Use of amiodarone and digoxin specific Fab antibodies in digoxin overdose

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SUMMARY A 61 year old man with mild aortic stenosis and chronic depression took 12.5 mg digoxin in a suicide attempt. Ventricular tachycardia and fibrillation were resistant to lignocaine and to phenytoin but responded to intravenous amiodarone, with restoration of pacing. Because of persistent hyperkalaemia he was also treated with Fab fragments of digoxin specific antibody, which bound most of the ingested digoxin.

It is suggested that the treatment of choice in severe digoxin poisoning is amiodarone for ventricular arrhythmias followed by pacing if necessary and the use of Fab antibody fragments if hyperkalaemia persists.

Digoxin overdose is an infrequent but serious medical emergency, characterised by arrhythmias, hyperkalaemia, and resistance to pacing. The overall mortality is about 20%,¹⁻³ very high serum digoxin concentrations usually being associated with a fatal outcome.⁴⁻⁷ The use of Fab fragments of digoxin specific antibody to reverse toxicity has been described recently.⁸⁻¹⁰ In addition, amiodarone may be an effective drug for controlling ventricular arrhythmias secondary to digoxin overdose.¹¹ We report a case of severe digoxin poisoning in which, for the first time, both methods of treatment were used.

Case report

A 61 year old man with a long history of depressive illness requiring previous inpatient care and electroconvulsive therapy received maintenance treatment with amitriptyline. In June 1983 he developed breathlessness and palpitation and was investigated by another hospital. An echocardiogram showed mild aortic stenosis, and 24 hour electrocardiographic monitoring showed sinus rhythm with occasional ventricular extrasystoles. Treatment was started with digoxin 0.25 mg daily and the amitriptyline withdrawn. After this he became more depressed. In November 1983 he attempted suicide by taking 50 tablets of 0.25 mg digoxin because he understood that "they would slow the heart down." One hour later no

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effect was apparent so he incised both radial arteries. The bleeding soon stopped, and he gave up his suicide attempt.

On arrival at our casualty department four hours after ingestion of the tablets he was pale but alert with no nausea. An electrocardiogram showed a PR interval of 240 ms with widespread ST segment depression. Haemoglobin concentration was 8 g/dl, serum potassium concentration 4.7 mmol/l, and serum digoxin concentration 11 µg/l. Shortly after admission, he developed ventricular tachycardia and fibrillation alternating with periods of asystole requiring 13 DC cardioversions despite the intravenous administration of lignocaine 100 mg on two occasions and of phenytoin 250 mg. During insertion of a temporary transvenous pacing wire the unstable rhythm continued and required a further 36 DC cardioversions. Figure 1 shows the rhythms recorded at this time: ventricular tachycardia, ventricular fibrillation, asystole with artefacts due to cardiac compression, and failure of pacing to capture despite maximum output (12 V).

Seven hours after ingestion of the tablets amiodarone 150 mg was given intravenously over five minutes. An electrocardiogram at this time showed restoration of pacing capture (threshold 1.3 V) and finally a regular junctional rhythm accompanied by good cardiac output (Fig. 1). A further intravenous dose of amiodarone was given (total 5 mg/kg loading dose) followed by an infusion of 900 mg over 24 hours.

Nine hours after ingestion of the digoxin tablets his cardiac rhythm was stable, but the serum digoxin concentration had risen to $14 \mu\text{g/l}$ and the serum potassium concentration to 6.8 mmol/l . It was decided to treat him with Fab fragments of digoxin specific antibody, but as there was only one batch of antibody available in the United Kingdom the anti-

Fig. 1 Electrocardiogram (lead II) showing rhythms ((a)–(d)) before and ((e)–(h)) after the intravenous administration of amiodarone 150 mg: (a) ventricular tachycardia; (b) ventricular fibrillation; (c) asystole with external cardiac compression; (d) failure of capture of pacing despite maximum output (12 V); (e) ventricular fibrillation at one minute; (f) a regular rhythm at two minutes; (g) capture of pacing (threshold 1.3 V) at three minutes; and (h) a junctional rhythm at four minutes.

body was not available for use until 18 hours after ingestion of the tablets. A test dose of 2 mg of antibody was given followed 30 minutes later by 600 mg (60 times the amount ingested assuming 80% absorption) contained in 100 ml of 5% dextrose and infused over 15 minutes.

