Toxins that affect the cardiovascular system

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Introduction

Cardiotoxic effects account for a large proportion of the mortality arising from drug overdose, and many drugs can cause cardiovascular manifestations, which include effects on heart rate and blood pressure, electrocardiographic (ECG) abnormalities and arrhythmias (Table 1). This article discusses the cardiovascular management of toxicity with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), β blockers, calcium channel blockers, cardiac glycosides and tricyclic antidepressants.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Mechanism of toxicity

The ACE inhibitors block the conversion of angiotensin I to the potent vasoconstrictor angiotensin II, whereas ARBs competitively inhibit angiotensin II receptor binding. The major toxic effects of ACE inhibitors and ARBs are haemodynamic, and these are most pronounced when the drugs are taken in combination with other drugs that decrease blood pressure.

Clinical features

The onset of hypotension is rapid, usually within 1–2 hours of ingestion, and may persist for more than 24 hours.[1] In most cases, haemodynamic effects are mild,[2] but severe hypotension occasionally may give rise to acute renal failure, myocardial ischaemia and metabolic acidosis. The clinical consequences of hypotension are usually most severe in patients with pre-existing cardiovascular disease, who are less able to compensate for changes in blood pressure. Hyperkalaemia may occur as a result of impaired renal function and also perhaps as the direct effect of inhibition of ACE or angiotensin receptor blockade on renal electrolyte transport.

Management

Early management should be directed towards detecting severe hypotension and evidence of organ hypoperfusion. Patients should be monitored closely, with frequent assessment of heart rate, systemic blood pressure and cognitive state. Concentrations of electrolytes, urea and creatinine in serum, urine output, fluid balance and electrocardiographs should be monitored.

The main aim of treatment is to preserve adequate systemic blood pressure to allow adequate tissue perfusion and oxygenation. Sufficient intravenous crystalloid fluids should be given to correct dehydration and, thereafter, to maintain hydration. Severe hypotension must be determined on an individual basis, with consideration given to the 'usual blood pressure' before drug overdose. Hypotension should be considered severe when there is clinical or investigative evidence of organ hypoperfusion or when systolic blood pressure has decreased by more than 30 mmHg or is consistently lower than 90 mmHg.

If severe hypotension occurs despite adequate intravenous hydration, the use of intravenous pressor agents should be considered. This normally should be undertaken in a critical care environment, with close attention paid to fluid status, electrolyte balance and organ perfusion. Intravenous administration of angiotensin II, where available, allows systemic blood pressure to be restored after overdose with an ACE inhibitor, but it is not expected to be very effective after overdose with an ARB. Other pressor agents, such as norepinephrine (noradrenaline), exert a direct pressor effect on blood vessels and may improve systemic blood pressure. High doses may be required, and caution is needed to avoid exacerbating organ hypoperfusion. Where pressor agents are used, these are normally required only for ≤12 hours.

β adrenoceptor blocking drugs

Mechanism of toxicity

Stimulation of β_1 receptors on cardiac myocytes results in an increase in the level of cyclic adenosine monophosphate (cAMP), which promotes calcium influx via voltage-gated L-type channels.

Key Points

- **After drug overdose, cardiovascular toxicity may manifest as haemodynamic instability, electrocardiographic changes or rhythm disturbances**
- **Patients who ingest drugs with cardiovascular effects should have frequent monitoring of vital signs and continuous cardiac monitoring**
- **Glucagon may be helpful in reversing the cardiac effects of β blocker overdose**
- **Insulin and glucose treatment shows promise for calcium channel blocker overdose refractory to conventional treatment**
- **Digoxin-specific Fab antibody fragments are available to treat hyperkalaemia and arrhythmias associated with digoxin toxicity**
- **Arrhythmias that result from tricyclic antidepressant poisoning are best treated with hypertonic sodium bicarbonate rather than antiarrhythmic agents**

KEY WORDS: arrhythmia, calcium channel blocker, hypotension, poisoning, sodium bicarbonate, tricyclic antidepressants

All β adrenoceptor blocking drugs antagonise these effects and can cause serious cardiotoxicity in overdose, particularly in elderly people and those with underlying ischaemic heart disease. Non-selective β adrenoceptor antagonists and those with membrane-stabilising properties (for example, propranolol) are particularly toxic. Sotalol also blocks the delayed rectifier potassium current and delays ventricular repolarisation.

