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CASE REPORT

Foxglove poisoning: diagnostic and therapeutic differences with medicinal digitalis glycosides overdose

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ABSTRACT

We report a case of a 19-year-old woman who ingested Digitalis purpurea leaves as a suicide attempt. She developed gastro-intestinal symptoms, loss of colour vision, cardiac conduction disturbances as well as an elevated serum potassium. Treatment was initiated in analogy to medicinal digoxin poisoning by means of digoxin-specific Fab-fragments with a good effect. However during the further course we faced difficulties of prolonged intestinal absorption and inability to estimate the ingested dose or half-life of the vegetal cardiac glycoside compounds. To prevent further absorption and interrupt enterohepatic recycling, multi-dose activated charcoal was administered. Because of a relapse of cardiac conduction disturbances and hyperkalemia, two supplementary doses of Fab-fragments were given, up to a total dose of nineteen vials (one vial containing 40 mg). The important diagnostic and therapeutic differences of vegetal digitalis intoxication as compared to medicinal intoxication and the applicability of existing guidelines on medicinal digitalis intoxication in the light of these differences will be discussed here.

KEYWORDS

Digitalis purpurea poisoning; fab fragments; digitoxicity; foxglove

Background

Reports on poisoning with the foxglove plant (Digitalis purpurea) are scarce compared to those with digitalis glycosides in medicinal form. Accidental foxglove poisoning is infrequent because of its bitter taste and generally distinct appearance. However, there are reports of mistaking foxglove for edible plants like comfrey, resulting in the ingestion under the form of preparations ranging from tea to stew and even ravioli containing digitalis [1–3]. Intentional poisoning with the plant has only rarely been reported [4,5]. Literature on the practical approach of digitalis glycoside poisoning is scarce.

Case presentation

A 19-year-old biology student presented to the emergency department at 7 PM. She had a history of mental illness with suicidal ideations but no previous suicide attempts. One hour prior to presentation, while returning home from a lecture at the university, she noticed a foxglove plant at the side of the road. Aware of its toxic properties, she had picked and ingested an estimated total of 20 leaves. After arrival at home, she immediately informed her mother and both rushed to the regional hospital. Upon initial examination by the admitting physician, she looked pale and was perspiring but showed no other abnormal clinical signs. She denied co-ingestion of other substances. The physical examination revealed a slow but regular heart rate of 40 bpm with a normal blood pressure and no signs of circulatory problems. Shortly after admission, she reported abdominal pain and experienced nausea with vomiting. In addition, she mentioned experiencing a blurry vision and a marked reduction of colour vision.

Emergency department approach and referral

An electrocardiogram (ECG) showed a sinus rhythm (40 bpm) with a second-degree atrioventricular (AV) block (Mobitz type I), a marked concavity of the depressed ST-segment in the inferolateral leads with an inverted T-wave (Figure 1). A blood analysis showed an elevated serum potassium of 7 mEq/L (normal range 3.5–5.1 mEq/L) and a reduced serum bicarbonate of 19 mEq/L (normal range 22–26 mEq/L). Plasma lactate was slightly elevated at 1.54 mmol/L (normal range < 1.25 mmol/L).

She was treated with 10 ml of a glucose 30% solution with 10 IU of rapidly acting insulin intravenously (IV) and as well as an aerosol of salbutamol 5 mg/1 ml in 2 ml of NaCl 0,9% solution by inhalation to lower the serum potassium. For the nausea, she was given 50 mg of alizapride and 4 mg of ondansetron IV. One milligram of atropine was administered IV for an episode of

