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Selected Topics: Toxicology

CARDIAC TOXICITY FROM INTENTIONAL INGESTION OF PONG-PONG SEEDS (*CERBERA ODOLLAM*)

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Abstract—Background: A variety of plants contain cardiac glycosides. This has resulted in many of them being used to commit suicide. In southeast Asia, *Cerbera odollam* (pong-pong or suicide tree) is frequently used for suicidal ingestion. Seeds, or kernels, of this plant can cause hyperkalemia, heart block, and death due to the effects of its cardiac glycosides. **Case Report:** We describe six cases of pong-pong seed ingestion reported to US poison centers. The most common symptoms were vomiting and bradycardia. Three patients survived and three died. All patients who died had heart block, serum digoxin levels > 1.0 ng/mL, and were treated with anti-digoxin immune FAB. Anti-digoxin immune FAB may be ineffective in a large pong-pong seed ingestion. Patients ingesting pong-pong seeds who develop a potassium level > 8.0 meq/L or have a digoxin level > 1.0 ng/mL may be at a higher risk for death. **Why Should an Emergency Physician Be Aware of This?:** The apparent ease of acquiring *C. odollam* seeds on the Internet makes knowledge of it important, as it can be used as a means to commit suicide. The apparent failure of digoxin immune FAB to treat toxicity from pong-pong is important, as other lifesaving techniques, such as extracorporeal membrane oxygenation, might be needed in severely toxic patients. © 2018 Elsevier Inc. All rights reserved.

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INTRODUCTION

Indigenous to certain areas of India and Southeast Asia, *Cerbera odollam* is a tree belonging to the same family (apocynaceae) as oleander (1–3). Ingestion of the seeds from this tree is a common means to commit suicide in Asia, where it is sometimes called the pong-pong tree or the suicide tree (1,3–5). The fruit kernels of seeds (Figure 1) contain a number of cardiac glycosides including cerberin, cerberoside, and neriifolin (2,3,6). In animal models, these glycosides inhibit the sodium–potassium adenosine triphosphate exchanger in myocardial cells (2,5). Like other cardiac glycosides, ingestion of pong-pong seeds can cause vomiting, various degrees of bradycardia, heart block, and hyperkalemia (1,3–5,7–9). Ingestions have resulted in a significant number of intentional deaths in countries where the plant is found (1,3,4,7). Poisonings outside this tree's natural habitat are, however, rare. The one prior pong-pong case reported in the United States involved ingestion of seeds from an online retailer. The patient developed hyperkalemia, was treated with anti-digoxin immune FAB, and survived (8). We present six cases, and three deaths, of

Two of the cases in this series were presented at the 2016 North American Congress of Clinical Toxicology Meeting in Boston, Massachusetts.

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Figure 1. Pong-pong seeds were obtained through the Internet. The image shows the fibrous shell of a single pong-pong seed with the enclosed kernel of one seed. A US quarter is shown for size comparison.

self-poisoning by ingestion of pong-pong tree seeds reported to US Poison Centers. As pong-pong seeds are readily available on the Internet, these cases have important public health implications.

CASE REPORTS

Death 1

A 22-year-old, previously healthy, transgender female ingested one pong-pong tree seed in a suicide attempt. Seven hours after the ingestion, she was taken to the emergency department (ED) with symptoms of vomiting and diarrhea. On arrival to the ED, she was awake and

alert and complaining of chest pain and palpitations. Her first reported vital signs included a heart rate (HR) of 69 beats/min, blood pressure (BP) of 42/32 mm Hg, respiratory rate (RR) of 19 breaths/min, SpO₂ 100% on room air, and a temperature of 97.1°F. Her initial electrocardiogram (ECG) showed a ventricular rate of 51 beats/min, ectopic atrial tachycardia with 2:1 conduction block, a QRS interval of 90 ms, a QTc interval of 278 ms, and inferior and anterior T-wave changes (Figure 2). Her initial laboratory results were remarkable for a potassium of 5.2 meq/L, carbon dioxide of 20 meq/L, creatinine of 1.0 mg/dL, calcium 10.6 mg/dL, troponin of < 0.05 ng/mL, and serum digoxin level of 1.3 ng/mL. Other toxicology testing (acetaminophen, salicylate, and ethanol levels) was negative.

