Learning from errors

Digoxin – ‘A friend or foe’

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Summary

The authors report about a patient who was admitted after developing nausea, vomiting, change in vision and lethargy. She was on digoxin 250 mcg once daily among all her other medications in the wake of a recent stroke that was accompanied by atrial fibrillation (AF). Her digitalis levels shortly before and on admission were 3.4 and 2.9 ng/ml, respectively. Her admission rhythm was slowly conducted AF at an average of 35 bpm. After a careful assessment by the cardiology consultant in charge, she received Digibind infusion for a chronic digitalis toxicity with the digoxin immune Fab dose based on the formula recommended in the product literature.³ A few days observation on the ward ensured that her resting heart rate rose to 65 bpm and that she did not need a pacemaker for a slow AF. Her functional status remained reasonably good as she enjoyed a satisfactory recovery postthrombolysis for her recent stroke.

BACKGROUND

The patient's condition and life had already been affected to a significant degree by her recent stroke. Despite her adequate recovery thanks to the timely thrombolysis she received, her presentation with the digoxin intoxication impacted her further in a negative way. The circumstances surrounding her case included an advanced age, impaired renal function and a greatly increased thrombo-embolic risk related to atrial fibrillation (AF). In fact, in a short space of time, she suffered both the most dreaded complication of AF, namely a stroke, and consequently digoxin toxicity.

CASE PRESENTATION

This case involves a septuagenarian lady who had had a stroke 1 month before this admission but her presentation on this occasion included different symptoms. This 76-year-old lady's stroke was related to her AF and she also had underlying renal impairment (CKD 3) and hypertension. Therefore, with a resultant risk of thrombus formation equalling seven based on the CHA₂DS₂-VASc, she had strong indications for receiving anticoagulation. She lived on her own and managed to mobilise well with a walking frame. With regard to her medical history, she has had long-standing arterial hypertension, breast cancer in 2005 (underwent surgery) and osteoarthritis (also requiring surgery).

The hospitalisation of this patient came after she developed some typical features of a digoxin excess: malaise, change in vision (disappearance of colour vision), vomiting, diarrhoea and loss of appetite. Importantly, she received a prompt assessment by her general practitioner (GP) including blood tests with a digoxin level. Consequently, the discovery of a digoxin level of 3.4 ng/ml (reference at our institution 0.8–2.0) led to her referral to the medical team on call at the local DGH. Her initial physical assessment demonstrated blood pressure within the normal range but her heart rate was in the interval of 35 to 38 bpm as a result of slow AF (figure 1). In addition, her right lower leg evinced erythema and warmth to the touch. Connecting these two admissions, she had developed a large haematoma in the right-lower leg during the hospital stay for

her stroke postthrombolysis. Otherwise, the examination of her other systems showed only irregular heart sounds and an increased body mass index (about 100 kg). Also, her admission medications included amlodipine 5 mg once daily, lisinopril 5 mg once daily, indapamide SR 1.5 mg once daily, simvastatin 40 mg once daily, clopidogrel 75 mg once daily, bisoprolol 2.5 mg once daily, digoxin 250 mcg once daily, omeprazole 40 mg once daily and erythromycin 250 mg four times a day which was prescribed by her GP for the right-leg cellulitis. The admission blood tests manifested a creatinine of 117 micromol/l (stage 3 CKD) and once again a raised concentration of digoxin at 2.9 ng/ml. Her status was deemed stable and it was only on the next morning when the consultant cardiologist on call decided to offer her a ‘Digibind’ infusion. The rationale for the use of digoxin antibodies included her symptoms of intoxication and the consideration of a large amount of digoxin present in our patient. The aim was to segregate the accumulated quantity of digoxin in a quicker and more efficient method.