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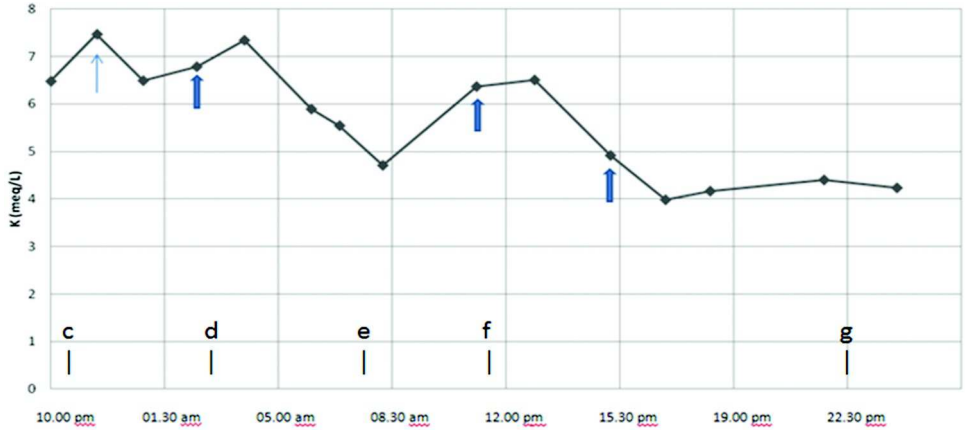


Figure 1. Time course of the ECG findings. a. 7 PM. ECG at presentation in the referring hospital, showing a second degree AV block Mobitz type I with a ventricular rate of 39 bpm. b. 8.30 PM. ECG after administration of 1 mg of atropine intravenously, showing a sinus tachycardia of 122 bpm with normal PR duration. c. 10.20 PM. ECG after transfer to the university hospital, showing a second degree AV block Mobitz type I, with ventricular rate of 73 bpm. d. 3.41 AM. ECG after a first administration of Fab-fragments a 02 am (280 mg), showing a sinus rhythm of 55 bpm with first degree AV block (PR interval 286 ms, normal 120–200 ms). e. 8.06 AM. Six hours after the administration of Fab-fragments. Relapse of second degree AV block with 3:1 AV conduction. Ventricular rate of 38 bpm. f. 11.30 AM. Thirty minutes after second administration of Fab-fragments. Sinus rhythm of 96 bpm with short PR of 108 ms (normal 120–200 ms). g. 10.30 PM on day 2. Relapse second degree AV block. Ventricular rate 48 bpm.

bradycardia of 35 bpm (with a normal blood pressure). A short episode of a sinus tachycardia of 122 bpm with normal PR duration occurred, followed by a relapse of the second-degree AV block (30–40 bpm) after 10 minutes. The patient was transferred to the intensive care unit (ICU) of the university hospital for further follow-up and treatment.

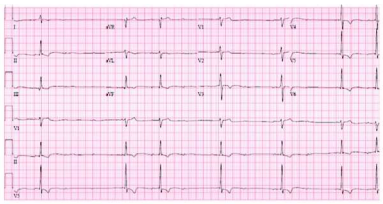
ICU admission

Upon arrival at 10 PM, the nausea had slightly improved. Her consciousness remained fully preserved and there was spontaneous improvement of the colour vision. ECG monitoring showed a continuous bradycardia of 30–40 bpm with a second degree AV block, varying between Mobitz types I and II. On arterial blood gas, she had a mild compensated metabolic acidosis (pH 7.44 – PCO2 28 mm Hg – bicarbonate 19 mEq/L) and a persistently elevated serum potassium of 7.1 mEq/L. A digoxin assay was repeated awaiting the results from the first assay in the referring hospital, showing an unexpectedly low digoxine level of 0.31 µg/L (therapeutic range between 1–2 µg/L).

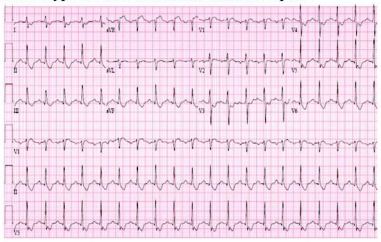
All available vials of digoxin-specific Fab fragments (DigiFab®) were administered at 2 AM, amounting to a total dose of 280 mg (7 vials). The manufacturer recommends 20 vials (800 mg) in case of acute ingestion with an unknown amount of digoxin, but no dosage is recommended for vegetal intoxication [6]. Meanwhile the pharmacists contacted other hospitals in the region and also the Belgian poison centre to obtain additional vials.

