The acute management of poisoning

William Stephen Waring

Abstract

Poisoning is commonly encountered in acute medical practice and can involve toxicity arising from exposure to any one of a large number of different drugs or chemicals. Clinical toxidromes can help to define particular pharmacological mechanisms of toxicity, so that appropriate treatments and antidotes can be considered. Electrocardiography and arterial blood gases are particularly important in assessing poisoned patients, and laboratory drug confirmation plays a role in some circumstances. Oral activated charcoal is capable of reducing gastrointestinal absorption of a number of drugs and chemicals. A wide range of specific antidotes are available, including acetylcysteine; generalized strategies to minimize toxicity arising from certain agents include haemodialysis and intravenous lipid administration. Poisons units provide access to specialist expertise and poisoning management advice; in the UK advice can be sought from the National Poisons Information Service online via TOXBASE or by telephone.

Keywords Acetylcysteine; antidote; clinical toxicology; overdose; paracetamol overdose; poison

Key points

- Poisoning is a common acute medical disorder; the effects depend on the type of drug or chemical and the dose
- Clinical features can help to defined the main pharmacological mechanism or mechanisms of toxicity so that appropriate antidote therapy can be considered, even if the specific chemical or drug is unknown
- Oral activated charcoal serves to minimize gastrointestinal absorption of many chemicals and drugs, and repeated doses can increase the clearance of specific drugs
- A broad range of antidotes are available for specific poisonings, and specialist advice is available via TOXBASE or telephone contact with the National Poisons Information Service

Introduction

Poisoning can present to acute medical services in different ways. Self-declared intentional poisoning is comparatively common, but patients may also present after inadvertent drug ingestion or unexpected toxicity arising from recreational drug abuse. Poisoning may not be obvious on initial presentation to hospital but become apparent where there is a cluster of cases or unexplained clinical features including coma or severe metabolic acidosis. A small, possibly unrecognized number of patients present after covert poisoning by a third party.

Poisoning and intentional drug overdose account for around 1–2% of all coded emergency department attendances in the UK. Studies show that patient reports of the ingested drug and dose correspond reasonably well with confirmatory laboratory assays, although this cannot be relied upon in every patient. Initial risk assessment aims to take account of the suspected drug or toxin, interval between exposure and presenting clinical features and laboratory investigations, which can include quantitative drug assays. Patients with suspected poisoning can be characterized as:

- low risk of toxicity and considered medically fit for discharge
- requiring periodic observation, supportive care, antidote or other treatment
- needing or expected to need intensive and invasive treatments, frequent observations and specialized life support measures, requiring management in a critical care area.

Pharmacology versus toxicology

The toxicological behaviour of certain drugs can differ from what might be expected based on the effects of therapeutic doses:

- Drug effects can persist for longer than expected. For example, the subcutaneous injection of large doses of 'short-acting' insulin causes hypoglycaemia that can persist for up to 5 days.[1]
- Toxicological effects can be irreversible. For example, therapeutic doses of β-adrenoceptor blockers can be overcome by the administration of isoprenaline via competitive binding at cardiac β-adrenoceptors. However, β-adrenoceptor blocker overdose causes covalent drug–receptor binding so that isoprenaline is ineffective.
- Tissue selectivity can be lost. For example, therapeutic doses of dihydropyridine calcium channel blockers (e.g. nifedipine) are comparatively selective for peripheral blood vessels and cause vasodilatation, whereas diltiazem and verapamil cause bradycardia and delay cardiac conduction. In the context of overdose, there is significant overlap and both calcium channel blocking actions are observed.
- 'Off-target' effects that are unrelated to the primary pharmacological mechanism can be more prominent in the context of drug overdose. Examples include QT prolongation after methadone overdose, severe ataxia after carbamazepine overdose, methaemoglobinaemia after zopiclone overdose, and serotonergic toxicity after tramadol overdose.

Toxidromes

A number of clinical toxidromes have been described. These are characterized by a cluster of clinical features that help to identify

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a pharmacological mechanism of toxicity, thereby allowing the selection of appropriate antidotes and other treatments. Some common toxidromes are summarized in Table 1.

The electrocardiogram

The electrocardiogram (ECG) is particularly valuable in poisoned patients and can give important clues to the underlying mechanism of drug toxicity. Bradycardia and complete heart block can be caused by β-adrenoceptor blockers, calcium channel blockers and digoxin. A wide variety of drugs can provoke tachycardia, including drugs that possess anticholinergic properties (e.g. tricyclic antidepressants, antihistamines) and sympathomimetic agents (e.g. amphetamine, cocaine).