The initial therapy included 200 mg (five vials) of digoxin immune FAB with an increase in HR to 90 beats/min. An additional 200 mg (five vials) of digoxin immune FAB was administered for “dropped beats.” Approximately 1.5 h after ED arrival, and 8.5 h post ingestion, she developed bradycardia with HR in the 30s. She became unresponsive and pulseless. Therapy included dextrose 50% and insulin bolus (10 U) for presumed hyperkalemia, dopamine, and norepinephrine infusions. Standard advanced cardiac life support (ACLS) measures, including cardiopulmonary resuscitation (CPR), atropine, and sodium bicarbonate, were administered. She was given an additional 400 mg (10 vials) of digoxin immune FAB and a 100-mL bolus of 20% lipid emulsion. Despite aggressive resuscitative efforts, including CPR for > 2 h, the patient died.

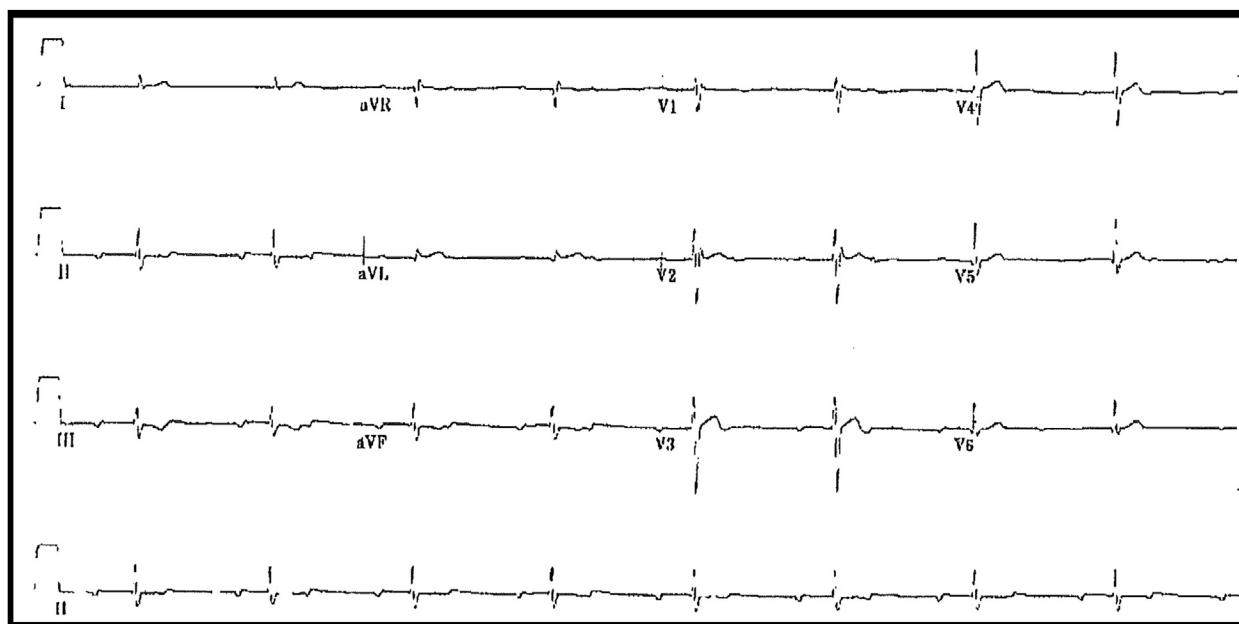


Figure 2. The presenting electrocardiogram (ECG) from a 22-year-old patient who ingested a single pong-pong seed. The ECG shows a heart rate of 51 beats/min with a second-degree atrioventricular (AV) block with 2:1 AV conduction. It also shows inferior and anterior T-wave abnormalities.

