

Volume 35:11 November 2007 Available online at www.medicinjournal.co.uk
www.medicinjournal.co.uk

Medicine

The continuously updated review of clinical medicine

Poisoning

Part 2 of 3

POISONOUS SUBSTANCES

Acetone Sally Bradberry	581	Carbon monoxide D Nicholas Bateman	604
Amfetamines including MDMA (Ecstasy) Allister Vale	582	Chlorine Jan Meulenbelt	606
Ammonia Jan Meulenbelt	583	Cocaine Allister Vale	607
Anticonvulsants Allister Vale	585	Copper Sally Bradberry	608
Antidepressants D Nicholas Bateman	587	Corrosives D Nicholas Bateman	609
Antidiabetic drugs W Stephen Waring	590	Cyanide Allister Vale	612
Antihistamine poisoning S H L Thomas	592	Digoxin Andrew Dawson	613
Antipsychotic drugs D Nicholas Bateman	594	Ethanol Allister Vale	615
β-blockers Allister Vale	596	Ethylene and diethylene glycol Allister Vale	617
β-agonists Allister Vale	597	Gamma-hydroxybutyric acid Ruben Thanacoody	619
Benzodiazepines D Nicholas Bateman	598	Household products D Nicholas Bateman	620
Calcium channel blockers Nick Buckley	599	SELF ASSESSMENT	
Cannabis Allister Vale	603	Self-assessment/CPD Eric Beck	622

Chapter editors

Allister Vale MD FRCP FRCPe FRCPsM FRACI FRCGS
is Director of the National Poisons Information Service (Birmingham Unit) and the West Midlands Poisons Unit at City Hospital, Birmingham, UK. He is the Past-President of the British Toxicology Society, a Past-President of the European Association of Poisons Centres and Clinical Toxicologists, and a Past-Trustee of the American Academy of Clinical Toxicology.

D Nicholas Bateman MD FRCP FRCPe FRPharmacoS FRCGS
is Professor in Clinical Toxicology and Director of the National Poisons Information Service (Edinburgh Unit) at the Royal Infirmary, Edinburgh, UK. He is the Past-President of the European Association of Poisons Centres and Clinical Toxicologists.

Medicine Publishing
An imprint of Elsevier Ltd

© 2007 Elsevier Ltd ISSN 1353-3059

Poisoning Part 2 of 3

This article was published in an Elsevier journal. The attached copy is furnished to the author for non-commercial research and education use, including for instruction at the author's institution, sharing with colleagues and providing to institution administration.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>

Digoxin

Andrew Dawson

Nick Buckley

Abstract

Digoxin and other cardiac glycosides cause a large number of cardiac effects in overdose leading to both bradyarrhythmias and tachyarrhythmias. Acute poisoning is usually less severe than chronic toxicity. The specific antidote, digoxin-Fab antibodies, is expensive but effective and is generally reserved for the treatment of severe poisonings.

Keywords cardiac glycosides; digoxin; toxicity

Although this contribution focuses on digoxin, the toxicological mechanisms and treatment are similar for poisoning with digitoxin and cardiac glycoside-containing plants.^{1,2}

Mechanism of toxicity

Digoxin inhibits the Na⁺/K⁺-ATPase transport mechanism in myocardial and cardiac conducting tissue, preventing potassium transport into cells and causing intracellular increases in sodium and calcium ions.³ Automaticity and excitability with early and late after-depolarizations are thereby increased. Digoxin also causes atrioventricular (AV) nodal block and reduced conduction velocity throughout the His–Purkinje system.

Binding of digoxin to the Na⁺/K⁺-ATPase transport system is inhibited by high levels of potassium, and the activity of this enzyme is increased by the presence of magnesium. Thus, both hypokalaemia and hypomagnesaemia increase digoxin toxicity, and hyperkalaemia and hypermagnesaemia are protective.

Various other drugs may slow the AV node (e.g. verapamil, β-blockers), or may lead to hypokalaemia and hypomagnesaemia (e.g. diuretics), or alter renal clearance of digoxin (e.g. quinidine, verapamil). Sensitivity to digoxin is increased in patients with myocardial disease, respiratory disease or hypothyroidism.⁴

Andrew Dawson MBBS FRCPE is Project Director for the South Asian Clinical Toxicology Research Collaboration. His research interests include pesticides, the epidemiology of poisoning, and models of service delivery. Competing interests: none declared.

