and the failure of digoxin values to increase after Fab treatment in patient 5 is difficult to interpret. We avoided this problem in patient 6 by measuring apparent free digoxin levels after equilibrium dialysis of his serum against an equal volume of normal saline solution using a dialysis membrane with a 5,000-dalton cutoff. This separates Fab fragments from smaller molecules such as the bufadienolides and also results in a 1 to 1 dilution of the final sample. The bufadienolides appear to have higher cross-reactivity with digoxin immunoassays when present at low concentrations than when present at high concentrations. This phenomenon, which has been described for digoxin metabolites,\(^{41}\) results in a less than linear decrease in apparent digoxin concentration, with decreasing concentrations of the bufadienolides. Thus, the finding in patient 6 that apparent free digoxin levels fell from 1.7 nmol/L (1.3 ng/mL) before Digibind to 1.3 nmol/L (1.0 ng/mL) afterwards may represent a consequential decrease in free bufadienolide concentration and is consistent with substantial binding of the bufadienolides in “Love Stone” to digoxin Fab fragments.

To our knowledge, our report represents the first use of digoxin Fab fragments in the treatment of patients poisoned by toad venom. Previous recommendations for toad venom poisoning have focused on gastric decontamination and supportive care.\(^{4,7}\) Although propranolol has been shown to decrease mortality in dogs poisoned with toad venom,\(^{42}\) we do not recommend it because of the high incidence of bradydysrhythmias seen in patients poisoned by cardioactive steroids. Patients who have ingested cardioactive steroids all require cardiac monitoring and supportive care. Gastric emptying is usually not required because most patients will present with copious vomiting. Activated charcoal should be given after vomiting is controlled. The decision on when to administer digoxin Fab fragments to patients with suspected cardioactive steroid toxicity is difficult. As discussed above, the apparent digoxin level does not correlate with toxicity. Hyperkalemia is predictive of a poor prognosis in acute digoxin overdose\(^{43}\) but has not been studied in other cardioactive steroid poisoning and was not present in the third patient in our series who died with a potassium level of 4.3 mEq/L. Cardiac dysrhythmias were present in all of our patients and are the usual cause of death in patients with fatal cardioactive steroid poisoning. The prognostic importance of specific dysrhythmias has been defined in digoxin toxicity,\(^{44,45}\) but not for other cardioactive steroids. Given the lack of accurate prognostic markers, the decision to administer digoxin-specific antibody fragments must be made on clinical grounds. We recommend empiric administration of large doses of digoxin Fab fragments (10 vials) to all patients with suspected cardioactive steroid overdose who have hyperkalemia or any abnormalities in cardiac rhythm. This is justified because of the high fatality rate which occurs in these patients and the apparent efficacy of digoxin Fab fragments. Repeat doses of antibody fragments should be given based on the patient’s clinical response.

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