Case Reports

'Outfoxed' – Out of Season

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Teaching points
1. The principle cardiac glycoside in *Digitalis purpurea* is digitoxin.
2. Serum digoxin levels in cases of plant poisoning is semi quantitative because of the presence of a cocktail of cross reacting cardioactive glycosides and their mtabolites.
3. In cases of toxic over dose with digitalis glycosides, bradycardia may be more due to their direct effect on the conducting tissue and hence not fully reversible with atropine.
4. Following plant poisoning prolonged monitoring for arrhythmias and repeat doses of digoxin-specific antibody fragments (Fab) may be required due to prolonged half lives, and late appearance of, cardioactive metabolites and their differing immune-reactivities to Fab.

Case Report

A 65 year old woman presented to the Emergency Department of our district general hospital three hours following ingestion of a blended mixture of apples and foxglove leaves, mistaking them for spinach leaves. She complained of nausea, vomiting, abdominal cramps, dizziness and blurred vision.

On examination in the Emergency Department, she was in atrial fibrillation with a heart rate of 35 beats per minute. Blood pressure was 130/50mmHg. Temperature was 36°C. She had a murmur consistent with mitral stenosis. Examination was otherwise unremarkable. Routine haematology and biochemistry blood tests including urea and electrolytes, were normal. A blood sample was sent for measurement of serum digoxin concentration. This revealed a value of 7.41ng/ml by particle enhanced-turbidimetric immunoassay (Multigent Architect/Aeroset Abbott Diagnostics:therapeutic range 0.8–2.0). Digoxin specific antibody fragments (Digibind® Glaxowellcome) were administered at a dose of 380mg in 50ml of normal saline over one hour. Eighteen hours post-ingestion, she remained in atrial fibrillation, at a rate of 30 per minute.

Symptomatic bradycardia continued 24 hours post ingestion, despite Atropine (Fig 1, strip a and b), necessitating temporary venous pacing. There were also occasional episodes of ventricular trigemini (Figure 1 strip c). Trans-thoracic echocardiography revealed mild mitral stenosis and a dilated left atrium (4.08cm).

At day 16, atrial fibrillation with slow ventricular response continued. (Figure 1, strip d) A permanent pacemaker was inserted due to persistent symptomatic bradycardia.

However at this time, the serum digoxin levels had reached sub therapeutic levels (0.4–0.7ng/ml).

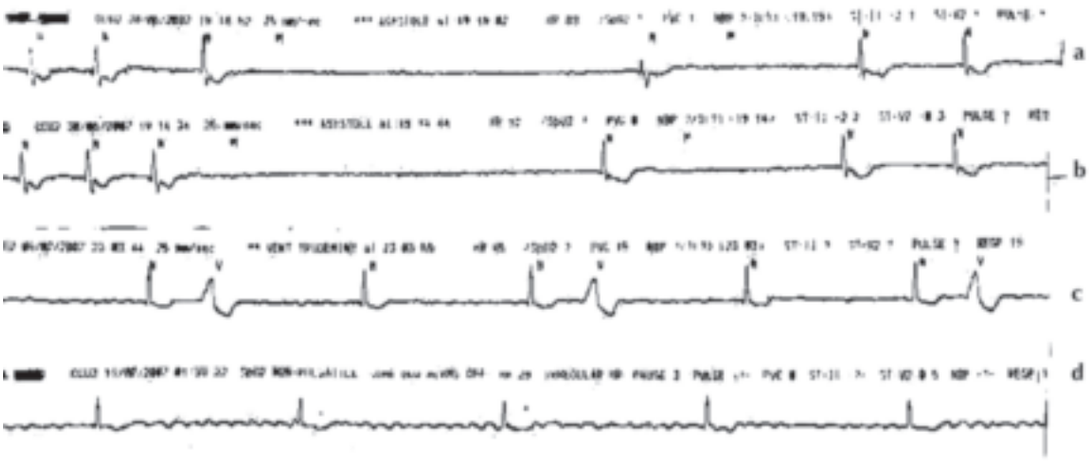

Figure 1. Rhythm strips.

