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Severe digoxin intoxication: a case report of the use of digoxin-specific Fab antibody fragments

Huda zastrupitev z digoksinom: prikaz primera z uporabo za digoksin specifičnih Fab protitelesnih delcev

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Abstract

Digoxin is a cardiac glycoside that has been used for several decades to treat heart failure and atrial fibrillation. Several doctors prescribe it to their patients, although it is not the first choice for either condition. In rare cases, intoxication can occur, leading to life-threatening cardiac arrhythmias. Here we report the case of an 84-year-old Caucasian woman who presented to the emergency department with dyspnoea, cough, and bilateral lower limb oedema. Eight days prior to her presentation, she had been prescribed methyldigoxin. As the patient had undiagnosed dementia and was taking medication without supervision, she ingested toxic amounts of the drug. Electrocardiogram showed the presence of arrhythmia, which resolved after using digoxin-specific Fab antibody fragments. In elderly patients, special care should be exercised when prescribing drugs with narrow therapeutic windows.

Izvleček

Digoksin je srčni glikozid, ki se že več desetletij uporablja pri zdravljenju srčnega popuščanja in atrijske fibrilacije. Številni zdravniki pogosto predpisujejo to zdravilo, čeprav ni zdravljenje prve izbire pri tej bolezni. V redkih primerih lahko pride do zastrupitve, ki lahko vodi v življenje ogrožajočo srčno aritmijo. Predstavljamo primer 84-letne ženske, ki je prišla v Urgentni center zaradi težkega dihanja, kašlja in obojestranskega otekanja nog. Osem dni pred to obravnavo je pričela zdravljenje z metildigoksinom, ki je pri bolnici z neprepoznano demenco in uživanjem zdravil brez nadzora vodilo v zastrupitev. Elektrokardiogram je pokazal prisotnost aritmije, ki je izzvenela po uporabi za digoksin specifičnih protitelesnih delcev Fab. Zato je potrebna posebna pozornost ob predpisovanju zdravil z ozkimi terapevtskimi okni pri starostnikih.

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1 Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia in adults worldwide, with an estimated prevalence between 2% and 4%. It is associated with significant morbidity and mortality and a high economic burden. Its treatment is integrated into the "ABC" pathway and under 'B' Better symptom management, ventricular rate control is a possible and important strategy for the management of patients for whom multiple medications such as beta-blockers, non-dihydropyridine calcium channel blockers, digoxin, and amiodarone are available (1).

Digoxin is a cardiac glycoside derived from the *Digitalis lanata* plant, also known as foxglove, a poisonous plant described in the literature for several hundred years (2). Digoxin inhibits sodium-potassium adenosine triphosphatase (ATPase). It indirectly causes an increase in intracellular calcium of cardiac muscle cells by acting on ryanodine receptors and subsequently forming transmembrane calcium channels and increasing cardiac contractility – inotropic effect (2-5). In addition, it causes an increase in vagal activity and a decrease in sinus node activity - negative chronotropic effect - and a prolongation of excitation conduction in the atrioventricular node – antiarrhythmic effect (2,4). In the history of cardiology, it has been widely used to treat heart failure (HF) and AF. However, there are few studies evaluating its efficacy, and some observational studies even show possible evidence of harm (1,3,6).

Digoxin has a narrow therapeutic range, which has been reduced over the last decade from 0.8 - 2.0 ng mL^{-1} to 0.5 - 0.9 ng mL^{-1}, as several reviews have shown less harm especially at levels < 1.0 ng mL^{-1} compared to higher levels (3,4,7). The recommended dosage of digoxin depends on the route of administration, but should be adjusted to the patient's renal function and serum levels (1,2). Digoxin is mainly excreted by the kidneys and has an elimination half-life of 1.5-2 days. In addition, lower body weight, hypokalaemia, hypomagnesaemia, and concomitant use of amiodarone, verapamil, macrolides, azole antifungals, and cyclosporine may result in higher digoxin serum levels due to the inhibition of P-glycoprotein transport (2,4,5).

