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CASE REPORT

Clinical judgement perplexed by initially undisclosed use of herbal medicine and unexpected cross-reactivity of immunoassay

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Abstract

We report a case of symptomatic bradycardia caused by consumption of a Chinese herbal medicine which was initially undisclosed to the attending emergency physician. The scientific name of the herb is *Panax japonicus*. Electrocardiogram revealed sinus bradycardia. Laboratory tests were normal except for the detection of a high serum digoxin level. Further interrogation of the patient eventually disclosed ingestion of the herb which, however, did not contain any digoxin. Other active ingredients in the herb include various types of ginsenoside. These are digoxin-like substances that had caused the observed false-positive detection of digoxin by fluorescence polarization immunoassay due to cross-reactivity. Our case-report provides an important insight about a blind-spot in the field of laboratory medicine (clinical pathology), namely, the false positive detection of digoxin due to cross-reactivity in the immunoassay when we come across digoxin-like substances in clinical scenarios, which has barely received attention in the medical literature. It also conveys a clear educational message that with full understanding of the laboratory methodology and its mechanistic rationale there are actually some tricks-of-the-trade that allow us to optimize the specificity of the biochemical tests and the treatment of digoxin-like substances overdose.

Keywords: ginsenoside, digoxin-like substances, immunoassay, cross-reactivity

INTRODUCTION

Nowadays, over 100 million Europeans are alternative medicine users, with 20% regularly using alternative medicine (e.g. Chinese herbs) and the other 20% preferring healthcare which includes alternative medicine.[1] There are even more alternative medicine users in Australia, North America, Asia and Africa.[2] It has been estimated that around 60% of Australians access some form of alternative health services, reflecting the fact that there is actually a widespread acceptance of alternative medicines, including consumption of Chinese herbal medicine.[3] In some countries such as the Republic of Korea and Singapore where the conventional health-care system is quite well established, 86% and 76% of the respective populations still use alternative medicine frequently.[4]

In daily clinical practice of conventional medicine, it is not uncommon that patients often fail to inform their physicians about their consumption of various kinds of alternative medicine, therefore healthcare workers should always maintain a high index of suspicion for such undisclosed history which might end up obscuring accurate observations and overlooking the ultimate aetiology that has actually caused the presenting symptoms. Such perplexity is sometimes made worse when clinicians believe that they could rely on toxin screening tests or therapeutic drug monitoring system of the central laboratory in untangling the clinical puzzle.

CASE REPORT

A 62-year-old man with no medical history presented to the emergency department with a history of sudden onset dizziness, nausea, and vomiting. On arrival, his blood pressure was 104/55 mmHg, his pulse rate was 32 beats per minute (bpm), and his body temperature was

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37.1°C. On examination, he was fully conscious, neither anaemic nor icteric, with a slow heart beat and breathing at a rate of 22 breaths per minute. Pulse oximetry revealed 99% blood oxygen saturation. His abdomen was flat without tenderness, with normoactive bowel sounds. No pre-tibial pitting oedema was found. A bruise area of about 4 cm x 5 cm was noted on his left forearm. The patient recalled a recent accidental blunt contusion as the cause of the dermal ecchymosis.

An erect chest X-ray radiograph revealed normal heart size and bilateral clear lung fields. Initial blood tests revealed the following findings: glucose, 6.49 mmol/L; white blood cell counts, 9.1 x 10^9/L; hemoglobin, 145 g/L; creatinine, 88.4 µmol/L; blood urea nitrogen, 7.25 mmol/L; sodium, 137 mmol/L; potassium, 4.4 mmol/L; magnesium, 0.25 mmol/L; ionized calcium, 1.29 mmol/L; troponin I, 0.02 µg/L; B natriuretic peptide, 15 ng/L; aspartate transaminase, 0.47 µkat/L; alanine transaminase, 0.4 µkat/L. Electrocardiogram showed sinus bradycardia. Serum digoxin level (TDx analyzer, Abbott Laboratories) was found to be 4.24 nmol/L.

