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Food-induced Hypotension and Bradycardia: A Case Report

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Abstract

A 64-year-old woman with no past medical history presented with tongue numbness, perioral tingling, palmar pruritus, and multiple episodes of emesis and diarrhea beginning 15 hours prior to arrival. Blood pressure was 88/30 mm Hg; EKG showed sinus bradycardia (40 bpm). Normal saline and atropine 0.5 mg were administered intravenously; heart rate improved to 69 bpm and blood pressure to 104/38 mm Hg. When her heart rate and blood pressure again declined, dopamine (10 mcg/kg/min) was started. Vital signs improved to blood pressure 129/44 mmHg, heart rate 57 bpm. Family revealed that, 24 hours prior to presentation, she consumed a Brazilian candlenut tree seed laxative supplement. She was admitted on a dopamine drip (10 mcg/kg/min). Dopamine was weaned as her vital signs self-normalized. She was discharged on hospital day 8. Brazilian candlenut toxicity is uncommon and can easily be misdiagnosed and improperly treated. Other items on the differential diagnosis for bradycardia, hypotension, and gastrointestinal symptoms are more common; therefore, candlenut toxicity would be easy to miss, particularly among patients concurrently taking other agents with a similar toxicity profile (eg. digoxin). Treatment is symptomatic, with inotropic and vasopressor support as needed (eg. intravenous hydration, antiemetic medications, electrolyte replacement, and dopamine drip).

Keywords: Brazilian candlenut; Bradycardia; Hypotension; Toxicity; Laxative

Abbreviations: ED: Emergency Department; EKG: Electrocardiogram; WBC: White Blood Cells; Na: Sodium; K: Potassium; CO_2: Carbon Dioxide; BUN: Blood Urea Nitrogen; Cr: Chromium; Ca: Calcium; HCO_3: Bicarbonate; pCO_2: Pressure of Carbon Dioxide; pH: Potential Hydrogen; TSH: Thyroid Stimulating Hormone; CCU: Cardiac Care Unit; MICU: Medical Intensive Care Unit; MAP: Mean Arterial Pressure; HPF: High Power Field; ICU: Intensive Care Unit

Introduction

Digestion is a complicated job that requires precise coordination between the digestive, nervous, and circulatory systems. It involves rerouting extra blood to the stomach and small intestine. To compensate for this diversion, the heart beats faster and harder while blood vessels far from the digestive system narrow. These two actions maintain blood pressure and blood flow to the brain, legs, and everywhere in between. In some people, the heart and blood vessels don't respond as they should. That causes blood pressure to decrease everywhere but the digestive system. The sudden drop usually announces itself as dizziness or lightheadedness. In this report, we describe a case of a 64-year-old woman with no significant past medical history presented with food-induced Hypotension and Bradycardia.

Case Presentation

A 64-year-old woman with no significant past medical history presented to the Emergency Department (ED) with multiple episodes of emesis and diarrhea beginning 15 hours prior to arrival. The prior evening, the patient developed tongue numbness, perioral tingling, and palmar pruritus. Shortly after, she became nauseated and had multiple episodes of non-bloody, non-bilious emesis and non-bloody diarrhea. She did not improve with ondansetron given at an urgent care center and went to the ED for further evaluation. In the ED, the patient endorsed nausea, lightheadedness, and crampy abdominal pain. She denied wheezing, chest pain, shortness of breath, hives, known food or medication allergies, recent travel or illnesses, insect bites or bee stings, sick contacts, fever or chills, hematochezia, or hematuria.

Initial vital signs were: temperature 36.7°C, heart rate 59 bpm, blood pressure 88/30 mmHg, respiratory rate 16/minute, and room air oxygen saturation 94%. She was alert and oriented, but appeared pale and tired. Cardiac monitor revealed sinus bradycardia at 30-40 bpm. Pupils were 3 mm bilaterally, equally round and reactive; mucus membranes were dry. There was no wheezing, abdominal tenderness, guarding or rebound, hives, lacrimation, or salivation.

EKG showed sinus bradycardia (40 bpm) with flat and biphasic T waves, without PR prolongation; QTc was 306 (Figure 1). Labs revealed a serum WBC of 13,000/μL, Na 141 mmol/L, K 5.1 mmol/L, CO_2 27 mmol/L, BUN 25 mg/dL, Cr 1.42 mg/dL, Ca 9.5 mg/dL, phosphorous 2.8 mg/dL, lactate 1.5 mmol/L, pH of 7.32, pCO_2 63 mm Hg, HCO_3 26 mmol/L, and TSH 1.59 IU/mL. Urinalysis demonstrated 25 WBCs/hpf; urine culture did not grow organisms.

She was volume-resuscitated with normal saline (2 liter bolus, followed by 150 cc/hour in the ED). Ceftriaxone was started for possible sepsis of urinary tract origin. Atropine 0.5 mg intravenously was administered; her heart rate improved to 69 bpm and blood pressure to 104/38 mmHg. Benadryl 50 mg was administered for possible allergic reaction; epinephrine and steroids were not given. When the heart rate again decreased to 40-50 bpm, she was started on a dopamine infusion at 10 mcg/kg/min to maintain a MAP>65 mmHg

and heart rate>50 bpm. Her vital signs improved to a heart rate of 57 bpm and a blood pressure of 129/44 mmHg.

