Cardioactive drugs

Although rare, poisoning with cardioactive drugs can be serious. Each of the three classes of cardioactive drugs that may be taken in overdose presents different problems in management:

1. Beta-adrenoceptor antagonists.
2. Calcium channel blocking drugs.
3. Cardiac glycosides.

Beta-adrenoceptor antagonists

Mode of action
Beta-adrenoceptor antagonists occupy the beta-receptors and prevent the action of endogenous catecholamines. The drugs associated with the greatest toxicity are non-selective with membrane stabilising effects: for example, propranolol and those with class III arrhythmia activity such as sotalol.

Clinical features
Most patients who have taken a large dose of a beta-blocker will demonstrate bradycardia and hypotension. With very large doses there will be coma, convulsions and profound hypotension. A variety of cardiac dysrhythmias and ECG abnormalities are described. The more serious of these can result in cardiorespiratory arrest. These include:
- heart block
- intraventricular conduction defects
- ST segment elevation
- absent P waves, and
- ventricular fibrillation or asystole.

Management
Gastric lavage and activated charcoal (50–100 g) may be considered if a large overdose has been taken within one hour of presentation, although evidence of efficacy for both is poor. Atropine (600–1,200 μg) is commonly given to treat bradycardia and hypotension. If cardiogenic shock is unresponsive to atropine, glucagon is usually administered (as a bolus of 50–150 μg/kg over one minute), although its reputation is mostly based on its widespread use rather than on results of comparative trials. Glucagon activates adenyl cyclase to increase cyclic AMP production which stimulates the beta-receptors. A variety of other inotropes (eg isoprenaline, dopamine, dobutamine and phosphodiesterase inhibitors) have been used in resistant cases, and pacing is often required if the patient presents late. With the exception of propranolol overdose, convulsions are usually short-lived and rarely require treatment.

Calcium channel blocking drugs

Mode of action
Calcium channel blocking drugs act by preventing the opening of voltage-gated calcium L channels in cardiac and smooth muscle cells. This results in vasodilation, negative inotropic activity and delay in cardiac conduction. Serious problems relate to effects on the heart, so diltiazem and verapamil, which have major effects on cardiac contraction and conduction, are more likely to cause serious toxicity. Sustained-release preparations, which are widely available, produce delayed and prolonged toxicity.

Clinical features
Vasodilation, myocardial depression and heart block combine to cause profound hypotension in severe overdoses. These effects can be delayed for up to 18–24 hours if a controlled-release preparation has been ingested. Sinus bradycardia is common but in severe overdose patients can develop junctional and idioventricular rhythms which can result in asystole. Several factors are associated with a poor prognosis, including:
- old age

Management
Full resuscitation facilities should be available for all but the most trivial of overdoses. The advice given for overdoses with beta-adrenoceptor antagonists relating to gastric lavage and use of atropine also apply to calcium channel blockers. Repeated doses of activated charcoal and whole bowel irrigation with polyethylene glycol electrolyte solution for slow-release preparations have been advocated, but their value is uncertain.

Intravenous calcium is frequently used as an initial treatment in patients who have taken verapamil or diltiazem and demonstrate evidence of heart block. It is not universally effective and the dosage regimens vary widely. A commonly recommended regimen is an initial dose of 5–10 ml of 10% calcium chloride solution (0.2 ml/kg in children) infused at a rate no faster than 1–2 ml/min. This can be followed by further doses every 3–5 min if there is no response. Large doses (up to 10 g initially, 30 g in total) have been used successfully without evidence of calcium toxicity. If there is an initial response, a continuous infusion of 1–10 ml/hr (0.03–1.0 ml/kg/hr in children) of 10% calcium chloride can be given. Careful monitoring of the cardiac rhythm and serum calcium is required, but it is important to remember that a degree of hypercalcaemia is necessary for effective treatment.

Hypotension is usually best treated by volume expansion and occasionally with pressor agents. Glucagon is sometimes used to reverse myocardial depression, and isoprenaline and noradrenaline are given to increase heart rate and blood pressure. In resistant cases, ventricular...
pacing may be required. There is recent evidence that insulin-dextrose infusion may be useful in reversing hypotension, bradycardia and metabolic acidosis in patients unresponsive to conventional treatment.

Cardiac glycosides

Mode of action

Digoxin (and other cardiac glycosides) inhibit the Na\(^+\)/K\(^+\) ATPase transport mechanism in myocardial and cardiac conducting tissue. This results in an increase in intracellular sodium, which in turn reduces the release of calcium from the cell by a Na\(^+\)/Ca\(^{2+}\) exchange mechanism. Intracellular concentrations of calcium subsequently rise. The overall haemodynamic effects are:

- a relatively weak inotropic effect
- delay in conduction at the atrioventricular (AV) node and His-Purkinje system, and
- increased automaticity and excitability.