2 Case report

An 84-year-old Caucasian woman, previously treated for HF, AF, arterial hypertension (AH), and osteoporosis, presented to the emergency department (ED) of the University Medical Centre (UMC) Maribor for shortness of breath, cough, and swelling of the lower extremities. She complained of exertional dyspnoea that had persisted for about two weeks and occurred with minimal activity. Additional information from her son revealed that she was already under the care of her general practitioner, who performed a chest X-ray (CXR) and started furosemide 40 mg twice daily, spironolactone 25 mg, and methyldigoxin 0.1 mg once daily eight days prior to her presentation at the ED. In addition, the electronic medical record confirmed that her chronic therapy consisted of vitamin D3 7000 IU per week, ferrous (III) sulphate 80 mg, perindopril/indapamide 2/0,625 mg, and denosumab 60 mg per six months.

History suggested possible memory impairment and the presence of dementia, while clinical examination revealed decreased breath sounds at the base of the right lung, cardiac arrhythmia with a systolic murmur, and bilateral pretibial pitting oedema. Her blood pressure was 150/82 mm Hg, heart rate 71 min^{-1}, and peripheral oxygen saturation (SpO2) was normal. The electrocardiogram (ECG) at the time of the ED visit showed a left cardiac axis, an irregularly irregular rhythm with no discernible P waves, ventricular rate of 71 min^{-1}, QRS complexes in pairs of two and three - possible ventricular bigeminy or trigeminy, and complete left bundle branch block (LBBB). CXR confirmed the presence of a right pleural effusion, an enlarged heart, and signs of congestion. Initial laboratory findings showed a normal complete blood count, elevated creatinine (93 µmol L-1), elevated gamma-glutamyl transferase (1.84 µkat L-1), and lactate dehydrogenase (5.94 µkat L-1), and a low estimated glomerular filtration rate (49 ml min-1 1.73m-2). No electrolyte abnormalities were present: Na 135 mmol L^{-1}, K 4.47 mmol L^{-1}, Cl 105 mmol L^{-1}, Ca 2.35 mmol L^{-1}, Mg 0.98 mmol L^{-1}. Based on the ECG changes shown in Figure 1 and the information about the newly prescribed methyldigoxin, we also tested serum digoxin levels, which were elevated to above 5.0 µg L^{-1} (reference range 0.5-0.9 µg L^{-1}). Specific values could not be determined because specialised laboratory technicians were unavailable on call. When interviewed, the patient stated that she regularly took one tablet of methyldigoxin per day but could not remember the time of the last intake. She also reported a visual disturbance with a yellow colour.

As part of the initial treatment at the ED, we prescribed furosemide 40 mg *i.v.* We consulted the toxicologist at the national poison centre in Ljubljana, Slovenia, who recommended using activated charcoal 50 g *p.o.*,