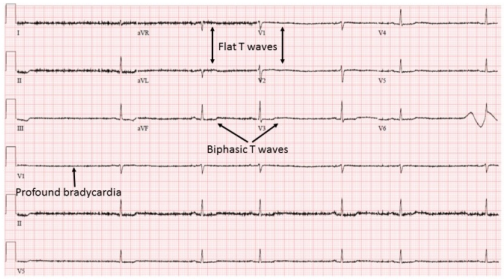

Figure 1: EKG showing profound bradycardia.

Deeper questioning of family revealed that, 24 hours prior to presentation, the patient had consumed one commercially-available laxative supplement. Through an extensive website search with her family, we ascertained the ingestion was Brazilian candlenut tree seed, identifying the exact product/bottle from which the nut she had consumed had come.

The Cardiac Care Unit (CCU), Medical Intensive Care Unit (MICU), and Toxicology services were consulted for further evaluation and care. She was admitted to the MICU on a dopamine drip (10 mcg/kg/min), with a target MAP>65 mmHg and heart rate>50 bpm. Normal saline drip was continued at 1.5 cc/kg/hour (75 cc/hour for this 49 kg patient). She was continued on dopamine infusion overnight and, when her blood pressure was 130/95 mmHg and heart rate 90 bpm, was transitioned to oral terbutaline 5 mg every 4 hours to provide (weak) beta-1 agonist activity. After the first terbutaline dose was administered, the intravenous dopamine was continued for 2 hours and then weaned off; dopamine had been utilized for a total of 39 hours, 45 minutes (1,191 mg). Off dopamine (and on terbutaline), her blood pressure and heart rate dropped overnight to 90/40 mmHg with HR 55 bpm. A second oral agent (albuterol 2 mg every 6 hours) with weak beta-1 agonist properties was added. The terbutaline and albuterol were continued together for one night (Day 2 into 3). Afterward, her blood pressure improved to 95-105/60-70 mmHg and heart rate from 60-75 bpm and was maintained in these ranges. On ICU day 3, she was stable and transferred out of the ICU. Terbutaline and albuterol were discontinued the following day, without adverse consequences. During her MICU course, her serum potassium decreased to 3.6 mmol/L from 5.1 mmol/L, and her serum phosphorous dropped to 1.9 mg/dL from 2.8 mg/dL, likely owing to loos through emesis and diarrheal stool; these were repleted with potassium phosphate 15 mmol IV once and potassium acid phosphate/sodium acid phosphate No 2 (1 tablet with meals for 2 days). Acetaminophen was ordered to relieve abdominal pain, but was never requested by the patient, and by day 2 of admission, her gastrointestinal symptoms had resolved. When blood and urine cultures did not grow organisms, and serum WBC normalized, ceftriaxone was discontinued. She was discharged home on hospital day 8.

Discussion

Candlenut seeds are from the flowering tree *Aleurites moluccanus* (Family Euphorbiaceae) (Figures 2-5) and have been traditionally used in cuisines around the world. Indonesian, Malaysian, Filipino, and Hawaiian cuisines use the fruit and/or other parts of the tree for cooking [1]. The seed of the candlenut tree, rather than its thin epicarp (exterior shell) or pericarp (interior wrapping, which is tightly-adherent to the seed), is the toxic component [2]. (Figure 6) There is limited literature regarding candlenut seed toxicity. It is also not clear the exact chemical constituent responsible for toxicity, although candlenut seeds contain phorbol esters [3]. Phorbol (Figure 7) is a plant compound belonging to the larger diterpene class. Diterpenes are naturally-occurring organic compounds found in a variety of plants, most notably the Euphorbiaceae and Thymelaeaceae families. Terpenes are natural pesticides against herbivores.

Figure 2: *Aleurites moluccanus* (candlenut) tree.

Figure 3: *Aleurites moluccanus* (candlenut) tree leaves and flowers close up.

Phorbol esters constitutively activate Protein Kinase C (PKC) into a form that irreversibly inserts into the cell membrane, and exert most of their effects on the cardiac and gastrointestinal systems [4]. Phorbol has potent negative inotropic effect on cardiac myocytes [5-7], reducing the number of beta-adrenoceptors and their affinity for beta-agonists [8]. They also decrease trans-sarcolemmal calcium influx, depressing cell contractility [5]. PKC activation triggers the Na^+/H^+ exchanger [9] and the phosphorylation and activation of calcium channels, both of which profoundly affect cardiac function [10]. In rats, Phorbol myristate acetate at a concentration of 10-9 mole rapidly

decreased cardiac function, reducing aortic flow rate 50% after 5 minutes of perfusion and eliminating it after 20 minutes [11]. Human patients can experience arrhythmias, heart block, and cardiac arrest [12,13].