Death 2

A 33-year-old female with depression presented to a hospital with altered mental status and vomiting. She admitted to ingesting an herbal supplement for weight loss purchased on the Internet. Although it is not clear if the intent was self-harm or weight loss, the patient's family reported that she had never expressed suicidal ideation. According to her family, the herbal agent ingested was pong-pong seeds. On presentation to the ED, she was verbal, diaphoretic, pale, and experiencing nausea and vomiting. She soon became nonverbal, agitated, and required restraints. Initial vital signs included HR 30–40 beats/min and systolic BP 80–90 mm Hg. An ECG showed no p waves and a wide-complex rhythm. The patient was not taking digoxin, but a plasma immunoassay for digoxin returned a concentration of 3.1 ng/mL. Initial potassium was 8.9 meq/L. The patient was resuscitated with i.v. fluids and pressors. She was intubated and received a total of 10 vials (400 mg) of digoxin immune FAB, but she expired < 3 h after presentation.

On autopsy, performed by the county coroner, the gross physical examination was unremarkable and post-mortem toxicology screening for drugs of abuse was negative. Analysis using liquid chromatography/mass spectrometry (LC/MS) of hepatic tissue and gastric fluid demonstrated the presence of the cardiac glycosides cerberin and neriifolin.

Death 3

A 30-year-old male with history significant only for schizophrenia was brought to the ED 12 h after intentional ingestion of an unknown number of pong-pong tree seeds. Home medications included aripiprazole, celecoxib, atomoxetine, fluphenazine, and trazadone. His family indicated he had purchased the seeds, as well as poison hemlock seeds, from eBay. He was given 1 mg atropine by emergency medical services for bradycardia. On ED arrival, he complained of blurry vision, headache, dizziness, and chest heaviness and vomiting. Initial vital signs showed HR of 60 beats/min and irregular, BP 123/77 mm Hg, RR 27 breaths/min, SpO₂ 98% on non-rebreather, and temperature of 98.0°F. He was alert and cooperative. Initial ECG showed atrial fibrillation (AF) with ventricular response of 60 beats/min, QRS interval of 108 ms, QTc interval of 350 ms, and nonspecific ST-T wave changes. Initial laboratory results were remarkable for potassium of 10.1 mmol/L, carbon dioxide of 24 mmol/L, creatinine of 2.8 mg/dL, calcium of 10.9 mg/dL, troponin of 0.178 ng/mL, B-type natriuretic peptide of 1710 pg/mL, and serum digoxin of 1.6 ng/mL. Toxicology testing showed negative acetaminophen, salicylate, and ethanol

levels. A urine drug screen was positive for benzodiazepines, methadone, and tricyclic antidepressants. The tricyclic antidepressants immunoassay screen was positive, presumably from the patient's prescribed fluphenazine, as it can cause a positive screen (10).

ED therapy included atropine, calcium gluconate, calcium chloride, sodium bicarbonate, dextrose 25%, regular insulin, and lactated Ringer's bolus, followed by a continuous infusion. In addition, he was given 10 vials (400 mg) of digoxin immune FAB. At this time, he was airlifted to a tertiary referral center.

On arrival to the intensive care unit (ICU), he was diaphoretic but alert with HR of 74 beats/min and BP of 135/70 mm Hg. ECG showed a first-degree block with AF with ventricular response of 92 beats/min and normal QRS and QTc intervals. Repeat laboratory tests were remarkable only for a potassium level of 7.4 mmol/L and creatinine level of 1.98 mg/dL. ICU therapy included continuous bicarbonate infusion and 3 h of hemodialysis for hyperkalemia. Approximately 33 h post ingestion, he became markedly bradycardic with cardiac pauses and subsequent hypotension. Therapy included orotracheal intubation, transcutaneous pacing (with initial capture), isoproterenol infusion, and three more vials of digoxin immune FAB (120 mg). He progressed to asystole and standard ACLS measures, including CPR, epinephrine, and sodium bicarbonate were initiated. Despite ongoing resuscitative efforts for 1 h, he expired. Repeat serum, but not free digoxin level, obtained at the onset of cardiac arrest was 0.7 ng/mL.