The QRS duration can be prolonged by drugs capable of blocking cardiac sodium channel conductance, for example flecainide, quinine and tricyclic antidepressants (circulating tricyclic concentrations correlate with the extent of QRS prolongation). QRS prolongation is significant because it predicts the occurrence of potentially fatal arrhythmia and generalized seizures. Administration of intravenous sodium bicarbonate 8.4% allows restoration of a normal QRS duration after tricyclic poisoning, and can be titrated to achieve an arterial pH of 7.45 to minimize the risk of arrhythmia.[2] The pharmacological mechanism of sodium bicarbonate is somewhat controversial: a pH-dependent increase in tricyclic ionization in an alkaline environment causes drug-trapping in the circulating compartment, thereby lowering drug concentrations within the myocardium.

QT prolongation is a characteristic toxic feature of certain drugs, namely selective serotonin reuptake inhibitors, macrolide antibiotics, chlorpromazine and antihistamines. QT prolongation can herald an increased risk of torsade de pointes arrhythmia, particularly when QT values are higher than the QT–heart rate nomogram (Figure 1).[3] The clinical significance is that patients with QT prolongation should be monitored closely for development of arrhythmia and have electrolytes corrected; in addition, co-administered drugs that can prolong the QT interval should be avoided.

Arterial blood gas analyses and acid–base status

Metabolic acidosis is commonly encountered in poisoned patients and can be the first indication of poisoning where the diagnosis has not initially been suspected. Some recognized causes are summarized in Table 2. Treatment is directed at providing supportive care and minimizing continuing exposure to the causative agent. In some specific poisonings (e.g. aspirin, tricyclic antidepressants), correction of metabolic acidosis can reduce tissue drug concentrations, thereby minimizing toxicity.

Methaemoglobinaemia can be associated with a blue–grey discoloration of the lips and mucous membranes, which fails to respond to adequate oxygenation. It is potentially hazardous because of inadequate oxygen delivery to the tissues. A number of causes are recognized, including exposure to sodium nitrite, organic nitrites, phenol and other industrial chemicals.

Carbon monoxide poisoning may be detectable on an arterial blood gas analysis performed soon after the patient is removed from exposure. However, carbon monoxide readily dissipates from the body, so a normal analysis does not exclude the possibility of carbon monoxide exposure several hours previously. Analyses require cautious interpretation because healthy people can have low concentrations of arterial carbon monoxide, typically 1–5%, and recent tobacco smoking can cause carbon monoxide concentrations of up to 10%.

Paracetamol (acetaminophen)

Paracetamol is the most common means of self-poisoning in the UK (and many other countries), implicated in around half of all patients presenting to hospital after intentional overdose.

Selected toxidromes with common features and causes

Toxidrome	Characteristic features	Typical causes
Opioid	Central nervous system depression, respiratory depression, hypotension, meiosis including 'pinpoint' pupils	Opioid analgesics
Sedative–hypnotic	Depression of central nervous system, respiratory depression, hypotension (in contrast to opioid toxidrome, pupil size is normal)	Benzodiazepines, ethanol, antipsychotics
Serotonergic	Agitation, acute delirium, hyperreflexia, myoclonus, tremor, fever, unstable heart rate or blood pressure, seizures	Drugs that enhance serotonin in the central nervous system, typically when combined: selective serotonin reuptake inhibitors, tricyclic antidepressants, venlafaxine, monoamine oxidase inhibitors, tramadol, linezolid, St John's wort, cocaine, ecstasy, amphetamines, novel recreational drugs
Anticholinergic	Tachycardia, dry mouth, agitation with or without acute psychosis, acute urinary retention	Tricyclic antidepressants, antipsychotics, antihistamines