Between 2 and 8 AM, there was a drop in serum potassium to 4.7 mEq/L with the ECG showing a first-degree AV block mere minutes after administration of the Fab fragments. By 8 AM, the second-degree AV block reoccurred as well as a rise in serum potassium to 6.15 mEq/L (Figure 2). Furthermore, the nausea worsened and resulted in vomiting of greenish vegetal material, possibly containing undigested foxglove leaves. Therefore, after protection of the airway with endotracheal intubation - because of protracted vomiting -multiple doses of activated charcoal (MDAC) were administered with an initial dose of 50 g followed by 20 g every four hours. At 11 AM, 7 supplementary vials of Digifab (280 mg) had arrived and were administered. This resulted again in a normalization of both the cardiac rhythm (50 bpm with signs of a first-degree AV block) and serum potassium (4.9 mEq/L). The second-degree AV block reoccurred after 30 minutes. Because of a persistent second-degree AV block and bradycardia, 5 more vials of Digifab® (200 mg) were given at 3 PM. Before the third administration, serum potassium was no longer elevated (4 mEq/L) (Figure 2).

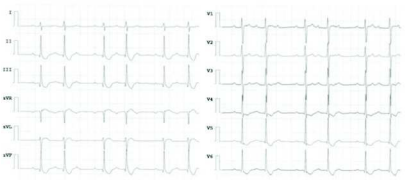
After 24 hours of MDAC, the administration of activated charcoal was stopped and the patient was extubated after verification by nasogastric aspiration that no gastric residue was left. After regaining consciousness, she was asymptomatic. ECG monitoring showed a persistent second-degree AV block without significant bradycardia. After a total of four days in the ICU, she was transferred to a critical cardiac unit for a further 7 days of monitoring. The second-degree AV block persisted up to 7 days after intoxication but no other arrhythmias were observed.



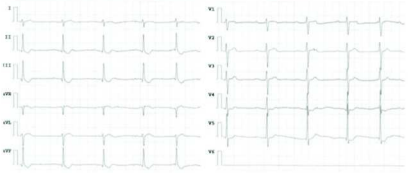
a. 7 PM. ECG at presentation in the referring hospital, showing a second degree AV block Mobitz type I with a ventricular rate of 39 bpm.□



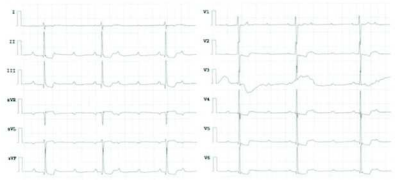
b. 8.30 PM. ECG after administration of 1 mg of atropine intravenously, showing a sinus tachycardia of 122 bpm with normal PR duration. □



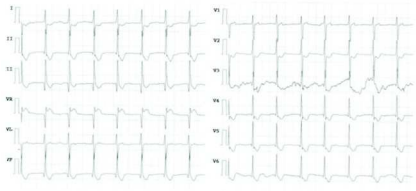
c. 10.20 PM. ECG after transfer to the university hospital, showing a second degree AV block Mobitz type I, with ventricular rate of 73 bpm.□



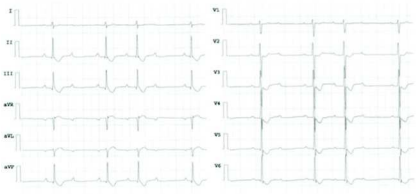
d. 3.41 AM. ECG after a first administration of Fab-fragments a 02 am (280 mg), showing a sinus rhythm of 55 bpm with first degree AV block (PR interval 286 ms, normal 120-200 ms). □



e. 8.06 AM. Six hours after the administration of Fab-fragments. Relapse of second degree AV block with 3:1 AV conduction. Ventricular rate of 38 bpm. □



f. 11.30 AM. Thirty minutes after second administration of Fab-fragments. Sinus rhythm of 96 bpm with short PR of 108 ms (normal 120-200 ms).



g. 10.30 PM on day 2. Relapse second degree AV block. Ventricular rate 48 bpm.