Figure 2 shows the total serum digoxin concentrations measured from the time of ingestion of tablets (0 hours). Within 30 minutes of the administration of the test dose of antibody the total serum digoxin concentration increased 10-fold from 19 to $190 \mu\text{g/l}$ and the serum potassium concentration fell from 6.2 to 4.0 mmol/l .

Free digoxin was not detected in plasma until 47 hours after ingestion of tablets ($2.4 \mu\text{g/l}$) and declined thereafter. Urine digoxin concentration was 90–640 $\mu\text{g/l}$ in the six hours before the administration of antibody and rose to a maximum of 2470 $\mu\text{g/l}$ four hours after treatment.

The patient made an uneventful recovery from his overdose and has continued to take oral amiodarone 200 mg daily with satisfactory control of his cardiac symptoms. He was transferred for psychiatric care, treated with mianserin and psychotherapy, and is now back at work.

Fig. 2 Total (●) and free (○) serum digoxin concentrations ($\mu\text{g/l}$) at intervals after ingestion of 12.5 mg digoxin at 0 hours. Fab digoxin specific antibody 2 mg was given at 18 hours and 600 mg at 18.5 hours after drug ingestion.

MEASUREMENT OF DIGOXIN CONCENTRATION

Plasma digoxin concentrations were measured by fluorescence polarisation immunoassay (Abbott TDx); the limit of accurate measurement for this method is 0.2 µg/l. Free digoxin was measured after equilibrium dialysis.⁸ Total digoxin concentrations, after treatment with antidigoxin antibody fragments, were measured after heating the samples for one hour at 100°C and dilution with digoxin free heparinised human plasma. Plasma amiodarone concentrations were measured using high performance liquid chromatography.¹²

Discussion

The ventricular tachyarrhythmias observed after severe digoxin poisoning may be resistant to treatment. In this case, amiodarone stabilised the cardiac rhythm whereas lignocaine and phenytoin had previously been ineffective, confirming the clinical value of amiodarone in this situation.¹¹ Control of the ventricular arrhythmias was maintained by infusion of amiodarone, which produced plasma concentrations in the range of 0.6–0.8 mg/l. For comparison, chronic oral treatment with amiodarone 200 mg daily produces plasma concentrations of about 1 mg/l.¹³ The reasons for the efficacy of amiodarone in the treatment of digoxin induced ventricular arrhythmias is not clear, but in addition to the antiarrhythmic action of amiodarone it may also displace digoxin from myocardial binding sites.¹⁴ This produces an increase in the plasma concentration of digoxin¹⁵ but may possibly reduce myocardial toxicity. It is interesting to note that in our patient amiodarone also reduced the pacing threshold.

Although amiodarone may stabilise the rhythm disturbances, there remains a large body pool of digoxin to clear. Conventional methods of treatment such as haemodialysis are ineffective because the plasma is constantly replenished from a large tissue compartment. Hyperkalaemia is a sign of severe toxicity^{3,4} as it implies failure of the myocardial membrane adenosine triphosphatase pump.^{16,17} Although dialysis or glucose/insulin may reduce the serum potassium concentration in some cases, in others the concentration continues to increase and may cause fatal arrhythmias. For this reason, it is important to enhance the clearance of digoxin if hyperkalaemia is present. The effectiveness of digoxin specific antibody in clearing digoxin is shown in this and in the other cases reported.^{8–10}

We suggest that the treatment of choice for severe digoxin poisoning should be intravenous amiodarone for life threatening ventricular arrhythmias followed by pacing if bradycardia is evident and the use of digoxin specific antibodies if hyperkalaemia is present.

We thank the Wellcome Foundation for supplies of antibody and Mrs Bowman and the British Red Cross Society for transporting the antibody.

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