Table 1

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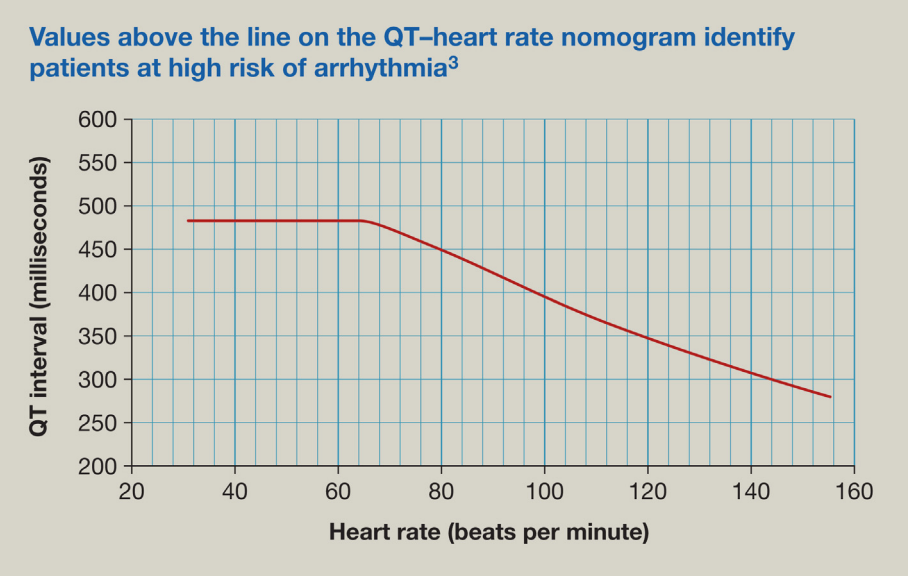

Figure 1

Acetylcysteine is an effective antidote for preventing liver failure, provided that administration can be commenced within 8 hours after overdose; its effectiveness declines if started after a longer interval.

In the UK, acetylcysteine is administered only to patients considered to be at significant risk of liver damage, which is based on an estimate of paracetamol exposure. After an acute, single time point ingestion, a timed paracetamol concentration can be compared with a nomogram to identify if the concentration is sufficiently high to indicate a need for antidote (Figure 2). The nomogram method cannot be relied upon if there have been repeated paracetamol doses or an overdose has been ingested over more than 1 hour (staggered or repeated supratherapeutic ingestion), so drug exposure is then based on the dose reported by the patient.[4] Both methods rely on the time of ingestion and quantity as reported by the patient, which can be prone to error. It is appropriate to administer acetylcysteine when there is uncertainty over the reliability of the patient's history.

Standard acetylcysteine treatment involves an intravenous infusion lasting 21 hours. The occurrence of liver damage after paracetamol overdose is delayed and may not become detectable for up to 24 hours after ingestion. Checks are normally performed at the end of the acetylcysteine infusion or 24 hours after the last paracetamol dose, whichever occurs sooner, as summarized in Table 3. If there are abnormalities indicating acute paracetamol liver injury, the acetylcysteine infusion can be continued, with reassessment every 6–8 hours and referral to a specialist liver unit where appropriate.

Recreational drug toxicity

Several hundred different chemicals have been identified as subject to recreational abuse, including classical agents (e.g. heroin, cannabis) and novel recreational drugs (e.g. synthetic cathinone derivatives). In clinical practice, it is rarely possible to establish the specific chemical substance because the 'street' name supplied by the user often fails to link to a specific chemical, and confirmatory laboratory tests are rarely available in clinical practice. Laboratory confirmation of the specific chemical is unlikely to aid acute clinical management. Broadly speaking,

Some poisonings associated with metabolic acidosis and mechanism

Mechanism of acidosis	Example
Ingestion of acidic drug (pK_a <7)	Aspirin, tricyclic antidepressant
Substances that are metabolized to anions	Ethanol, ethylene glycol, methanol
Altered liver blood flow, lactate formation	Salbutamol, paracetamol
Lactate dehydrogenase inhibition	Metformin
Impaired oxidative metabolism	Cyanide, carbon monoxide
Seizures or rhabdomyolysis	Tricyclic antidepressants, venlafaxine, antipsychotics
Acute kidney injury	Non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors