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'Outfoxed' – Out of Season

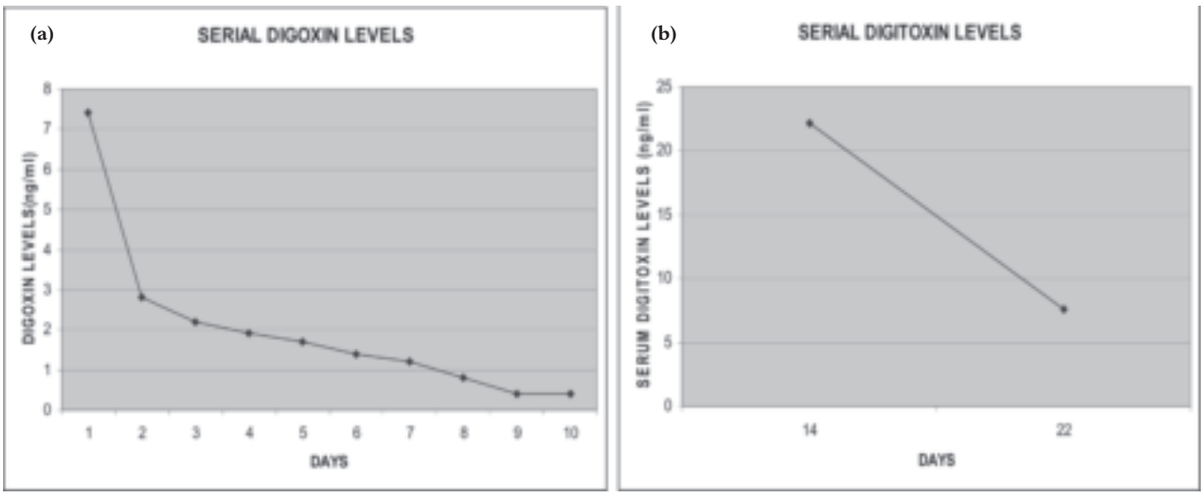

Figure 2.(a) Serial serum digoxin levels. (b) Serial serum digitoxin levels.

(Figure 2a). Measurement of serum digitoxin level by Electro-chemi-luminescence immunoassay, on day 14 was 22.2ng/ml (ref range 9–31 ng/ml).

Our patient was subsequently discharged on day 22. Digitoxin levels at time of discharge were 7.6ng/ml (ref range 9–31 ng/ml), (Figure 2b).

Discussion

This case illustrates the clinical effects of *Digitalis purpurea,* poisoning in a patient with atrial fibrillation and mitral stenosis.

In the absence of characteristic flowers in the pre-flowering phase (Figure 3c), the plant can be easily mistaken for a number of other plants such as dandelion[1] and common comfrey[2] or spinach, as in our patient. Patients have consumed tea made with *D purpurea* leaves as a herbal "heart tonic."[3,4] Accidental poisoning with *Digitalis lanata,* has occurred after consumption of herbal products marketed as "internal cleansing agents".[5,6] Para-suicidal ingestion of *D purpurea* leaves has been reported.[7,8]

Interestingly while *D purpurea* so called after its purple coloured flowers (Figure 3a), does not contain any digoxin, our patient showed an initial serum 'digoxin' level of 7.4ng/l. Digoxin comes from *D lanata,* (the woolly foxglove), *D grandiflora,* and *D orientalis,*[9] while the principle cardiac glycoside in *D purpurea* is digitoxin.

The Multigent Digoxin assay is based on the principle of competitive agglutination. Digoxin in the serum sample and the digoxin coated onto a micro-particle compete with each other for antibody binding sites of the digoxin antibody present in the reagent. The digoxin present in the sample partially inhibits the agglutination reaction between the antibody and the digoxin coated onto the micro-particle. This inhibition leads to a slow down in the rate of absorbance change which can be measured photometrically and is directly proportional to the rate of agglutination of the particles. Although the antibody used in the reagent is a monoclonal antibody raised against the digoxin-albumin complex in mice, it still cross reacts with other cardio-active glycosides. The percent cross reactivity of the assay with digitoxin is 3.1%.[10]

The apparent digoxin in our patient was the result of the cross reacting antibody used in the immunoassay detecting other cardiac glycosides and their metabolites present in the *D purpurea* leaf.

Figure 3. (a) Digitalis purpurea. (b) Digitalis lanata. (c) Pre flowering phase.