Figure 2. Time course of the serum potassium levels. The fine arrow indicates administration of insulin-glucose solution and use of a salbutamol nebulizer. The thick arrows indicate administration of Fab-fragments. The characters c-d-e-f-g indicate the respective timing of the ECG in.Figure 1

Discussion

The foxglove plant contains digitalis glycosides, also named cardiac glycosides, because of their known effect on cardiac rhythm and function. These compounds have an inhibitory effect on the sodium-potassium membrane pump (Na^+-K^+-ATPase) with intracellulair retention of Na^+, and a secondary potentiation of calcium influx by the sodium-calcium exchanger. This results in a build-up of calcium in the sarco-endoplasmic reticulum of the cardiac muscle cell, which is released in the cytoplasm upon depolarization. This causes a stronger troponin-tropomyosin cross-bridging and consequently a more forceful contraction. In acute exposures, hyperkalemia is the hallmark of cardiac glycoside poisoning. The negative chronotropic effect is caused by a prolongation of the refractory phase in the AV node cells and an increase in vagal nerve activity, among other possible effects [7]. This explains why an overdose can cause both conduction disorders and life-threatening tachy-arrhythmias [8,9]. Other common signs of intoxication include gastro-intestinal symptoms like anorexia and vomiting. Vision disturbance and color blindness are typical and are caused by a retrobulbar neuritis of the optic nerve. Neurological symptoms such as dizziness, confusion and convulsions also occur [8,10]. The most common and important biochemical hallmarks are an elevation of serum potassium (caused by inhibition of the inward flux into the cells) and an accompanying metabolic acidosis. ECG findings are quite characteristic and include a downsloping ST segment depression, shortened QT and widened PR-intervals. These changes may suggest the diagnosis in case of an intoxication with an unknown substance, but do not correlate with toxicity as they are also often seen in patients with therapeutic digoxin levels. Moreover, toxic manifestations and arrhythmias may occur even in the absence of these ECG changes [10].

There are important pharmacokinetic differences between cardiac glycosides with regard to the degree of protein binding, lipid solubility and biotransformation. Digoxin and digitoxin have been used for medicinal purposes. The preference for digoxin in therapeutic use is because of its relatively short half-life of 40 hours, low protein binding and renal excretion with little biotransformation or enterohepatic cycling. These factors make digoxin the most predictable compound in terms of obtaining therapeutic serum concentrations [11].

Cardiac glycosides can be found in several plant leaves, flowers and seeds. These plants include but are not limited to foxglove (Digitalis purpurea), Digitalis lanata, lily of the valley (Convallaria majalis), oleander (Nerium oleander), yellow oleander (Thevetia peruviana), Strophanthus kombe, squill (Urginea maritima/sea onion/indica bulbs), dogbane (Apocynum cannabinum), and Adonis vernalisare [12]. It is important to realize that these plants contain not one but many different compounds with cardiac glycoside effects, such as digoxin, digitoxin, digitoxigenin and digoxigenin [13]. Many of these compounds have complex pharmacokinetic properties with entero-hepatic recirculation and biotransformation to active metabolites (including digoxin) and are eventually excreted by the kidneys. These characteristics result in a long plasma half-life of up to seven days [11]. The exact composition of these plants is known to be highly variable due to seasonal differences and genetic differences [13]. With regard to pharmacodynamics, the inotropic effects of different Digitalis purpurea leaf compounds have been compared by Lüllman et al. in animal studies, showing an almost equal inotropic dose-effect relationship for digoxin and digitoxin but other compounds such as digitoxigenin were shown to be even more potent. It is unknown whether these differences correlate with the risk of arrhythmias [14].