Further interrogation of the patient eventually disclosed ingestion of a Chinese herbal medicine known as *Panax japonicus* (Fig. 1) several hours before the onset of his symptoms. The Chinese herbal practitioner reported prescription for *Panax japonicus* for the removal of the patient's bruise on his left forearm.

Interestingly, perplexing questions arose when the emergency physician was informed of (1) the non-existence of digoxin in the prescribed *Panax japonicus* by the experts of Chinese herbal medicine, and (2) the denial of consumption of any other prescribed conventional medications (e.g., digoxin) by the patient. Subsequent cardiac sonographic studies demonstrated normal structures and performance of his heart. Laboratory tests follow-up revealed progressive decrease of serum digoxin levels corresponding to the increasing of the patient's heart rate with a gradual restoration to normal sinus rhythm (24 hours after admission: digoxin level, 3.36 nmol/L → heart rate, 55 bpm; 36 hours after admission: digoxin level, 1.85 nmol/L → heart rate, 67 bpm) (Fig. 2a-c).

FIG. 1: *Panax japonicus*

In order to clarify the aetiological mechanism, we looked up the official database of Chinese herbal medicine for the ingredients of *Panax japonicus.* The database confirmed that digoxin does not exist in this plant, instead various types of ginsenoside (Rd, Re, Rg1, Rg2) are present. Ginsenosides are structurally similar to digoxin[5] (Fig. 3). Such structural similarities were reported to contribute to the false-positive detection of digoxin by fluorescence polarization immunoassay in patients using

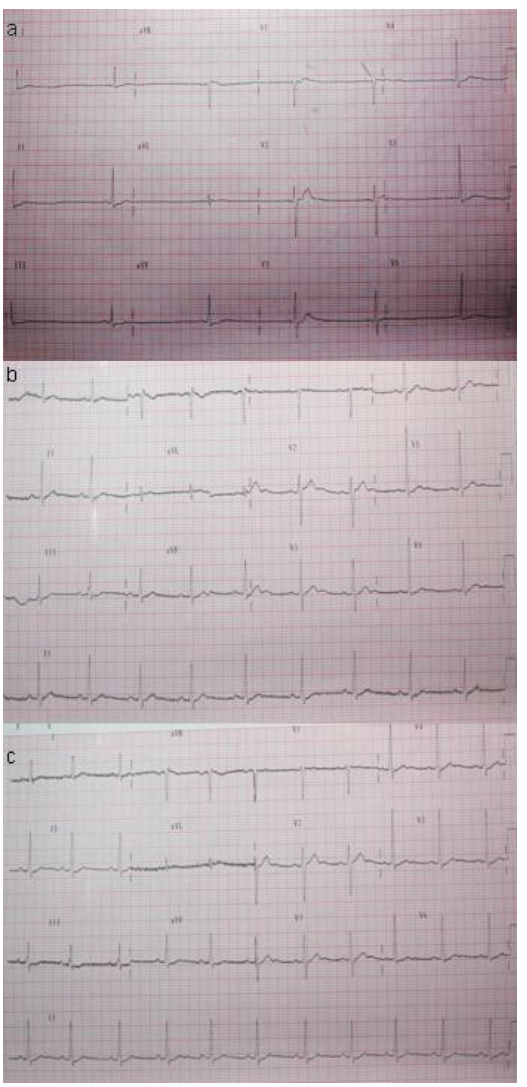

FIG. 2a–c: Electrocardiographs recorded showing progressive increase of the patient's heart rate corresponding to the gradual decline of apparent digoxin levels detected