Clinical features

The main cardiac effects are bradycardia and hypotension, which may lead to syncope, pulmonary oedema and cardiogenic shock. Conduction abnormalities – for example, sinoatrial block and atrioventricular block – may occur. Sotalol may cause QTc prolongation and torsade de pointes after overdose. Seizures, delirium and coma may occur after overdose with lipid-soluble β blockers. Respiratory depression, bronchospasm and hypoglycaemia have also been reported.

Management

Administration of atropine (up to 3 mg intravenously) may be used for the initial management of bradycardia and hypotension. Isoprenaline infusion or temporary cardiac pacing may be used for resistant bradycardia or atrioventricular block. Unless the patient has pulmonary oedema, hypotension should be corrected initially with intravenous fluids, preferably with central venous pressure monitoring. Glucagon acts on glucagon receptors to activate adenyl cyclase, which leads to an increase in cAMP, which, in turn, causes an increase in myocardial intracellular concentrations of calcium, thereby enhancing myocardial contractility. Glucagon has been used successfully to treat cardiogenic shock and should be administered as an intravenous bolus of 5–10 mg.[3] Further boluses or an infusion of glucagon should be used only if there is a good clinical response. Adverse effects of glucagon include vomiting, hyperglycaemia, hypokalaemia and hypocalcaemia.

In patients with refractory hypotension, other inotropes (dobutamine, dopamine and phosphodiesterase inhibitors) and the use of intra-aortic balloon counterpulsation may help maintain an adequate cardiac output.

Calcium channel blocking drugs

Mechanism of toxicity

Calcium channel blockers (CCBs) are direct inhibitors of calcium influx through voltage-gated L-type calcium channels. Dihydropyridine-based CCBs (for example, nifedipine and amlodipine) act mainly on vascular smooth muscle and cause peripheral vasodilatation, while diltiazem and verapamil act on myocardial and conducting tissue and reduce myocardial contractility and conduction. Calcium channel blockers also reduce pancreatic secretion of insulin.

Table 1. Some drugs characteristically associated with significant cardiovascular toxicity.

Bradycardia	Tachycardia
Amiodarone	Amphetamines
β adrenoceptor antagonists	Antipsychotics
Calcium channel blockers	β_2 receptor agonists
Cholinesterase inhibitors	Caffeine
Clonidine	Cocaine
Digoxin	Ecstasy (MDMA)
GHB	Monoamine oxidase inhibitors
Opiates	Nitrates
	SSRIs
	Sympathomimetic agents
	Theophylline
	Tricyclic antidepressants
	Venlafaxine
Hypotension	**Hypertension**
Angiotensin-converting enzyme inhibitors	Amphetamines
	Cocaine
Anticonvulsant drugs	Ecstasy (MDMA)
Antihistamines	Monoamine oxidase inhibitors
Antipsychotic drugs	
β adrenoceptor antagonists	
Benzodiazepines	
Calcium channel blockers	
SSRIs	
Tricyclic antidepressants	
Venlafaxine	
QRS prolongation	**QTc* prolongation**
Tricyclic antidepressant drugs	Amiodarone
Flecainide	Antihistamines
	Antipsychotic drugs
	Azole antifungal agents
	Macrolide antibiotics
	Methadone
	SSRIs
	Sotalol
Atrioventricular block	**Tachyarrhythmia**
β blockers	Antihistamines
Diltiazem and verapamil	Antipsychotic drugs
Digoxin	Digoxin
Lithium	Flecainide
Zopiclone	SSRIs
	Thyroid hormones
	Tricyclic antidepressants
	Venlafaxine

*Heart rate-corrected QT interval. GHB = gamma-hydroxybutyric acid; MDMA = 3,4-methylenedioxymethamphetamine; SSRI = selective serotonin reuptake inhibitor.