Many digoxin assays have been developed for the purpose of therapeutic drug monitoring [15,16]. These assays are primarily designed for the detection of digoxin and there is highly variable cross interference with other cardiac glycosides. This explains the discrepancy of the measured levels between the referring and our hospital. The former used the immunoassay of Roche® with a reported cross reactivity for digitoxin of 1.18% while the latter used the ARCHITECTi Digoxin assay of Abbott®, which has a cross reactivity for digitoxin of only 0.3%. Likewise, the cross reactivity of digitoxigenin for example also differs greatly between those assays namely 0.18% versus 0.3% [15,16]. Therefore, although in many case reports digoxin assays are used [1–5], these assays are not designed for determining the amount of ingestion in intoxications other than medicinal [15,16]. They can be used for qualitative purposes, but caution is also needed due to false negatives which was almost the case in our patient [8].

Since vegetal cardiac glycoside intoxications are rare, practical guidelines have not been established, in contrast with medicinal overdoses of digitoxin and digoxin for which recommendations are available. According to these recommendations, the first step after establishing a diagnosis and excluding co-ingestion is to carry out a risk evaluation. Dally et al. studied 179 cases of medicinal digitoxin intoxication and proposes sex, age, presence of AV block and plasma potassium concentration as the main prognostic factors for mortality. In his study, male patients older than 55 years with an AV block and a plasma potassium higher than 4.5 mEq/L showed the highest mortality (i.e. 74%) in contrast to young females without AV block or high potassium who showed a mortality of 2% [8,17]. The earlier mentioned risk factors are largely in accordance with the guidelines for the administration of digoxin-specific Fab fragments

as an antidote for medicinal overdose (Table 1) [6]. Fab fragments are manufactured from immunoglobulins of immunized sheep and bind digoxin with a higher affinity than its cardiac receptor, resulting in lower receptor binding [6,8]. The Fab-digoxin complexes are cleared by either the kidney or the reticuloendothelial system. Fab-fragments reduce the free plasma digoxin concentration, though digoxin assays will show an initial increase because the usual assays do not distinguish between bound and unbound cardiac glycoside, making these assays inadequate for response evaluation in any case of intoxication [6,15,16]. Fab-fragments are considered safe and have very few side-effects. It is however important to mention the risk for low potassium level upon administration of Fab fragments, definitely in combination with other potassium lowering measures [8]. There are two commercially available preparations: DIGIBIND (38 mg/vial; GlaxoSmithKline Inc.) and DigiFab (40 mg/vial; BTG, Inc.). Though the dosage in milligram is different, a single vial of both DIGIBIND and DigiFab will bind 0,5 mg of digoxin in vivo. Therefore, the clinical claims, dose recommendations (in vials) and administration of these preparations are identical [18]. For this reason, many authors mention an amount of vials rather than a dosage in milligrams.

The use of Fab-fragments in vegetal cardiac glycoside poisoning has been shown to be effective in case reports but it remains difficult to determine the optimal dosage [8,19]. There was a frequent need for repeat dosing amounting to a total dose of 10 up to 37 vials [1–3,5]. An initial dose of 20 vials is suggested by the manufacturer. Other sources suggest between 10 and 20 vials as a starting dose, with increasing dose should symptom resolution be incomplete [20]. The need for a higher dose of the Fab-fragments may be due to either pharmacokinetic differences between cardiac glycosides and the inability to quantify the body burden adequately. We could not find studies that report the affinity of FAB fragments for cardiac glycosides other than digoxin. A factor that should also be considered is prolonged absorption as presumably occurred in our patient. Absorption from vegetal material is less predictable than of medicinal digoxin preparations and prolonged absorption of glycosides from an undigested reservoir in the gastro-intestinal tract is possible. Bearing in mind that the half-life of the Fab-fragments is relatively short (i.e. about 15 hours), the delayed absorption may exceed this time [6].