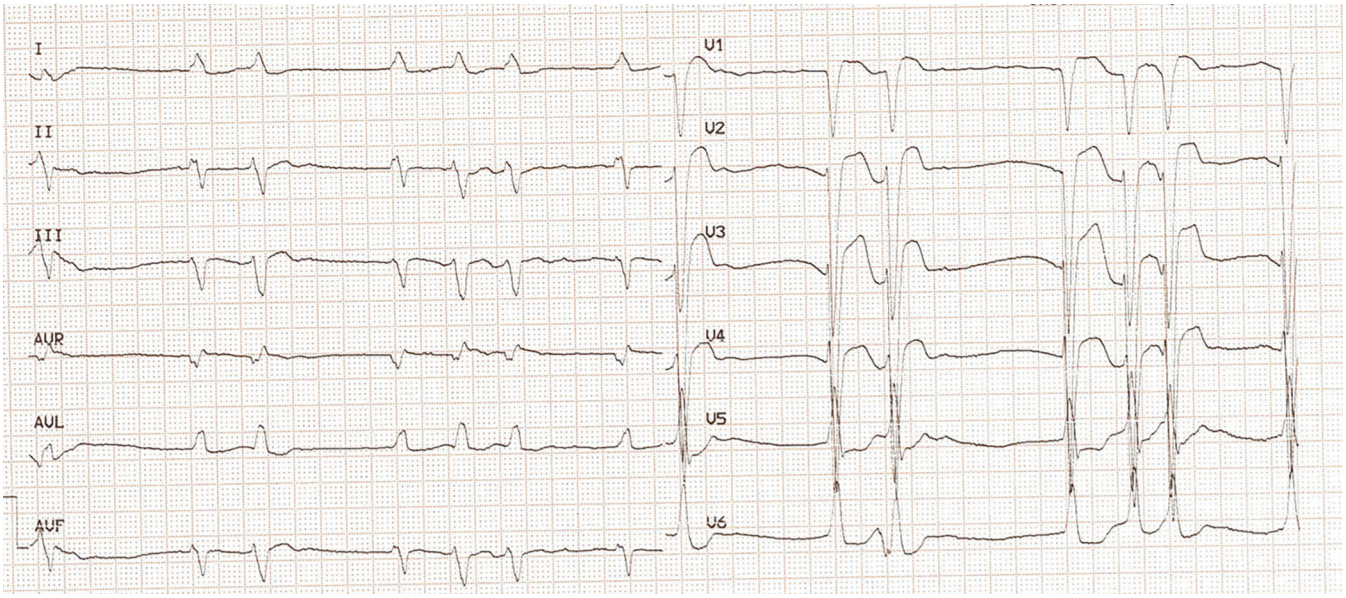

Figure 1: The patient´s ECG recorded upon presentation to the emergency department.
Source: archive of University Medical Centre Maribor, Slovenia.

lactulose syrup 10 ml (6670 mg) *p.o.*, and digoxin-specific Fab antibody fragments. The patient was admitted to the cardiac intensive care unit.

On admission, she received the digoxin-specific Fab antibody fragments (Digifab®) as instructed. Three vials (120 mg together) were diluted in 100 mL 0.9 % sodium chloride (NaCl) and infused *i.v.* over 30 minutes. In addition, she received 20 g activated charcoal *p.o.* with lactulose 4 hours after the first dose. No premedication was given before the application of Fab antibody fragments. After completion of the infusion, another ECG was recorded (see Figure 2), showing AF with a ventricular rate