Nick Buckley MD FRACP is Associate Professor in Clinical Pharmacology and Toxicology at the Australian National University Medical School, Canberra, Australia. His research interests include clinical trials and epidemiology, and pesticides, psychotropic and cardiac drug toxicology. Competing interests: none declared.

Clinical features

Patients initially complain of nausea, vomiting and diarrhoea. In chronic toxicity, confusion and visual changes may develop. Early electrocardiogram (ECG) changes in digoxin overdose include extrasystoles and minor degrees of AV nodal block. In addition, there may be ST depression, which may mimic ischaemic changes. Bradyarrhythmias include second-degree and third-degree heart block and atrial fibrillation with a slow ventricular response. Junctional and atrial tachycardias occur; these often exhibit rates of 80–100 beats per minute and could therefore be considered accelerated escape rhythms or slow supraventricular tachycardias. Ventricular tachycardias result from increased automaticity and early and late after-depolarizations. Ventricular fibrillation may also complicate poisoning.⁵

Management

Assessment of severity – all patients should undergo urgent ECG, and electrolyte (particularly magnesium and potassium) and digoxin concentrations should be determined. In acute digoxin toxicity, potassium levels of more than 5.0 mmol/L are predictive of major toxicity. Digoxin concentrations define both the need for therapy and the dose of digoxin antibody fragments (Fab) required. However, plasma digoxin concentrations are often spuriously high in samples taken within 6 hours of ingestion, because the digoxin is in its distribution phase. Samples taken after 6 hours enable more accurate estimation of the body's digoxin burden.

Treatment – patients who have ingested an acute overdose of more than 0.1 mg/kg less than 2 hours previously should be given activated charcoal. Repeat doses of activated charcoal are of benefit following plant ingestion,⁶ and may increase elimination of digoxin.⁷ Endotracheal intubation and gastric lavage can lead to increased vagal tone and worsen bradyarrhythmia, and premedication with atropine is advisable if these interventions are undertaken.

Cardiac monitoring should be undertaken and intravenous access obtained in all patients who have ingested significant amounts of digoxin. Normal saline is the intravenous fluid of choice. Glucose may worsen hypokalaemia.

Hypokalaemia and hypomagnesaemia should always be corrected. Normokalaemia or hypokalaemia is more common in patients with heart disease who develop chronic toxicity, because of the use of diuretics and renal excretion of potassium over preceding days.

Indications for digoxin antibody fragments

Any of the following:

Life-threatening dysrhythmias

Ventricular tachycardia/ventricular fibrillation

Third-degree heart block

Cardiac compromise – in patients with underlying cardiac disease

Serum potassium > 6 mmol/L

Digoxin > 7.8 µg/L (10 nmol/L) 6 hours after acute overdose or in chronic toxicity

Table 1

Calculation of digoxin antibody fragments (Fab) dose

From dose ingested

One 40 mg vial of digoxin-Fab binds 0.6 mg of digoxin; thus, ingestion of 3 mg of digoxin requires 5 vials

From serum digoxin concentration

This method uses the estimated volume of distribution (adults 8 L/kg, children 2–10 years 13 L/kg, infants 2–24 months 16 L/kg, neonates 10 L/kg) and the measured digoxin concentration

Total body burden of digoxin = concentration in $\mu\text{g/L}$ (nmol/L \times 1.28) \times weight (kg) \times volume of distribution

Number of 40 mg vials of digoxin-Fab required = total body burden/0.6

By titration

The digoxin-Fab dose may be titrated against the clinical response; 4–6 vials of digoxin-Fab are given and further vials are administered depending on their clinical effect. This method may be more useful in patients with hyperkalaemia or heart block than in patients with ventricular tachyarrhythmias, in whom treatment is more urgent.

This contribution was adapted with permission from Buckley NA, Dawson AH, Whyte IM. *HyperTox 2006 for Windows and PDA: Assessment and Treatment of Poisoning*. www.hypertox.com

Table 2

No attempt should be made to correct mild-to-moderate hyperkalaemia, this is simply an indicator of the extent of potassium binding site antagonism, and can be monitored over time to determine if further treatment is indicated. Potassium concentrations of more than 6 mmol/L are usually present in severe acute toxicity, and are an indication for digoxin-Fab. It is controversial as to whether correction of this degree of hyperkalaemia is beneficial if digoxin-Fab is not available. Administration of digoxin-Fab is the primary treatment for all the major cardiac complications of heart block and arrhythmias (Table 1).^{8,9} If this is unavailable, heart block should be treated with pacing and tachyarrhythmias may be treated with magnesium.¹⁰ Dextrose and insulin infusion has prolonged survival in animal models of digoxin toxicity.¹¹