Table 1. Indications for the administration of Fab-fragments for medicinal intoxication according to the manufacturer, with additions from Goldfrank in italic [6,20].

Indications for the administration of Fab-fragments for medicinal overdose of digoxin
Severe ventricular arrhythmias, progressive bradycardia, and second or third degree heart block with insufficient response to atropine. *Any glycoside related life threatening dysrhythmia.*
Serum potassium levels exceeding 5.5 mEq/L in adults or 6 mEq/L in children, especially in case of impaired renal function
High digoxin levels > 10 µg/L
High age, renal, cardiac or hepatic comorbidity
Poisoning with cardiac glycosides other than digoxin (these include vegetal intoxication)

It is recommended to monitor all patients with potential ingestion of digoxin at least eight hours and transfer them to an ICU department [8]. Previously it was reported that severe toxicity may not occur until 24 h post-admission for digoxin, or up to 5 days for digitoxin poisonings [7]. For medicinal digoxin it is stated that if the patient remains asymptomatic, the ECG does not show any brady- or tachyarrhytmias and potassium is within the reference range, the risk of developing significant poisoning is low. The recommended eight-hour time-window cannot be extrapolated to vegetal cardiac glycosides, as serious dysrhythmias may develop up to 92 hours after ingestion [7].

Decontamination by means of **gastric lavage** is advocated by some although there is little evidence to support it. In general, it is not recommended since it could delay the use of activated charcoal, which is likely more effective when prolonged absorption is expected [7]. **Oral activated charcoal** has been shown to reduce the digoxin serum concentration in acute medicinal poisoning, when given within the first two hours after ingestion [8,19]. Whether prolonged gastro-intestinal absorption in vegetal intoxication makes later administration useful is unproven since a lot of cases regard accidental poisoning of an extract or preparation (e.g. tea of stew) and differences in the preparations probably change the bio-availability [1–3]. If a prolonged absorption is to be expected, for example after eating raw plant leaves, activated charcoal might still be considered even beyond the two-hour window. It may then be administered in a **multiple dose charcoal regimen** (MDAC) to additionally interrupt enterohepatic cycling of toxins, to assist elimination, based on pharmacokinetic data [7]. Theoretically, **whole-bowel irrigation** could be considered for undigested plant residues, but this has not been described in case reports. Since digoxin is only poorly dialyzable, **extracorporeal removal techniques** for medicinal overdosing are not useful [8]. Other cardiac glycosides than digoxin as present in for example Digitalis purpurea have a higher fat solubility and a higher distribution volume, so it can be assumed that removal with dialysis will be even less efficient with a higher chance of rebound after dialysis. Dialysis may still be considered to treat serious hyperkalemia or metabolic acidosis [8].

Correction of potassium by other methods than Fab-fragment administration remains dubious since it is unclear which potassium concentration is safest in terms of arrhythmias [8,20]. In case of severe hyperkalemia, insulin-glucose or sodium bicarbonate can be used. In an animal model, dextrose seemed to be cardioprotective in digoxin toxicity. Use of calcium is dissuaded because it

may potentiate the cardiac effects with disastrous consequence. A low serum potassium might however potentiate the effect of cardiac glycoside toxicity and should be corrected. As mentioned before, potassium levels should be monitored after administration of Fab-fragments since reinstitution of the Na+/K+ exchange can cause profound hypokalemia [20]. **Anti-arrhythmic drugs** have only a limited and short-lived effect when compared to Fab-fragments so repeated dosages or continuous administrations of the former are needed. Phenytoin reverses the AV conduction prolongation and can terminate supraventricular dysrhythmias other than atrial flutter or fibrillation. Lidocaine has been used for the same purpose. Atropine can be useful to block the vagotonic effects in supraventricular brady-arrhythmias. Propranolol and procainamide should be avoided due to the risk of depression of cardiac conduction [8,20]. **Magnesium sulfate** has proven useful for tachy-arrhythmias even with elevated magnesium levels. Hypomagnesaemia should be avoided since it increases cardiotoxicity in a similar manner as hypokalemia [20]. **Cardiac pacing**, either transvenous or transcutaneous, is contra-indicated because of the risk of pacing-induced arrhythmias and lack of reduction in mortality when compared to Fab-fragments [8,21]. Electrical cardioversion is generally ineffective, and should be reserved for cases with ventricular dysrhythmias refractory to other treatments using low energy levels (e.g. 20–100 J) [7].

