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Thevetia peruviana intoxication and electrocardiographic manifestations: a case series

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Abstract

The use of herbal compounds for weight reduction, such as Thevetia peruviana, has toxic (or cardiotoxic) effects that cause various cardiac arrhythmias or atrioventricular block. Three cases of cardiac arrhythmias after ingestion of Thevetia peruviana and its management with activated charcoal are presented.

Keywords: *Thevetia peruviana. Cardioglucósidos. Bloqueo auriculoventriular. Bradicardia. Intoxicación.*

Introduction

The use of herbal products to try to lose weight is very common in Mexico. The "Brazilian Seed" or "Indian Nut" is marketed as a natural weight loss product; however, it has been reported to contain Thevetia peruviana. This, also known as "Friar's Elbow" it is a shrub belonging to the Apocynaceae family which is native to tropical and subtropical areas, with worldwide distribution. It is an ornamental shrub that can reach up to 9 meters in height, has yellowish funnel-shaped flowers and elongated leaves (about 15 cm) that produce a milky sap. The leaves are pointed in shape and have a dark green upper surface and a lighter green lower part. The edges are often curled and the fruits are rounded fleshy drupes and have 2 to 4 seeds in the stony inner section; turns yellow when ripe. All parts of this plant, especially the seeds and leaves, are poisonous to man. Active toxins include thevetin B, cerberin, nerifolin, thevetin A, ruvoside, and peruvoside (in ascending order of toxicity). The usual lethal dose comprises 15 to 20 g of roots or 8 to 10 seeds[1,2], this being not constant[4] considering the following: the variability of glycoside concentrations between seeds; variable crushing of the fruit before and during ingestion; limited absorptive capacity, vomiting in some patients after ingestion, and individual cardiovascular response and/or comorbidities[2].

Its toxic effect is mainly due to the presence of cardiac glycosides (cardenolides) that bind to sugars, hence its name. Physiopathologically, the clinical manifestations are explained due to the inhibition of the Na^+-K^+-ATPase pump in the heart and other tissues, which causes intracellular Na^+ retention followed by an increase in intracellular Ca^{++} concentrations. The high intracellular concentration of Ca^{++} promotes inotropy and bradycardia, the intracellular accumulation of Na^+ and Ca^{++} causes a partial depolarization of the membrane that increases automaticity and ventricular ectopy[3].

It has been found that Thevetia peruviana presents a prolonged absorption, being able to extend beyond 50 hours after ingestion, however the terminal life is variable, with a median time of 42.9 hours[2,6]; the pharmacokinetics being little studied in humans.

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The most common manifestations of intoxication include gastrointestinal distress, bradycardia with AV block, hypotension, lethargy, and dizziness. Seizures, electrolyte disturbances (mainly potassium), diuretic effect, hypertension, and coma have been reported in severe poisoning. Mydriasis can occur. In a study of 300 ingestions of yellow oleander seeds with suicidal intent, 12% of the patients had palpitations, while 46% had some type of arrhythmia; Sinus bradycardia was present in 49% of the patients[5].

Regarding the changes observed in the electrocardiogram, flattening or inversion of the T wave and depression of the ST segment have been observed in mild intoxication. Moderate intoxication manifests as a prolonged PR interval (first degree heart block) or sinus bradycardia. Severe poisoning manifests as second or third-degree heart block due to inhibition of the atrioventricular node. Deaths from ventricular fibrillation resistant to electrical cardioversion have also been reported[2,4].

The following is a series of three cases of intoxication due to the ingestion of "Brazil seed" in which various electrocardiographic disorders were found from bradycardia to third degree AV block, its presentation and its treatment with activated charcoal as well as measures of support.

