Rapid firing

Electrophysiologic similarities of overdose between digoxin and bufadienolides found in a Chinese aphrodisiac

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ABSTRACT

Classically derived from toad venom, bufadienolides are a group of cardioactive steroids with properties similar to digoxin. Some traditional Chinese medications, including several aphrodisiacs, contain bufadienolides. Owing to their physiologic similarities to digoxin, bufadienolides have been shown to produce a toxic profile similar to that of digoxin and there have been multiple case reports of the use of these aphrodisiacs resulting in death. This report will describe a case that illustrates the electrophysiologic similarities between bufadienolide toxicity and digoxin toxicity as well as the treatment of bufadienolide toxicity.

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1. Introduction

Derived from the foxglove plant, cardiac glycosides have been used for the treatment of heart failure for more than 200 years and are continued to be used today for patients with atrial fibrillation and heart failure. Currently, cardioactive steroid toxicity has become a well-known entity that even now, continues to be an issue. According to the National Poison Data System, in 2013, there were 26 deaths in the U.S. directly attributable to digoxin overdose, with many more non-fatal cases reported [1]. Bufadienolides are a group of cardioactive steroids with a chemical structure similar to digoxin. They are used in multiple traditional Chinese medications and aphrodisiacs. Because they are structurally similar to digoxin, they also display a similar toxicity profile. There have been multiple case reports of overdose with clinical presentations similar to digoxin toxicity [2], with death occurring owing to arrhythmia. Currently, the only available treatment is the same digoxin-specific antibody fragments used to treat digoxin overdose. In this paper, we will discuss the clinical and electrocardiographic similarities between digoxin and bufadienolide-containing substances.

2. Case

A 39-year-old man presented to the emergency department with vomiting and diaphoresis after eating a half block of “Piedra China”, an aphrodisiac intended to be applied topically. Vital signs at the time were within normal limits; heart rate was 65 BPM and regular, blood pressure was 157/66 mmHg, and respiratory rate was 20 breaths/min. Shortly after arrival, ECG revealed sinus rhythm at 100 BPM with complete heart block (Fig. 1). Potassium was 4.6 mEq/L and digoxin concentration was 1.14 ng/mL (normal = 0.5–0.8 ng/mL). He had acute hemodynamic decompensation with immediate ECG changes. Fig. 2 shows a QRS complex that is mildly wider than baseline, with 3:2 grouped beating; this would indicate supraventricular tachycardia (atrial or junctional with 3:2 block) or bidirectional ventricular tachycardia (VT) with 3:2 exit block. Ultimately, he deteriorated to ventricular fibrillation and underwent 90 min of resuscitation. Treatment included defibrillation, epinephrine, atropine, amiodarone, procainamide, and three repeated boluses of digoxin-specific antibody fragments. After each dose of antibody fragments (10 vials, 12 vials, and 11 vials respectively; 38 mg/vial), his rhythm converted to normal sinus with heart rate 70–80 BPM. These improvements were transient and, despite aggressive care, the patient repeatedly deteriorated to ventricular fibrillation, which eventually led to asystole.
3. Discussion

Digoxin has multiple effects on the myocardium and has multiple cardiac-related uses. In the treatment of atrial fibrillation, digoxin increases vagal tone to prolong the refractory period at the AV node, decreasing ventricular response to higher atrial rates [3]. Toxic doses of digoxin can lead to an automatic atrial tachycardia, commonly termed PAT, which, in the context of excessive AV nodal blockade, produces the classic arrhythmia called PAT with block [4]. In practice, digoxin can produce a number of dangerous arrhythmias other than PAT. As shown in Fig. 1, the patient’s initial ECG shows a sinus rhythm with a high degree of AV block. Without treatment, the patient developed supraventricular tachycardia (atrial or junctional with 3:2 block) or bidirectional VT with 3:2 exit block, as seen in Fig. 2; either of these arrhythmias are pathognomonic of digoxin.

Like digoxin, bufadienolide-containing substances are known to inhibit the Na\(^+\)/K\(^+\) ATPase pump. They also have some inherent sodium channel blocking activity [5]. Bufadienolides are structurally similar to digitalis, and as such, are able to replicate the electrophysiologic toxicity of digitalis. The structural similarity also explains the patient’s mild elevation in digoxin level. As in this case, an immunoassay is often used to detect digoxin levels. Although not a one-to-one comparison of drug levels or toxicity, previous reports indicate that bufadienolide ingestion results in a detectable serum digoxin concentration. This patient had a mildly positive immunoassay, supporting the hypothesis of bufadienolide ingestion. With a combination of a mildly positive assay and waveforms consistent with those produced by digoxin toxicity, the physicians attempted treatment with digoxin-specific antibody fragments. With every administration, the patient converted to sinus rhythm; however, the effect could not be sustained. Once the

![Fig. 1. Sinus rhythm, accelerating junctional rhythm with incomplete right bundle branch block.](image1)

![Fig. 2. AT or junctional tachycardia with 3:2 block or bidirectional VT.](image2)
supply of antidote was depleted, the patient relapsed into a terminal rhythm and eventually succumbed.

This patient provides an example of how bufadienolide toxicity and digoxin toxicity can progress in a similar manner. In addition, Figs. 1 and 2 show how bufadienolides and digoxin can produce similar toxic arrhythmias. Repeated reversion of the arrhythmia using digoxin-specific antibody fragments demonstrates that the treatment has some binding compatibility with bufadienolide-containing substances, which has been supported in the literature [3]. Unfortunately, for this patient, there was not enough of the antidote on hand to yield a sustained effect. One potentially viable treatment may be the use of hemodialysis to treat bufadienolide overdose. Whereas digoxin is not dialyzable due to its size, bufadienolides lack one of the side chains found on digoxin, potentially allowing them to be dialyzed.

In summary, there is increasing recognition that naturally produced substances, which may be used for recreational purposes, can have toxic effects. We discussed a case of a bufadienolide-containing aphrodisiac ingestion that resulted in a toxic profile similar to that of digoxin as demonstrated by his progressive electrophysiologic deterioration seen on ECG. There was insufficient antidote readily available for successful treatment and the patient expired.

Conflict of interest

All authors declare no conflict of interest related to this study.

Acknowledgement

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References

[1] Mowry JB, Spyler DA, Cantilena Jr LR, McMillan N, Ford M. Annual report of the American Association of Poison Control Centers’ National Poison Data System (NPDS): 31st annual report. Clin Toxicol 2013;52:1032–283.
[2] Brubacher JR, Lachmanen D, Ravikumar PR, Hoffman RS. Efficacy of digoxin specific Fab fragments (Digibind) in the treatment of toad venom poisoning. Toxicon 1999;37(6):931–42.
[3] Goodman DJ, Rossen RM, Cannom DS, Rider AK, Harrison DC. Effect of digoxin on atrioventricular conduction. Studies in patients with and without cardiac autonomic innervation. Circulation 1975;51(2):251–6.
[4] Lown B, Wyatt NF, Levine HD. Paroxysmal atrial tachycardia with block. Circulation 1960;XX.
[5] Bagrov AV, Rouskoyatkina NI, Fedorova OV, et al. Digitalis-like and vasoconstrictor effects of endogenous digoxin-like factors from the venom of Bufo marinus toad. Eur J Pharmacol 1993;234:165–72.