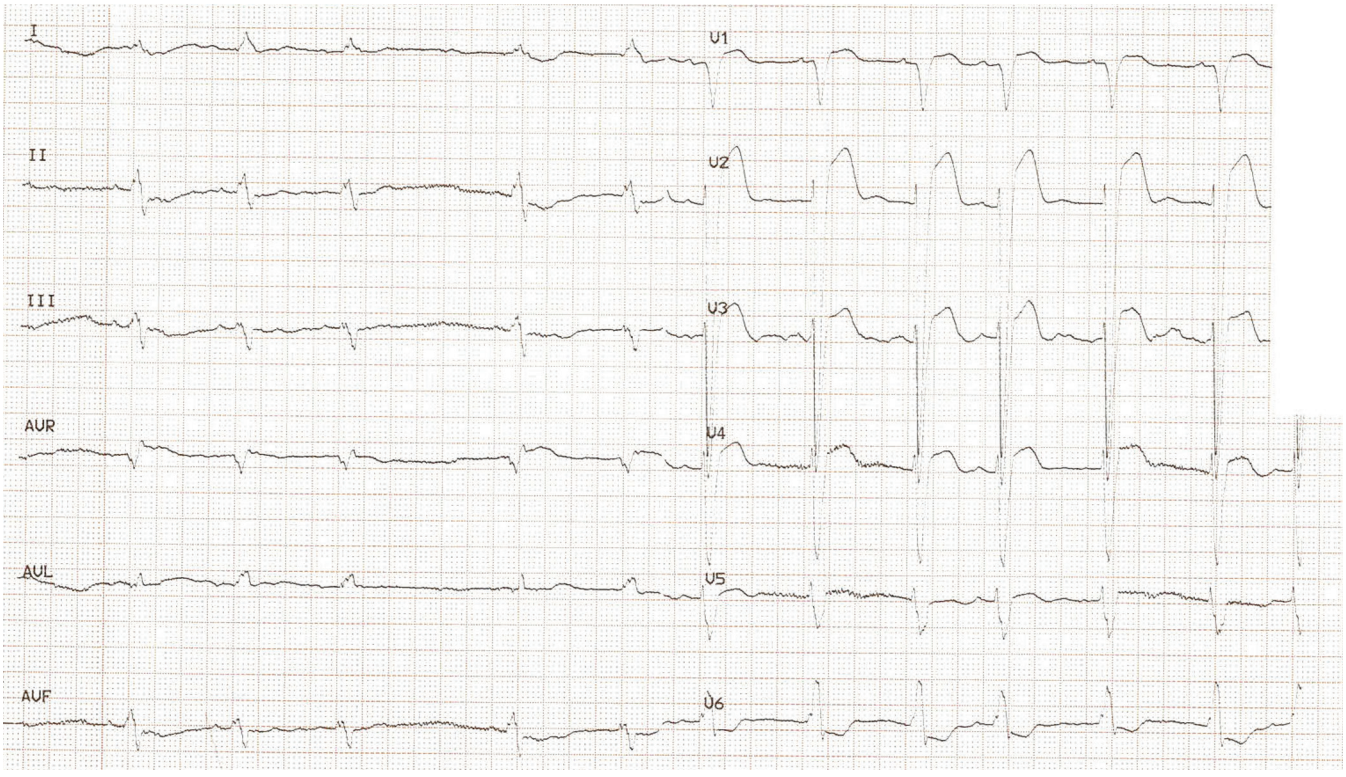

Figure 2: The patient´s ECG recorded after treatment with digoxin specific Fab antibody fragments.
Source: archive of University Medical Centre Maribor, Slovenia.

Table 1: Serial measurements of digoxin and other laboratory parameters.

Classification	1st day	2nd day	3rd day	6th day	Reference values
Digoxin (μg L^{-1})	5.26	7.26	4.1	1.8	0.5 - 0.9
Creatinine (μmol L^{-1})	93	103	103	74	49 - 90
eGFR (mL min^{-1} 1.73^{-1} m^{-2})	49	43	43	64	80 - 120
Potassium (mmol L^{-1})	4.47	4.24	3.68	3.8	3.5 - 5.3

Legend: eGFR – estimated glomerular filtration rate (CKD-EPI 2009 creatinine equation).

of 71 min^{-1}, LBBB, and resolution of QRS coupling. On admission, continuous ECG monitoring showed mild bradycardia, which later resolved and she was transferred to the Cardiology and Angiology Department ward. Serial measurements of digoxin and other laboratory values are shown in Table 1. On further discussion with her son, he pointed out that 23 tablets of methyldigoxin 0.1 mg were missing from the pack that had been prescribed eight days before admission.

Echocardiography revealed a normal-sized left ventricle with severely reduced ejection fraction (25-30%) and diffuse hypokinesia. The right ventricle was normal in size, with impaired systolic function (TAPSE 1.5 cm). Both atria were enlarged (LAVI 43 ml m^{-2}, RAVI 40 ml m^{-2}). She had mild mitral regurgitation, moderate aortic stenosis (mean gradient 35 mmHg) with mild regurgitation, mild tricuspid regurgitation, and severe pulmonary hypertension due to left heart disease with a maximum gradient of 58 mmHg. Her therapy at discharge consisted of acetylsalicylic acid 100 mg, bisoprolol 1.25 mg, perindopril 4 mg, furosemide 40 mg, and spironolactone 25 mg.

3 Discussion

This 84-year-old patient was admitted to our hospital and treated for digoxin intoxication. Considering all available information, we believe that possibly unrecognised dementia and poor participation of the patient in taking the medication without supervision may have led to the intoxication with digoxin, as she took 23 tablets in 8 days, which amounted to about 3 tablets of methyldigoxin 0.1 mg daily.