Case 1

Overweight 36-year-old woman with no chronic degenerative history came to the emergency room due to generalized abdominal pain, sweating, nausea, vomiting, and bradycardia of 50 beats per minute over 12 hours of evolution. The patient referred intake of Brazilian seeds (Thevetia peruviana) as a weight loss treatment, consuming a large seed and another small one every 24 hours, alternately, for 2 months, the last intake referred to 4 hours previously. An ECG was performed, showing a Mobitz II second-degree AV block (Fig. 1), with vital signs AT 112-60 mm Hg, HR 58 bpm, RR 24 rpm, Temp 36 °C, for which admission and evaluation by the toxicology service was decided. She did not present hydroelectrolytic alterations on admission or during his stay (Na^+: 135, K^+ 3.8, Cl 112, Mg^{++} 2.0, P 3.0, Ca^{++} 9.1). She was managed on admission with intravenous crystalloid-based hydration in the face of dehydration data and activated charcoal at a dose of 1 g/Kg plus 20 % mannitol at 5 mL/Kg on two occasions with an interval of 4 hours given the suspicion of Thevetia peruviana intoxication and the absence of hemodynamic instability. The patient presented clinical improvement and normalization of the heart rate at 12 hours and was discharged the next day with the following vital signs: BP 124-65 mm Hg, HR 78 bpm, RR 20 rpm, temperature 36°C with follow-up by the outpatient clinic of toxicology.

Case 2

A healthy 43-year-old woman with no chronic degenerative history, only overweight as a risk factor, went to the emergency department due to chest pain with anginal characteristics, sweating, nausea, vomiting, dyspnea and palpitations of 1 hour of evolution. The patient ingested seeds from Brazil (Thevetia peruviana) for two months, taking a large seed and another small one alternately, every 24 hours for a period of 5 weeks as a weight loss treatment, with the last intake 2 hours prior to admission. to the unit; Initially, ECG was performed in the emergency area which showed narrow complex supraventricular tachycardia, BP of 132-66 mm Hg, HR: 170-185 bpm, RR: 18 rpm, T: 36.2, SatO2: 94%; 150 mg of amiodarone were administered intravenously, a single dose with return to sinus rhythm, it was decided to initially hospitalize in the emergency department for monitoring, administering activated charcoal at a dose of 1g/Kg plus mannitol at 20 % at a dose of 5 mL/Kg on one occasion; However, a few hours later, he presented a third degree AV block, so dopamine infusion was started prior to the placement of a temporary pacemaker (Figs. 2A and 2B). Later, she was admitted to the intensive care unit, paraclinical tests were carried out, showing hydroelectrolyte alterations (Na: 139, K: 4.1, Mg: 1.2, Cl: 112, Ca: 9.8, P: 5.3) for which it was decided to administer 1 gram of sulfate magnesium every 8 hours for 24 h, carrying out new electrolyte controls (Na: 142, K: 3.9, Mg: 1.7, Cl: 111, Ca: 9.6, P: 5.0) being found normal, the administration of activated carbon is continued at doses of 1g/kg for 24 h with an interval of 6 hours, with clinical improvement, temporary pacemaker was removed without incident, continuing under surveillance for a further 24 hours with hemodynamic stability, finally deciding her discharge with follow-up in the toxicology outpatient clinic.

Case 3

A 41-year-old woman with a history of renal lithiasis without pharmacological management, came for renal colic and angina pectoris with radiation to the neck, dyspnea, nausea and palpitations of 2 hours of evolution. The patient referred the intake of Brazilian seeds (Thevetia peruviana) for a month, taking a large and a

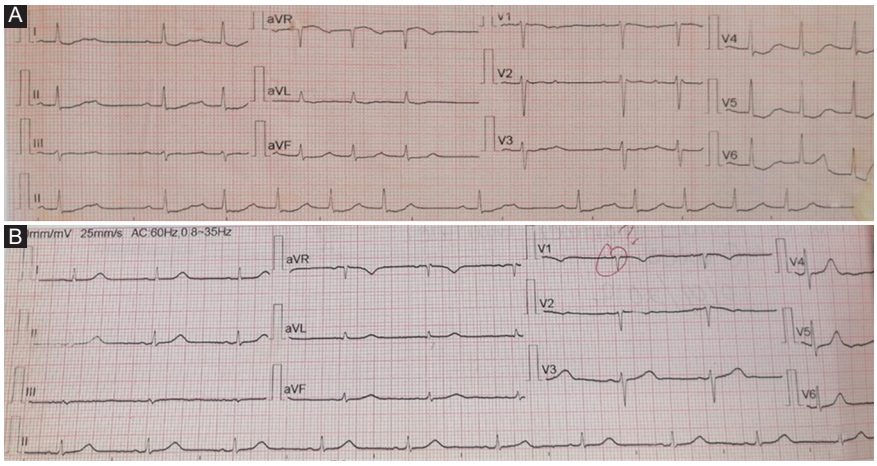

Figure 1. A: mobitz II second-degree AV block. **B:** EKG of egress.