Other general supportive measures include adequate emesis control to reduce vagal stimulation and maintaining hydration and renal output since excretion is primarily renal.

When above literature data are considered, our patient belonged to a high-risk group with a mortality risk amounting to 17% in view of the presence of a cardiac conduction disorder and an elevated serum potassium [17]. Consequently, there was an indication for the administration of Fab-fragments. Pending availability, she received atropine because of a low heart rate, which only had a very short-lived effect. Reducing the serum potassium level with glucose-insulin probably also had limited effect. In contrast, administration of Fab-fragments resulted in a fast correction of the serum potassium and rapid improvement of cardiac conduction disturbances.

In hindsight, earlier administration of MDAC, in this case started after a delay of 12 hours, potentially could have prevented prolonged absorption from vegetal material that proved to still be present in the gastrointestinal tract. A reason for the delay of MDAC was that this implicated intubation to ensure a safe airway and was therefore considered quite invasive. Seen the serious symptoms and expensive treatment with Fab-fragments, avoidance of absorption with reduction of poisoning is preferable over treatment with Fab-fragments solely. The second and third administration of Fab-fragments, respectively seven vials (11 hours after the first dose) and five vials (16 hours after), was given according to the availability, ECG findings and hyperkalemia, as no clear guidelines exist for this particular situation. It is unclear whether the administration of MDAC lowers risk of mortality or reduces the total dose of Fab-fragments needed.

Summary and conclusion

This case of ingestion of Digitalis purpurea as a suicide attempt posed no diagnostic problem because of a clear history and compatible ECG findings. However, cardiac glycoside poisoning by plants or plant extracts entails some important therapeutic particularities as opposed to medicinal overdosing.

Firstly, the use of digoxin assays in intoxications other than medicinal digoxin overdose is inaccurate and misleading because of highly variable cross-detection of the variety of cardiac glycosides present in plants [15,16]. Secondly, the various cardiac glycosides in plants show differences in terms of pharmacokinetics [11]. Absorption from a vegetal source is less predictable than a medicinal preparation and metabolism and excretion also greatly differ between cardiac glycosides, resulting in much longer plasma half-lives than medicinal digoxin [11]. Multiple dose activated charcoal (MDAC) should be considered even beyond the two-hour timeframe of single dose activated charcoal when delayed absorption and added value by interrupting enterohepatic cycling is expected [8]. Thirdly, digoxin-specific Fab fragments have proven effective in the context of plant intoxications. However, higher doses and more frequent administrations were given indicating a probable lower effectiveness than in medicinal digoxin intoxications [2,3,5].

Key points

- Medicinal and vegetal cardiac glycoside poisoning produce similar symptoms and toxicity, but show important diagnostic and therapeutic differences.
- Activated charcoal should be considered a soon as possible (preferably within two hours, but also after expiration of this time). Multiple dose activated charcoal (MDAC) is recommended in order to interrupt intestinal absorption and enterohepatic cycling.
- Digoxin assays exhibit variable cross reaction with other vegetal cardiac glycosides rendering them unuseful to estimate the ingested amount, but may be used qualitatively.
- Digoxin-specific Fab fragments remain the most effective measure to reduce life-threatening arrhythmias and mortality, though the optimal dosage in vegetal intoxications remains unclear.
- Digoxin assays have no place in follow-up of the antidotal effect of Fab-fragments.

Disclosure statement

No potential conflict of interest was reported by the authors.

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