Adverse effects occur in up to 20 % of patients taking digoxin, of which about 50 % are of cardiac origin. Because digoxin slows conduction through the sinoatrial and atrioventricular nodes, patients may suffer from various arrhythmias. The most common are sinus bradycardia, atrioventricular block, and ventricular ectopy, including ventricular bigeminy or trigeminy, but atrial and junctional tachycardia with atrioventricular block, ventricular tachycardia, and ventricular fibrillation may also occur. Other adverse effects may include constipation, loss of appetite, nausea, vomiting, headache, malaise, fatigue, disorientation, yellow and green colour vision disturbances, and other visual disturbances (2,4).

The treatment of acute digoxin intoxication varies widely, as no official evidence-based guidelines exist. However, several sources agree on the indications for treatment, namely life-threatening cardiac arrhythmias, cardiac arrest, and hyperkalaemia > 5 mmol L^{-1}. In addition, treatment should be considered if there is organ damage, severe gastrointestinal symptoms, acute ingestion of > 10 mg digoxin in adults, or very high serum concentrations of digoxin >12 ng ml^{-1}. Digoxin-specific antibody fragments are the most effective treatment and standard of care (4,5). The dosage depends on whether the intoxication is acute or chronic, as chronic intoxication also leads to tissue deposition, and the use of digoxin-specific antibody fragments leads to the binding of digoxin in the serum. In the case of acute intoxication, the recommended number of vials is calculated according to the formula: 0.8 x the dose taken / 0.5. In the case of chronic intoxication and known serum digoxin concentration, the number of vials containing digoxin-specific Fab antibody fragments (40 mg) is calculated according to the following formula: serum digoxin concentration (ng mL^{-1}) x weight (kg) / 100. The dose response usually begins about 20 minutes after application and is completed after about 90 minutes. If the response is insufficient, a repeat dose should be considered after 30 minutes. The bound digoxin is later excreted in the urine with a half-life of about 20-30 hours compared to 160 hours of spontaneous elimination (4,8,9). Recently, a study was published by Chan et al. in which they suggested using small, titrated doses of 1-2 vials, which resulted in a dose reduction of 65-75% and was safe and

efficient (10). In our case, the serum digoxin concentration was > 5.0 μg L^{-1} and the patient weighed about 60 kg. We used 5.0 μg L^{-1} for approximate calculation, which meant that we needed 3 vials. We then obtained the exact value of serum digoxin, which was 5.26 μg L^{-1}. It is important to note that the effect of using digoxin-specific antibody fragments is assessed clinically and not by serial measurements of digoxin because serum digoxin is useless for diagnosing rebound toxicity, as it also measures digoxin bound to the antibodies (4). This is also evident in our case, where the patient clinically improved while the measured digoxin rose even higher on the second day. Therefore, we decided against further use of digoxin-specific antibody fragments.

Other standards of care include a temporary pacemaker for high-grade atrioventricular block, antiarrhythmic drugs such as lidocaine for ventricular arrhythmias, maintenance of acid-base status, serum magnesium, and serum potassium (4,5). Cardioversion should be avoided as it can lead to ventricular fibrillation (4). Dialysis or extracorporeal treatment is not recommended for digoxin intoxication as it does not remove digoxin. However, haemoperfusion with a beta-2-microglobulin column has shown some beneficial effects (2,11). In addition, some case reports suggest plasma therapy in addition to Fab therapy in patients with renal failure (12).

The main strengths of our manuscript are a well-documented clinical vignette of an elderly patient with dementia, with information on serial measurements of serum digoxin up to 6 days and comparative ECGs before and after the use of Fab.

4 Conclusion

Cardiac glycosides have long been known as drugs that have a place in cardiology because they have inotropic and chronotropic effects. However, studies evaluating their efficacy and long-term benefits are lacking and should be conducted. Until then, their use is at the discretion of the prescribing physician, who should try to optimise the patient's therapy with other available drugs, as cardiac glycosides are not the first-line therapy, have a narrow therapeutic window, and there is a possibility of intoxication. However, if intoxication does occur, watch for the signs and symptoms mentioned and provide appropriate treatment.

Conflict of interest

None declared.

Inform consent of the patient

The patient gave informed consent for the publication of her case.

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