Just a couple of months before these events, it came to light that her heart rhythm was AF and the ventricular rate was about 150 bpm. This preoperative assessment with the aim of having an orthopaedic surgery resulted in the cancellation of the procedure and the arrangement to see a cardiologist. Certainly, her initial combination of medicines included digoxin 250 mcg and bisoprolol 2.5 mg. All the same, after about 2 weeks her attending cardiologist reduced the dose of digoxin to 125 mcg and in addition her echocardiogram showed only slight enlargement of the left atrium (4.55 cm) with normal size and function of the left ventricle and no left-ventricular hypertrophy. There was no significant valvular pathology either. Furthermore, the patient's heart rate never rose above 100 bpm during her preceding hospital stay for a stroke and the timeline shows that she had to be re-admitted with digoxin toxicity 14 days after discharging her poststroke and 28 days on a dose of 250 mcg of digoxin. The doubling of the digoxin dose from 125 to 250 mcg happened while she was recovering from her stroke in hospital and apart from the changes made on her drug chart no comments have been

Figure 1 (A, B) ECG recordings at admission (ECG1) and prior to discharge (ECG2).

recorded in her notes concerning this medication dose alteration.

Concerning digoxin, it is well known that this medication has a large apparent distribution and hence a high tissue concentration (4–7 l/kg). The key fact of digoxin metabolism is that it accumulates predominantly in organs like heart, liver, kidney, skeletal muscles and intestine. Furthermore, the ratio of heart to serum concentration is 70:1. Its metabolism involves only a minor degree of

hepatic conversion (16%) and a fraction of 50% to 70% is renally excreted. The half-life elimination of digoxin is 36 to 48 h with duration of action in adults of 3 to 4 days.^{1 2} Regarding ‘Digibind’ (or antidigoxin Fab fragments of ovine origin), its affinity for the digoxin molecules is greater than that of digoxin for its cardiac receptor (Na K ATPase). Digoxin immune Fab has a plasma half-life of 15 to 20 h and has a distribution in both serum and extra-cellular space.^{3 4} The dose of digoxin immune Fab was calculated using the

Figure 2 Digoxin level over the course of hospital admission.

formula advised for cases of chronic therapy and a known digoxin concentration:

$$\text{Dose in vials} = \frac{\text{Digoxin concentration (ng/ml)} \times \text{Weight (kg)}}{100^3}$$

With a weight of about 108 kg and a digitalis level of 2.9 ng/ml, the dosage of digoxin-specific antibody fragments was approximated to three vials or 114 mg of Digibind. This total dose of three vials was infused in 30 min and serial ECGs together with digoxin levels were performed at 30 min, 3 h and 6 h. The patient's blood pressure remained stable and her mean heart rate improved. In addition, the cellulitis of her right lower leg also improved on appropriate antibiotic treatment. Subsequently, she was discharged without any rate-limiting medications after ensuring that she did not need a pacemaker for a slowly conducted AF. Beside this, her GP was asked to initiate her warfarin treatment in the community following the standard approach to warfarinisation at our hospital (figures 2 and 3).

The accompanying graphs demonstrate the patient's heart rate over time and her digoxin concentration again plotted against time. It can be clearly seen how the average heart rate increases over the course of the next few days. Together with this, the level of digoxin tumbles only to reach a peak of 1.9 ng/ml 6 h postinfusion and then gradually falls to 1 mg/ml at 91 h. The initial decline in the digitalis level represents the adequate clearance of digoxin and we can see how concentration drops to about half of the first level in a matter of 36 to 48 h. Subsequently, the digoxin readings climb to another peak which is most likely the contribution of the digitalis antibodies retaining digoxin in the blood stream. In this respect, the manufacturer's Digibind information suggests that the levels of digoxin may increase steeply after the injection of Digibind. However, this should not be of concern as most of digoxin will be bound to the antibodies and hence unable to react with body receptors. Thus, it has been recommended to follow the patient's heart rate, blood pressure, ECGs and potassium plasma concentration rather than levels of digoxin after the administration of this antidote.⁴ With regard to the prolonged duration of this rebound phenomenon, it is probably the impaired renal function of this patient that accounts for the slow clearance of the digoxin-Digibind compound. Again, the product literature specifies several days for the complete excretion of the Fab fragments from the body and a week or longer for patients with impaired renal function.⁴

Figure 3 Heart rate over time.