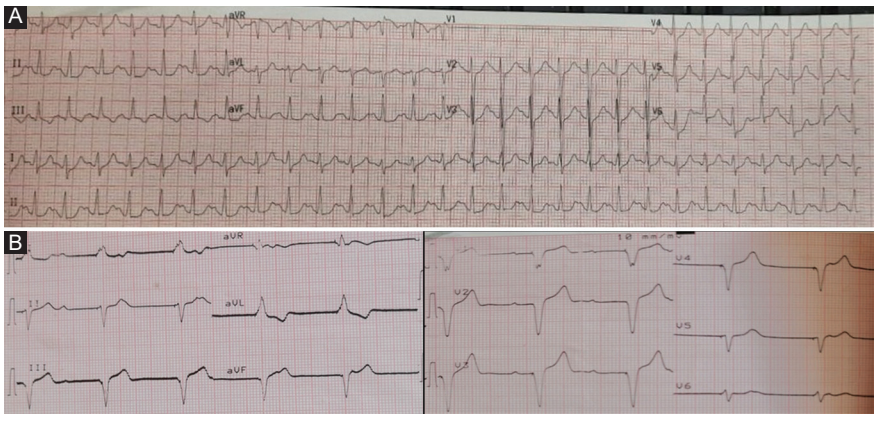

Figure 2. A: supraventricular tachycardia. **B:** temporary pacemaker placement.

small seed alternately every 48 hours; The patient was admitted to the emergency room and the following vital signs were found TA 134/72 mm Hg, HR 50, FR 24 rpm, temperature 36.8 ° C, an ECG was also performed that showed sinus bradycardia of 51 beats per minute (Fig. 3). by the toxicology service who indicates the administration of activated charcoal at a dose of 1g/Kg on one occasion, in addition anti-ischemic management, tamsulosin, analgesia is started; Paraclinical tests were collected, finding Na: 142, K 4.1, Cl 114, Mg 2.1, P 3.8, Ca 7.4, Albumin 4.5, Creatinine 0.7, for which management with calcium gluconate 1 g was added every 8 h. In the following hours, the patient presented an improvement in heart rate (70-80 beats per minute), was kept under surveillance for 12 hours and was discharged without complications with follow-up in the Toxicology outpatient clinic.

Discussion

Miracle products are substances that promise a health benefit but represent a risk to the consumer. The marketing of miracle weight loss products is very prevalent worldwide. These are advertised as safe and effective products. However, it has been proven that some of these products contain seeds of toxic plants, including Thevetia peruviana as in the case of our patients motivated to take it with the desire to lose weight.

Thevetia peruviana is cardiotoxic, since it contains cardiac glycosides that inhibit the Na +/K + ATPase pump in the heart, which can produce a decrease in automaticity (sinus bradycardia), alterations in atrioventricular conduction (second and third degree AV block), and arrhythmogenesis (ventricular fibrillation)[3]. More than half of the patients present arrhythmias or electrocardiographic

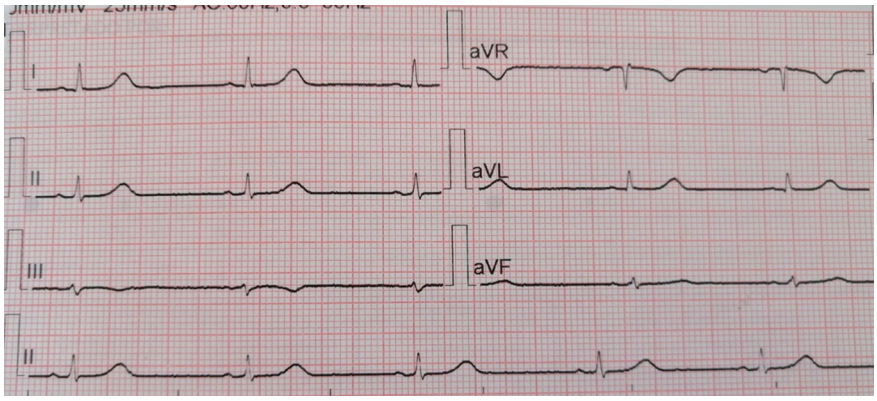

Figure 3. Bradicardia sinusal.

abnormalities, the most frequent being bradycardias and atrioventricular blocks, as occurred in this series. Severe cases of Thevetia peruviana poisoning have been reported, causing death due to resistant ventricular fibrillation and acute myocardial infarction[4-7]. In our series, no patient died.