Figure 4: *Aleurites moluccanus* (candlenut) tree seed close-up, in epicarp.

Figure 5: *Aleurites moluccanus* (candlenut) seed in pericarp (left) and completely unshelled (right).

Figure 6: *Aleurites moluccanus* (candlenut) pericarp and seed (toxic component).

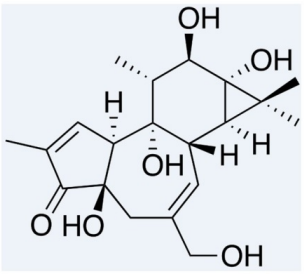

Figure 7: Phorbol molecular structure.

Phorbol esters also produce a potent inflammatory response; however, it is not clear whether its effect on PKC is responsible for candlenut seed's cathartic and mucosal irritant properties. Animal studies demonstrate the gastrointestinal toxicity of candlenut seed ingestion. Candlenut seed extract fed to goats and fish produced diarrhea, and dehydration, and reduced appetite and water intake [14-16]. In rats, the candlenut seed *Jatropha curcas* caused diarrhea and gastrointestinal inflammation; LD_{50} was 6 mL/kg [17]. Discomfort and nausea occur minutes after ingestion. These symptoms are followed by vomiting, crampy abdominal pain, and diarrhea, which may produce profound dehydration and electrolyte imbalance. Chronic ingestion may cause intestinal muscle atony. The patient's serum WBC of 13,000/μL and sterile urinalysis showing 25 WBCs/HPF may have been the manifestation of an aggressive inflammatory response [12,13].

Literature on human toxicity is limited to a few case reports. All toxicities occurred from using herbal-based products claiming to contain candlenut seeds. In Spain, a 33-year-old woman was hospitalized for vomiting, watery diarrhea, hypotension, and bradycardia (with 1st degree atrioventricular block) after ingesting a whole candlenut seed as a laxative for weight loss; she was managed with dopamine and discharged after 1 week [3]. In Argentina, at least 4 women were admitted to the ICU after ingesting the candlenut seed for weight loss [3].

The differential diagnosis of hypotension with bradycardia includes hypothyroidism, organophosphate poisoning, and Western or herbal medication overdoses which have digoxin, calcium channel blocker, or beta-blocker properties. Plants with such properties include foxglove, oleander, and squill [18]. This patient did not present with bronchorrhea, diaphoresis, abnormal urination, lacrimation, or salivation, all key features of organophosphate poisoning, nor was there high clinical suspicion of organophosphate exposure. TSH was normal; digoxin was not detected. The patient had no history of beta-blocker or calcium channel blocker use, and lacked other features of such overdoses (eg, hypoglycemia or altered mental status) [19-22].

Although no blood or gastrointestinal sampling was performed in this case to definitively demonstrate candlenut seed ingestion or quantity, several characteristics provide supportive evidence of a cause and effect relationship between the patient's self-reported ingestion and the diagnosis of candlenut seed toxicity. Photographic identification: we worked closely with the family to identify the exact product the patient consumed shortly before developing symptoms.

Temporality of association: the patient ingested candlenut seed, and, shortly thereafter, developed symptoms in multiple organs consistent with such exposure (cardiac, gastrointestinal, dry mucous membranes). Consistency with prior reports of animal and human toxicity: this patient manifested cardiac and gastrointestinal symptoms similar to those reported in prior animal studies and reports of human consumption. Alternative explanations were unlikely: other conditions on the differential diagnoses were explored, and excluded based on history, physical examination, or laboratory studies. These include hypothyroidism, digoxin toxicity, organophosphate poisoning, and other possible over the counter or herbal ingestions. Plausibility: the combination of positive identification of the exact product she consumed, clinical presentation (temporality of association, symptoms), consistency with mechanism of phorbol toxicity, and absence of alternative explanations made candlenut seed ingestion the most likely explanation of her presentation. There are no human reference/quantitative data to which a serum candlenut seed toxin (eg. phorbol) level could have been compared had one been obtained? Assessment of serum or gastric candlenut seed may have confirmed candlenut seed exposure, but not proven toxicity.

Conclusion

Case reports in humans have identified severe toxicity with as little as one candlenut seed ingestion. Given the family-confirmed ingestion and identification of a culprit toxin, timeframe, symptoms, physical examination, and lack of evidence for competing explanations, candlenut seed ingestion was the most likely explanation for her clinical presentation. Treatment of candlenut toxicity is symptomatic, with inotropic and vasopressor support as needed (eg. intravenous hydration, antiemetic medications, electrolyte replacement, and dopamine drip). In this case, dopamine 10 mcg/kg/min was chosen because, at that dose, it has both salutory chronotropic (beta-1) and inotropic (alpha) effects. To facilitate transition to lower level of care (eg. telemetry, rather than MICU), two agents with weak beta-1 agonist activity (terbutaline and albuterol) were added and the dopamine titrated off. In cases of acute ingestion with severe symptoms, activated charcoal and gastric lavage may also be necessary.

Competing Interest

The authors declare that they have no competing interests.

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