Clinical features

Myocardial depression and peripheral vasodilatation lead to profound hypotension. Bradyarrhythmias may occur, including junctional escape rhythms, second-degree and complete heart block and asystole.

Other non-cardiovascular features include nausea, vomiting, dizziness, agitation, confusion and occasionally coma in cases of severe poisoning. Metabolic acidosis, hyperkalaemia, hypocalcaemia and hyperglycaemia may be present. Seizures have been reported.

Management

Unless the patient has pulmonary oedema, hypotension should be corrected initially with intravenous fluids, preferably with central venous pressure monitoring. In patients with significant hypotension or bradycardia, calcium chloride should be administered (0.2 ml/kg of 10% solution over five minutes), with further doses at 15-minute intervals up to a maximum of four doses. Concentrations of calcium in serum should be monitored. Increasing evidence suggests that 'hyperinsulinaemic euglycaemia' (HIE) treatment is beneficial for hypotension after overdose with CCBs by reversing the state of relative insulin deficiency and resistance and improving myocardial carbohydrate uptake, thereby switching the main substrate of metabolism from free fatty acid to carbohydrates.[3] Insulin is administered as a bolus dose followed by a glucose and insulin infusion (Box 1).[4] Anecdotal evidence supports the use of a 10 mg intravenous bolus of glucagon, which is followed by an infusion (3–6 mg/hour) in responders. Catecholaminergic agents such as epinephrine, dopamine and metaraminol may be needed to maintain an adequate cardiac output; isoprenaline infusion may worsen hypotension. Temporary cardiac pacing should be considered for resistant bradycardia or atrioventricular block.

Box 1. Overview of hyperinsulinaemic euglycaemia protocol for management of β blocker and calcium channel blocker toxicity. Adapted from Reference 4.

Check concentrations of glucose in serum:

- If <10 mmol/l, give 50 ml of 50% dextrose

Check concentrations of potassium in serum:

- If <2.5 mmol/l, give 20 mmol KCL intravenously over at least 30 minutes

Give 1 unit/kg bolus of insulin followed by insulin infusion of 0.5–1.0 unit/kg/hour titrated to clinical response

Administer 10% dextrose intravenously during insulin infusion

Check capillary blood glucose every 20 minutes for one hour and then hourly

Check concentrations of potassium in serum hourly

Target systolic blood pressure >100 mmHg and heart rate >50 beats per minute

KCL = potassium chloride.

Table 2. Method for estimating dose of Digibind needed for complete neutralisation.

Known value	Equation to estimate dose of Digibind
Dose of digoxin ingested	Number of vials = amount of digoxin ingested (mg) × 1.6
Serum digoxin concentration	Number of vials = $\frac{\text{serum digoxin concentration (ng/ml)} \times \text{weight (kg)}}{100}$

Note: dose of ingested digoxin is in milligrams not micrograms.

Digoxin

Mechanism of toxicity

Cardiac glycosides inhibit the Na^+/K^+ ATPase pump in myocardial and conducting tissue. The increase in intracellular sodium leads to reduced calcium efflux by the Na^+/Ca^{2+} exchange mechanism, which results in increased intracellular concentrations of calcium.

Clinical features

Acute overdosage usually causes marked bradycardia with PR and QRS prolongation. Sinus arrest and varying degrees of atrioventricular block with dissociation or escape rhythms may occur and cause haemodynamic instability, but more serious ventricular dysrhythmias are uncommon.