Binding to the Na\(^+\)/K\(^+\) ATPase transport system is inhibited by high levels of potassium and magnesium. As a result, hypokalaemia and hypomagnesaemia increase digoxin toxicity and increased concentrations are protective. Drugs will also increase toxicity if they:

- retard conduction at the AV node (verapamil, beta-adrenoceptor antagonists)
- reduce serum potassium and/or magnesium (diuretics), or
- decrease the clearance of digoxin (quinidine, verapamil amiodarone).

Increased sensitivity to digoxin has also been described in cor pulmonale, hypothyroidism and chronic hypoxaemia.

Clinical features

Major adverse effects of the cardiac glycosides relate almost exclusively to their effects on cardiac conduction, although nausea, vomiting, diarrhoea and visual disturbances can be troublesome. Important bradyarrhythmias include second- and third-degree heart block and atrial fibrillation with a slow ventricular response. Relatively slow junctional or atrial tachycardias also occur, while ventricular tachycardias and fibrillation can occur as a result of increased automaticity and late after depolarisations.

Management

All patients require an urgent ECG, electrolyte estimation and serum digoxin measurement at least six hours after the overdose. Hypokalaemia and hypomagnesaemia should be corrected, but no attempt made to lower the serum potassium, as this is an indicator of the severity of digoxin poisoning and can be used to determine whether antibody treatment is required.

Digoxin antibodies are a specific treatment of digoxin overdose. They are indicated for patients with life-threatening dysrhythmias (ventricular tachycardia, ventricular fibrillation and complete heart block) and/or a serum potassium greater than 6 mmol/l and/or serum digoxin level greater than 10 mmol/l six hours after overdose. Patients with underlying cardiac disease who have been receiving maintenance digoxin may be considered for antibody therapy although they may not strictly meet the above criteria. Digoxin Fab bind rapidly to digoxin, and the complex is renally excreted (elimination half-life 12–24 hours) in those with normal renal function. As digoxin Fab binds to digoxin in a 1:1 ratio, the total dose required can be calculated in one of two ways:

- from the number of tablets ingested (if known): 3 mg digoxin requires 5 \(\times\) 40 mg vials of Fab (40 mg vial binds 0.6 mg digoxin), or
- using serum concentration and estimates of the apparent volume of distribution.

Alternatively, the dose can be titrated against the clinical response, especially when heart block and hyperkalaemia are the presenting features.

In general, antiarrhythmic drugs are problematical and should be avoided if possible. Pacing may occasionally be required if there is a delay in administering the digoxin antibodies. Atropine can be given to increase heart rate, and magnesium has been shown to be useful for some tachyarrhythmias. Class IB antiarrhythmic drugs are preferred to class IA as they do not impair AV conduction.

References

Ten self-assessment questions (SAQs) based on the published articles will appear at the end of each CME specialty featured in Clinical Medicine. The questions have been validated for the purpose of CME by independent experts. Two (2) CME credits will be awarded to those achieving 80% correct answers. This opportunity is open only to RCP Fellows and Collegiate Members in the UK who are registered for CME.

A loose leaf answer sheet is enclosed, which will be marked electronically at the Royal College of Physicians. Answer sheets must be returned by 21 May 2003 to:
CME Department (SAQs),
Royal College of Physicians,
11 St Andrews Place,
London NW1 4LE.
Overseas members only can fax their answers to 020 7487 4156
Correct answers will be published in the next issue of Clinical Medicine.

*Further details on CME are available from the CME department at the Royal College of Physicians (address above or telephone 020 7935 1174 extension 306 or 309).

Q1 A male teenager presents following taking an overdose of dothiepin. The following statements are correct:
(a) Prolongation of the QRS interval predicts the occurrence of seizures
(b) Toxicity is less likely than if he had taken lophepamine
(c) Gut decontamination improves clinical outcome
(d) Haemodialysis is indicated for life-threatening toxicity
(e) Phenytoin is the treatment of choice for convulsions unresponsive to an intravenous benzodiazepine.

Q2 An elderly woman taking lithium for a bipolar depressive illness presents with vomiting, diarrhoea, lethargy and confusion. A convulsion occurs on arrival at hospital. Hyperreflexia and myoclonic movements are present. A plasma lithium concentration is 3.2 mmol/l. She had recently been prescribed ibuprofen for non-specific joint pains.
(a) It is likely that hyponatraemia is present
(b) The history of ibuprofen use is likely to be significant
(c) Phenytoin is contraindicated as an anticonvulsant
(d) The plasma lithium concentration does not justify haemodialysis
(e) A high plasma lithium concentration is clinically more serious following chronic rather than acute lithium overdose.

Q3 A recognised indication for the use of digoxin-specific antibodies in digoxin overdose is:
(a) First-degree heart block
(b) A serum digoxin level of 6 nmol/l 6 hours after injection
(c) Ventricular tachycardia
(d) Atrial fibrillation less than 50 beat/minute
(e) Serum potassium of 5.5 mmol/l.