Gastrointestinal symptoms are also reported, which was found in our cases, however, the presence of chest pain was also observed, which is not frequent in the bibliography. Other findings are electrolyte disorders, hypokalemia being more frequent, however in our review normal values were found in all three cases, not so in the case of calcium and magnesium in which it was added to the management for its correction, since has reported that hypomagnesemia can worsen toxicity and predispose arrhythmias[16].

There is no scale to classify the severity of poisoning by this seed. The usual toxic dose is 15 to 20 grams of root or 8 to 10 seeds[4,9]. However, the toxic dose varies, since the concentration of glycosides is different between seeds and absorption differs between individuals[9-11]. Fact that could be observed in these cases in which the same dose of seeds consumed is referred and even for almost the same time, finding only one case in which a serious arrhythmia occurred.

Regarding its absorption, it has been observed that it is slow and can last up to 50 hours[4,13,14].Therefore, the manifestations of intoxication can appear late. For example, our patients developed intoxication after weeks of consuming the weight loss product.

An attempt has been made to relate the level of glycosides with the severity of symptoms or mortality[12,14], however this has not been achieved given the few studies and that not all units have the resources to determine it, as is the case in our unit hospitable.

There is no characteristic or pathognomonic clinical picture, therefore, given the presented clinical picture, the absence of important cardiovascular or hereditary factors, and a history of ingestion, thevetia peruviana intoxication was suspected, so a detailed medical history should always be taken.

The treatment will depend on the state of the patient's admission conditions, a general approach to the intoxicated patient is described[10,15], with support measures, support with vasoactive amines, use of pacemakers, if necessary, electrolyte correction. The administration of activated carbon is controversial, since it has not been possible to establish greater effectiveness between single versus multiple doses, because the ideal dose number is still unknown as well as the time necessary for its administration in cases of multiple doses[9,10, 13,14]. Activated charcoal reduces toxicity by two mechanisms: first by preventing the absorption of glycosides shortly after ingestion and, second, by interrupting their enterovascular and enterohepatic circulation[14,15]. thus increasing its elimination, which motivated its use in the patients of this report. In addition, there are some studies (although small) where it was observed that clearance increased from 12 to 18 L/h and the half-life decreased from 37 to 22 hrs[15].

The use of antigoxin Fab has also been described, without a proven ideal dose, but 1,200 mg diluted in 100 cc of saline solution in a single dose has been used, observing reversal of arrhythmias[15]; However, studies are lacking to support its use, as well as determination of the ideal dose, not to mention its high cost and that it is not available in all hospital units.

The lethality of intoxication is highly variable, with reports of 10% to 3% being found in other studies[16]. The differences in the results may be due to various factors such as the units' own resources, diversification

in treatments and referral criteria; patients usually die from ventricular tachyarrhythmias that are usually resistant to defibrillation.

The patients were discharged stable with follow-up to the toxicology outpatient clinic without recurrence of symptoms and with abandonment of the "miracle" product.

Conclusion

This case series exemplifies the different types of electrocardiographic manifestations of Thevetia peruviana poisoning. We clinically confirmed the prolonged cardiotoxic effect and the response to treatment with the use of activated charcoal at the standard dose, remitting the manifestations. It was found that they can be accompanied by various electrolyte disorders that worsen the clinical status of the patient, so complete serum electrolytes should be requested. We always suggest intentionally inquiring about the consumption of teas, miracle products or herbalism in young patients with electrocardiographic disorders and gastrointestinal symptoms, since in our review the patients initially denied their intake upon admission. Currently, Cofepris has prohibited the sale of Thevetia peruviana and products that contain this seed (example: Capslim), however, it must insist on disseminating it to the general population about the damage that these products can generate.

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Conflict of interests

The authors declare no conflict of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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