Management

A 12-lead ECG should be obtained, and cardiac rhythm should be monitored continuously. Serum electrolytes should be measured urgently, and any electrolyte disturbances (hypokalaemia or hypomagnesaemia) and acidosis should be corrected. Concentrations of digoxin should be measured at least six hours after ingestion. Atropine (1.2 mg intravenously) may be given for marked bradycardia and atrioventricular block.

Digoxin-specific neutralising Fab antibody fragments (Digibind) are indicated if hyperkalaemia is present, bradyarrhythmias are unresponsive to atropine or a patient has life-threatening ventricular arrhythmias. Doses sufficient for complete neutralisation of total body digoxin burden should be used in patients who take an acute overdose while on treatment with digoxin (Table 2), although lower doses may be effective for overdose in digoxin-naive patients and those with chronic digoxin intoxication.[5]

If digoxin-specific antibodies are not available, bradycardia or atrioventricular block unresponsive to atropine may be managed by temporary cardiac pacing, and ventricular arrhythmias may respond to intravenous magnesium (8 mmol intravenous bolus) despite a normal serum magnesium concentration.[6] The

Box 2. Pharmacological properties of tricyclic antidepressants thought to contribute to cardiovascular toxicity.

- Anticholinergic activity at autonomic nerve endings and in the brain
- Inhibition of norepinephrine reuptake at nerve terminals
- Vascular α_1 adrenergic blockade
- Cardiac sodium channel blockade (membrane-stabilising or 'quinidine-like' activity)
- Cardiac delayed rectifier potassium channel (I_{kr}) blockade
- Histamine-receptor blockade

use of class 1a and 1c antiarrhythmic drugs (for example, quinidine, flecainide and disopyramide) should be avoided, as they may worsen atrioventricular nodal conduction.

Tricyclic antidepressants

Mechanism of toxicity

Tricyclic antidepressants have complex pharmacological properties that contribute to their cardiotoxicity (Box 2).

Clinical features

Anticholinergic effects include sinus tachycardia, hot dry skin, dry mouth and tongue, dilated pupils, urinary retention and ileus. Central nervous system features include nystagmus, divergent squint, drowsiness and convulsions, which may progress to respiratory depression and deep coma. Increased tone and hyperreflexia may be present with extensor plantar reflexes, but all reflexes may be absent in deep coma. Seizures may occur, and the associated hypoxia may precipitate arrhythmias.

Delayed propagation of depolarisation in the atrioventricular node, His-Purkinje fibres and ventricular myocardium leads to prolongation of the PR and QRS interval and may give rise to ECG changes that mimic myocardial infarction (ST segment elevation and T wave inversion). The QTc interval may be prolonged because of delayed repolarisation. The most specific electrocardiographic sign of toxicity from tricyclic antidepressants is right axis deviation of the terminal 40-ms vector of the QRS complex in the frontal plane (T 40-ms axis), as indicated by an R wave in aVR, with an S wave in lead I.[7] The Brugada ECG pattern (downsloping ST segment elevation in leads V1–V3 in association with right bundle branch block) was seen in about 15% of cases of tricyclic antidepressant overdose.[8]

Management

Cardiac rhythm should be monitored continuously, and a 12-lead ECG should be performed to determine the QRS duration. Hypotension should be managed initially by administration of intravenous fluids. Seizures should be managed aggressively to minimise the risk of hypoxia.

Alkalinisation with intravenous boluses (50 ml) of hypertonic 8.4% sodium bicarbonate is the treatment of choice for arrhythmias and hypotension unresponsive to fluid administration. It should also be administered in patients who have metabolic acidosis or a QRS duration >120 ms. Further doses of sodium bicarbonate may be given cautiously until the ECG normalises or to achieve an arterial pH of 7.45–7.55.[9]

Antiarrhythmic agents (especially class Ia and Ic drugs) are best avoided if arrhythmias occur. After cardiac arrest, prolonged resuscitation may be successful and should be continued for at least one hour if appropriate.

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