The failure of atropine to reverse the symptomatic bradycardia in our patient is noteworthy and has been reported by other researchers.[3,8] Digoxin slows down conduction across the AV node by increasing the vagal tone and hence its effects should be reversible with atropine. However, digoxin at toxic doses depresses the AV node conduction directly, an effect which is not reversible with atropine. This may account for the inconsistent therapeutic effects of Atropine in a significant overdose with digitalis glycosides.[11]

The role of digoxin specific antibody fragments (Fab) is established in overdose with medicinal digitalis.[12] Experiences with plant derived poisons have yielded mixed results. Rich AS *et al.*[7] reported a case of a 22 year-old man who consumed a large amount of foxglove extract. Bradycardia continued despite repeated doses of digoxin specific Fab, which improved in parallel with the declining levels of digitoxin over 11 days.

Digoxin specific antibody fragments (Fab) are products of papain treated immunoglobulin G (IgG) collected from a large number of sheep immunized with digoxin-albumin conjugate. Treatment of the intact IgG with papain cleaves off the Fc fragment from the antibody making it less immunogenic and readily filterable by the glomerulus. Following intravenous administration, digoxin specific antibody fragments immediately bind to intravascular free digoxin, and then diffuse into the interstitial space to bind all free digoxin there. This creates a concentration gradient which drives the tissue bound digoxin into the intravascular space, thereby reversing the deleterious effects of massive Na/K pump inhibition.[13]

Reversal of digitalis toxicity with Fab is rapid. Spiegel and Marchlinski reported restoration of sinus rhythm within 30 to 45 minutes following termination of the antibody infusion.[14] Following administration of Fab, the total serum digoxin levels rise to approximately 10 to 30 times pre-treatment levels.[13] Remarkably, these effects were not observed in our patient**.**

Possible reasons for poor response could be the presence of a number of different biologically active cardiac glycosides in the plant[9] each with differing specificities for Digibind®.[15,16]

The prolonged symptomatic and bradycardic in-hospital course of our patient which remained unchanged after Digibind® can also be explained by a long half life of digitoxin(6 days),[11] and by the fact that it undergoes enterohepatic circulation.[5] Moreover the affinity of Fab for digitoxin is 30 to 100 times less than for digoxin.[15] The serum digitoxin level in our patient on day 14 was 22.2ng/ml. Electro-chemi-luminescence immunoassay used for measuring digitoxin levels employs a sheep polyclonal anti-digitoxin antibody and therefore cross reacts widely with other cardio-active steroids and their metabolites. Therefore it is likely that the value of 22.2 ng/ml does not represent only digitoxin levels.

The calculation of Fab dose required to neutralize the total body digoxin burden is based on the steady state digoxin concentration or an accurate knowledge of the amount of digoxin consumed. In cases of plant poisoning, accurate estimation of ingested dose is impossible and the serum concentrations are semi quantitative, and thus correlate poorly with the degree of clinical toxicity.[16] The use of a single empirical dose of Fab has shown mixed results in cases of plant poisoning.

Nancy R S *et al.*[5] reported a poor response to 380mg of Digibind® in a 23 year old woman who ingested an "internal cleansing & agent contaminated with *D lanata,* and presented with complete heart block.

Other researchers have reported favourable response with 380 mg of Digibind® after *Digitalis purpurea* leaf poisoning[3] or in cases where the original compound was unknown.[6]

To our knowledge no dose-finding studies or randomised controlled trials have ever been conducted on patients with foxglove poisoning. The largest placebo controlled randomised trial on the use of digoxin specific antibody fragments in cardiac glycoside poisoning of plant origin has been reported from Sri Lanka by Eddleston M *et al.*, in cases of para-suicidal yellow oleander poisoning.[16] These researchers also conducted an open label dose finding study. 1200mg dose was chosen for its consistent therapeutic efficacy for the trial. Whether a higher dose or repeated doses would have resulted in a favourable response in our patient remains unknown.

Conclusion

While herbal medicines can be beneficial in selected cases, unsupervised use of herbal remedies such as foxglove can be potentially life-threatening. Moreover the treatment of toxicities with plant poisons can be challenging. Difficulties include establishing the diagnosis and correctly identifying the ingested plant, accurate estimation of the dose ingested, the poor correlation between serum levels of the poison and clinical manifestations, the semi-quantitative nature of the assays and the less than perfect neutralizing ability of the available antidotes. Gardeners and herbalists should be encouraged to take great care not to confuse foxglove with other less toxic plants, particularly in the pre-flowering phase.

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