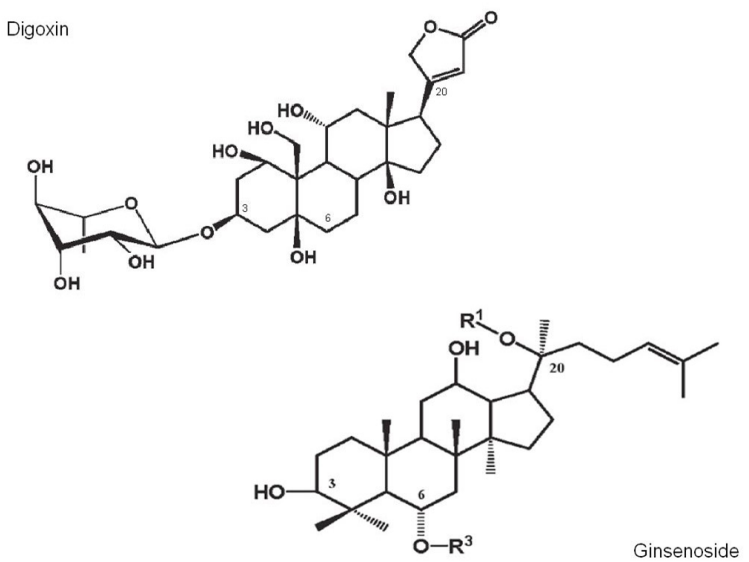

FIG. 3: Similarity between chemical structures of ginsenoside and digoxin

Asian, Siberian, and Indian ginsengs which contain ginsenosides.[6-9]

Polyclonal antibody is used in the fluorescence polarization immunoassay and due to its poor specificity, it is found to have a high false positive rate caused by digoxin-like substances produced endogenously or from exogenous sources such as traditional Chinese medicines. So far, this is the first reported incident of such misleading cross-reactivity after consumption of *Panax japonicus*, and bradycardia caused by the digoxin-like effect of ginsenosides after ingestion of this particular Chinese herb has not been reported before.

DISCUSSION

Consumption of ginsenosides can cause false-positive reading in serum digoxin fluorescence polarization immunoassay due to their cross-reactivity. Ginsenosides are not the only type of digoxin-like substances reported, other examples are spironolactone and bufalin which also bind to Na^+/K^+–ATPase and cross-react with antidigoxin antibody in a similar manner. With full awareness of this fact, emergency physicians could certainly be less bewildered by these misleading laboratory findings. Furthermore, although the chemical structures of digoxin-like substances (e.g. ginsenosides, spironolactone and bufalin) are similar to digoxin, unlike the poorly protein-bound (25%) digoxin, most of these digoxin-like substances are strongly protein-bound (80–90%) in human serum. It is a highly recommended trick-of-the-trade to minimize or even eliminate the digoxin-like substance interference by centrifuging the specimen at 1,500 g to 2,000 g in an ultrafiltration device for 20 to 30 minutes to obtain the protein-free ultrafiltrate before analyzing it by immunoassay.[10-13]

It is common standard practice to treat digoxin overdose patients who suffer from bradycardia with haemodynamic instability with digoxin-specific antibody fragments. As it has been reported that digoxin-specific antibody fragments are capable of binding the free digoxin-like immunoreactive components of the Chinese medicines Lu-Shen-Wan and Dan Shen,[14] it is reasonable for us to explore the potential in developing a novel use of an old drug. To date, although there are no officially approved means of treatment for patients who suffer from overdose of ginsenosides or other digoxin-like substances, the administration of digoxin-specific antibody fragments might prove to be another trick-of-the-trade for reversing the adverse condition. Dasgupta *et al* have reported attenuation of the effect of Brazilian, Indian, Siberian, Asian, and North American ginseng upon immunoassay of serum digoxin by the binding of digoxin-like immunoreactive components of ginseng with Fab fragment of antidigoxin antibody (Digibind).[14] In addition, recent advancement in therapeutic drug monitoring techniques, like chemiluminescent microparticle immunoassay and particle-enhanced turbidimetric inhibition immunoassay may have different cross-reactivity and may lead to a different outcome. Dasgupta *et al* reported

that the Tina-Quant (Roche, Indianapolis, IN) and the Synchron LX digoxin assay (Beckman, Brea, CA) are not subject to interference by cross-reactivity with digoxin-like substances found in Chinese herbs like Dan Shen.[14]

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