INVESTIGATIONS

Full blood count, renal function tests, serial levels of digoxin.

TREATMENT

Employing digoxin antibody fragments; observation; treating her right-leg cellulitis with antibiotics.

OUTCOME AND FOLLOW-UP

This patient's average heart rate improved from about 35 bpm on admission to 60 bpm on discharge (figure 1). Her antihypertensive medications were continued and her GP was asked to begin warfarin treatment in the community. Her AF remained of a persistent to permanent type and no rhythm- or rate-control medications were commenced during this admission. The skin infection of her right leg improved as well. Unfortunately, the patient developed a strong allergic reaction of skin type towards warfarin as well as acenocumarol and she eventually ceased her anti-coagulant treatment after a discussion between her GP and a haematologist. Nevertheless, she remains at a high risk of developing thrombo-emboli of cardiac origin and thus newer medicines such as dabigatran (a direct thrombin inhibitor) or rivaroxiban (factor X inhibitor) could be options in her case.

DISCUSSION

Digoxin toxicity can occur either as a deliberate overdose or accidental self-poisoning but it is more commonly the result of drug accumulation over a period of time. This is usually the consequence of a conjunction of factors: widespread use of digoxin, a large percentage of older and also patients with associated renal impairment being on this drug, narrow therapeutic index, the potential for numerous interactions with other medications and increased sensitivity of the myocardial tissue to digoxin in case of electrolyte derangements. According to statistics coming from the US, about 0.4% of all hospital admissions, 1.1% of outpatients and 10–18% of nursing home residents suffer digoxin toxicity.⁵ While the overall incidence of digoxin toxicity appears to have decreased, the trend to use digoxin in the treatment of heart failure, AF and atrial flutter persists and thence the need to follow precautions when prescribing this medication.⁶

As regards the overall approach to handling a case of digitalis intoxication, a few measures can be considered.

First, managing hyperkalaemia may require infusing intravenous dextrose and insulin.⁷ Second, for the treatment of arrhythmias caused by digitalis intoxication, atropine and β blockers can be employed.⁸ In the third place, digoxin specific antibodies can be considered for significant bradycardias.⁹ And finally, simply discontinuing the digitalis medication and observing the patient may suffice.

In general, no significant consequences affect the patients treated adequately.⁹ However, hyperkalaemia and unrecognised patients with chronic digoxin toxicity have an increased mortality risk.^{10 11}

An excerpt from this patient's letter which she has very kindly provided for instructional purposes:

'After returning home, I was still in a delicate state, and had a meagre appetite. After 4 weeks of not eating, I had dropped 2 stones in weight and felt very fragile and weak. For the next several months I lived on water, fruit juices, and a lunchtime soup only. It was at least 3 months before I was able to resume my own shopping, (using my mobility scooter) and I can truthfully say that it took me at least 6 months for my life to return to any sort of normality, and yet another 6 months (12 months in all) for me to feel really well again. I have been through more than my fair share of major surgical procedures in my 77 years, including breast cancer, but this episode of drug poisoning has to rate as the worst experience of my life. I have never felt so ill, and really thought that my life was nearing its end!!'

Learning points

- ▶ The fundamental points condense to the following resume.
- ▶ Even though digoxin is a viable option in the older, its dose should be reduced in this population in order to avoid adverse drug reactions. Moreover, the therapeutic margin of this medication is narrow and adding more medicines (including antibiotics) can change the plasma concentrations of digitalis.
- ▶ The digitalis antibody fragments prove to be a reliable tool for binding and extracting a larger and unwanted amount of a digitalis glycoside.
- ▶ Prescribing digoxin and selecting a specific dose needs to be done carefully because this medication can very easily turn from 'a friend' into 'foe' even in the same person and thus add iatrogeny.

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