Additional Cases

After two deaths involving *C. odollam* (including the case above) were called to the Indiana Poison Center, we solicited other cases through the American Association of Poison Control Centers medical directors listerv. This listerv contains the e-mail addresses of all the Poison Control Center medical directors. Six cases in total were identified from three poison centers (Indiana 1, California 2, and Tennessee 3). To facilitate the case series, a data collection form was created using REDCap (11). The data form solicited demographic, clinical, and outcome information, as outlined in Tables 1 and 2.

Six cases between March 2015 and February 2017 were identified (Table 1). Three from Indiana, two from California, and one from Tennessee. Data sources included local poison control center database (Toxicall and Visual DotLab Enterprise), hospital charts (two cases), and one local news report. The cases involved three men aged 21–46 years and three women aged 22–33 years. One patient consumed two seeds, 3 patients consumed one seed each, and 2 patients consumed an unknown number of seeds. In all of the deaths, the seeds

were obtained through the Internet. In two cases, they were listed as being purchased for suicide and the other for weight loss. While the suicidal nature of these seeds is readily available on the Internet, there is no information we could find advocating for the use of pong-pong seeds for weight loss. How the seeds were obtained by the survivors was not determined. The time to symptom onset ranged from 3 to 15 h. In all cases, patients initially developed vomiting. In all but one case, patients developed bradycardia (pulse < 40 beats/min). Treatment for patients varied. All patients who died were treated with atropine and vasopressors; no survivors required these. Calcium was used in 1 patient who survived and 1 who died. There was no apparent benefit to the use of digoxin immune FAB in severe overdose, as all patients who died received 10 or more vials (range 13–20 vials). Two survivors were given digoxin immune FAB, including the 1 patient who had hyperkalemia (K^+ 6.5 meq/L) and a reported digoxin level (0.5 ng/mL). In 1 patient, post-mortem testing was done, which detected, via LC/MS, the cardiac glycosides cerberin and neriifolin in hepatic tissue and gastric fluid. Table 2 compares HR, potassium, digoxin level, ECG abnormalities, and vials of digoxin immune FAB used in those who survived and those who died.

DISCUSSION

Ingestion of pong-pong (*C. odollam*) seeds, which are commonly sold online as ornamental pieces for home decoration, can cause fatal cardiac glycoside toxicity. This case series suggests that bedside examination, ECG, and serum digoxin levels can help determine prognostic risk in ingestions. The patients in our series presented with symptoms similar to those reported previously after ingestion of pong-pong seeds (1,3,4,8,9). As in other cases, ingestion of one kernel can lead to death (1).

As with previously reported pong-pong ingestions, patients developed vomiting and bradycardia. These do not appear to have prognostic value, however, as these were present in both survivors and deaths. Two previous case series of pong-pong ingestions have suggested that higher potassium levels correlate with mortality (1,4,8). This is well established for digitalis poisoning (12). However,

the rarity of poisoning from plants containing cerberin, cereberoside, and neriifolin has precluded establishing a defined serum potassium concentration that predicts mortality. In several cases series, there is significant overlap of serum potassium concentrations between survivors and decedents (4). In their series, Gaillard et al. reported mortality in 8 of 12 patients with a potassium of > 8 meq/L (1). In our series, we similarly noted this, with two of three deaths having peak serum potassium levels of > 8 meq/L. In addition, the only other reported case in the United States involved a woman who survived and had a peak potassium level < 8 meq/L (7.5 meq/L) (8). However, as our series and others demonstrate, death can occur in the absence of severe hyperkalemia. Heart block on ECG is also commonly reported after pong-pong ingestion (3). In our case series, no surviving patient developed heart block. Other reports, however, have described patients who developed heart block and survived (3,4,8,9).

A unique aspect of our case series is that all of the patients who died had a digoxin level > 1 ng/mL (Table 2). In the two survivors for whom a digoxin level was reported, one was 0.5 ng/mL, and one was only stated to be low. In the additional surviving patient, a digoxin level was not measured, but the only reported symptom in this patient was vomiting. In the only other reported pong-pong case in which a digoxin level has been reported, the patient survived, and the digoxin level was < 0.3 ng/mL (8). Our cases, along with the previous literature, suggest that a digoxin level > 1.0 ng/mL may be helpful for risk stratification. This finding is limited, however, by small sample size and variability in timing and assay techniques between individual cases. While our cases suggest that cardiac glycosides in *C. odollam* cross react with the digoxin immunoassay, which one of the glycosides (neriifolin, cerberin, or cereberoside) is not known. This is an important point, as different plant glycosides react differently to the digoxin assay (13). Therefore, depending on what plant was ingested, a negative digoxin assay cannot be assumed to confirm no exposure.