Digoxin-Fab – these digoxin-specific antibodies bind rapidly to digoxin, removing it from the Na^+/K^+ -ATPase pump. The Fab-digoxin complex is then excreted renally. Although total digoxin concentrations may increase manyfold, free serum digoxin concentrations decrease. The Fab-digoxin complex is excreted with a half-life of 12–24 hours (this may be greatly prolonged in the presence of renal failure).¹²

Digoxin-Fab binds to digoxin in a 1:1 ratio; thus, the total dose required depends on the amount of digoxin to be neutralized. The dose may be calculated from the known dose ingested or from

the digoxin level if the digoxin concentration has equilibrated (Table 2). In practice, complete binding of digoxin is not always required and 50% of the calculated loading dose followed by clinical review is a more economical and rational approach.¹³

Magnesium enhances Na^+/K^+ -ATPase activity without altering digoxin concentration or digoxin binding. It may be useful when digoxin-Fab are indicated but not immediately available. The calcium channel-blocking properties of magnesium make it useful in tachyarrhythmias, but may, paradoxically, initially worsen AV block in bradyarrhythmias.¹⁰

Other drugs – atropine (1 mg intravenously), repeated as necessary, should be given to all patients with bradyarrhythmia. If other anti-arrhythmic drugs are required, class 1B drugs should be used because they do not impair AV nodal conduction. Class 1A anti-arrhythmic drugs are contraindicated. Temporary pacing may be required in some patients. ◆

REFERENCES

- 1 Roberts D, Buckley N. Antidotes for acute cardenolide (cardiac glycoside) poisoning. *Cochrane Database Syst Rev* 2006; CD005490.
- 2 Eddleston M, Ariaratnam CA, Sjoström L, et al. Acute yellow oleander (*Thevetia peruviana*) poisoning: cardiac arrhythmias, electrolyte disturbances, and serum cardiac glycoside concentrations on presentation to hospital. *Heart* 2000; **83**: 301–06.
- 3 Wasserstrom JA, Aistrup GL. Digitalis: new actions for an old drug. *Am J Physiol Heart Circ Physiol* 2005; **289**: H1781–93.
- 4 Wofford JL, Ettinger WH. Risk factors and manifestations of digoxin toxicity in the elderly. *Am J Emerg Med* 1991; **9**(suppl 1): 11–15.
- 5 Ma G, Brady WJ, Pollack M, Chan TC. Electrocardiographic manifestations: digitalis toxicity. *J Emerg Med* 2001; **20**: 145–52.
- 6 de Silva HA, Fonseka M, Pathmeswaran A, et al. Multiple-dose activated charcoal for treatment of yellow oleander poisoning: a single-blind, randomised, placebo-controlled trial. *Lancet* 2003; **361**: 1935–38.
- 7 Ibanez C, Carcas AJ, Frias J, Abad F. Activated charcoal increases digoxin elimination in patients. *Int J Cardiol* 1995; **48**: 27–30.
- 8 Woolf AD, Wenger T, Smith TW, Lovejoy Jr FH. The use of digoxin-specific Fab fragments for severe digitalis intoxication in children. *N Engl J Med* 1992; **326**: 1739–44.
- 9 Eddleston M, Rajapakse S, Jayalath S, et al. Anti-digoxin Fab fragments in cardiotoxicity induced by ingestion of yellow oleander: a randomised controlled trial. *Lancet* 2000; **355**: 967–72.
- 10 Kinlay S, Buckley NA. Magnesium sulfate in the treatment of ventricular arrhythmias due to digoxin toxicity. *J Toxicol Clin Toxicol* 1995; **33**: 55–59.
- 11 Oubaassine R, Bilbault P, Roegel JC, et al. Cardio protective effect of glucose-insulin infusion on acute digoxin toxicity in rat. *Toxicology* 2006; **224**: 238–43.
- 12 Ujhelyi MR, Robert S, Cummings DM, et al. Influence of digoxin immune Fab therapy and renal dysfunction on the disposition of total and free digoxin. *Ann Intern Med* 1993; **119**: 273–77.
- 13 Bateman DN. Digoxin-specific antibody fragments: how much and when? *Toxicol Rev* 2004; **23**: 135–43.