The treatment approach for patients in our case series was variable. Most patients received conventional treatments for bradycardia and hyperkalemia. One of the most important findings in our cases was the apparent

Table 1. Patient Demographic Characteristics

Patient	Age	Sex	No. of Seeds	Time to Symptoms, h	Vomiting	Bradycardia (HR < 40 beats/min)	Hyperkalemia (K > 5.0 meq/L)	Outcome
D1	22	Female	1	7	Yes	Yes	Yes	Died
D2	33	Female	Unknown	3	Yes	Yes	Yes	Died
D3	30	Male	Unknown	12	Yes	Yes	Yes	Died
S1	32	Female	2	6	Yes	Yes	No	Survived
S2	21	Male	1	3	Yes	No	No	Survived
S3	46	Male	1	15	Yes	Yes	Yes	Survived

D = death; HR = heart rate; K = potassium; S = survived.

Table 2. Reported Clinical Effects and Treatment By Outcome

Patient	Lowest HR, beats/min	Highest K ⁺ , meq/L	Digoxin Level, ng/mL	Vials Digi FAB	ECG	Outcome
D1	30s	5.2	1.3	20	Second- and first-degree block	Died
D2	30s	8.9	3.1	10	Third-degree block, V-tach	Died
D3	37	10.1	1.6	13	First-degree block, Afib	Died
S1	40	<5.0	"Low level"	2	Afib	Survived
S2	NR	NR	NR	0	None	Survived
S3	49	6.5	0.5	5	Digoxin like ST changes	Survived

Afib = atrial fibrillation; D = death; ECG = electrocardiogram; HR = heart rate; NR = not reported; S = survived; V-tach = ventricular tachycardia.

lack of benefit from anti-digoxin immune FAB in severe overdose. In all three of our deaths, patients received 10 or more vials of anti-digoxin immune FAB. In the one previous fatal pong-pong case from the United States, the patient received 20 vials of anti-digoxin immune FAB (8). Whether or not larger doses would have helped our patients is not known. While we believe it is reasonable to try digoxin immune FAB, our case series suggests that, in severe cases, it might lack efficacy. One controversy in the treatment of digoxin poisoning is whether to use calcium to treat hyperkalemia (14). This is based on the theoretical concern for increasing cardiac intracellular calcium concentrations, leading to systolic arrest ("stone heart" syndrome). This has been demonstrated in animal models (frogs, dogs, and cats) of pong-pong toxicity (2). In our case series, 2 patients received calcium for hyperkalemia. One of these patients died. The timing of calcium administration in these cases is not known.

Two more recent advances in the treatment of severe cardiac toxicity are the use of lipid emulsion and extracorporeal membrane oxygenation (ECMO) (15,16). Using an online calculator (<http://www.vccclab.org/lab/alogps/start.html>) cerberin, the main glycoside in pong-pong, has an estimated lipid partition coefficient (log P) of 3.01. A common feature of toxins thought to benefit from lipid emulsion therapy is a log P of > 2.0 (17). The sole patient from our series who received lipid emulsion died. While ECMO would offer a theoretical benefit for a severe pong-pong ingestion, it was not used in any of our cases.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Emergency physicians should be aware of the availability and toxicity of the seed kernels from the pong-pong tree (*C. Odollam*). It has extensive distribution in Asia and is now available on the Internet for decoration, weight loss, and self-harm purposes. Ingestion of as little as one kernel can cause severe toxicity with vomiting, hyperkalemia, bradycardia, heart block, and death. Treatment with anti-digoxin immune FAB may be ineffective. Patients who develop heart block, have a potassium level of > 8.0

meq/L, or have a measured digoxin level of > 1.0 ng/mL may be at higher risk for mortality.

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