Table 2

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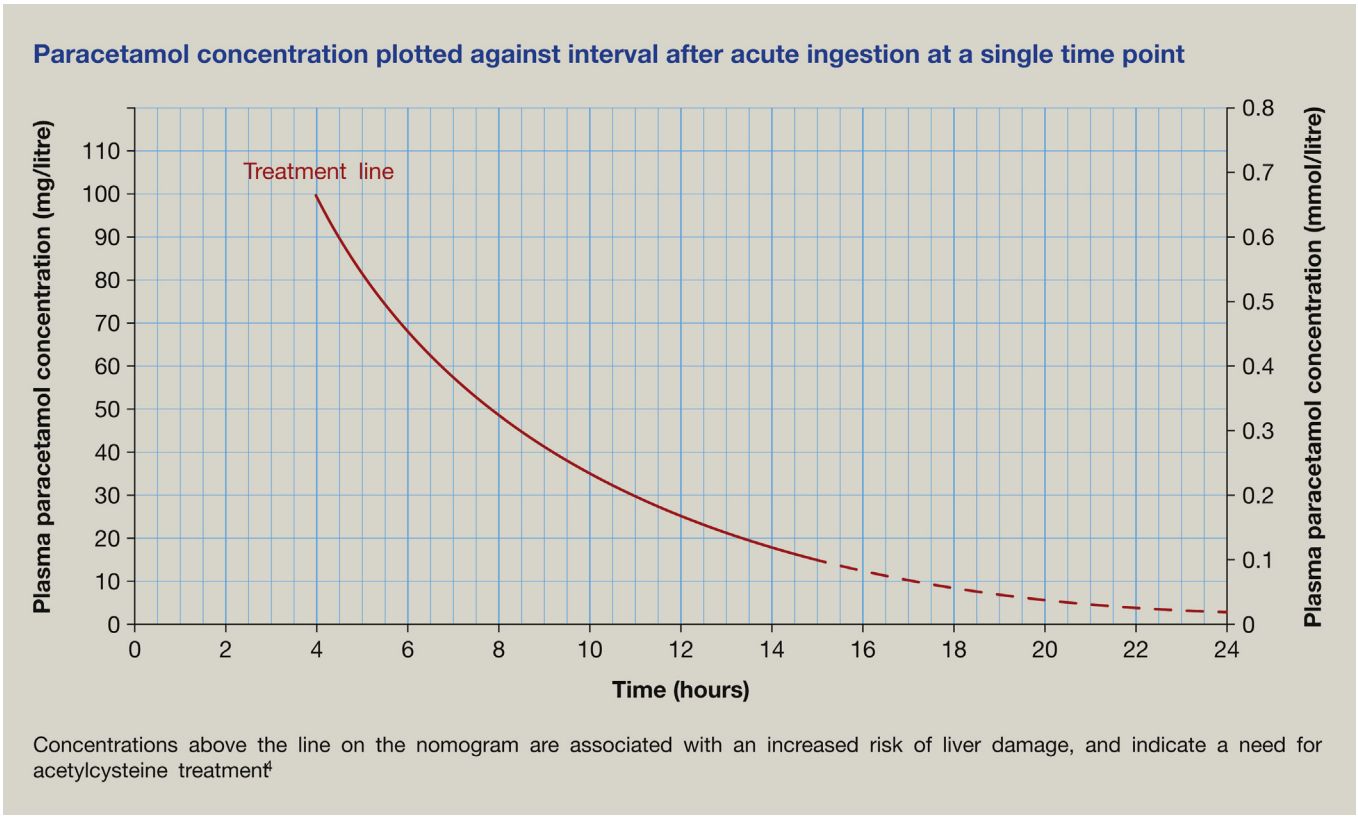

Figure 2

recreational drug toxicity can be considered as: (1) stimulant, (2) sedative, or (3) hallucinogenic.

Clinical management of stimulants normally involves the administration of benzodiazepines to control agitation, lessen muscle rigidity and control seizures; very large doses are sometimes required, and measures to protect the airway and ensure ventilation should be considered. In contrast, the management of sedative recreational drugs primarily involves airway protection, assisted ventilation, consideration of naloxone if appropriate and supportive care.

Oral charcoal administration

Oral activated charcoal is a particulate suspension with a very large surface area. It is effective in adsorbing a broad range of different drugs and chemicals, so gastrointestinal absorption is reduced and the target drug is eliminated via the gastrointestinal transit. Oral activated charcoal has been shown to reduce the extent of systemic drug exposure after paracetamol overdose, thereby lessening serum paracetamol concentrations so that fewer patients meet the criteria for being given intravenous acetylcysteine antidote. Charcoal administration is also effective in lessening the occurrence of QT prolongation on ECG after citalopram overdose.

Oral activated charcoal can be expected to reduce the gastrointestinal absorption of most drugs, although a few notable exceptions that are not adsorbed by charcoal include metals (e.g. lithium, iron) and alcohols (e.g. ethanol, methanol, ethylene glycol). Timing is important: charcoal must be administered soon after drug ingestion, usually within 1 hour of drug overdose, although it can be of benefit if given >1 hour after modified-release drug preparations or very large drug ingestions. Oral activated charcoal should be used with caution in patients with reduced conscious level because of the risk of aspiration, especially if vomiting or paralytic ileus is suspected. Charcoal can safely be administered via a nasogastric tube provided that the airway is protected, for example by an endotracheal tube.

Clinical and laboratory assessment of paracetamol overdose patients

Assessment	Outcome measures
Clinical symptoms and signs	Abdominal pain, right upper quadrant tenderness, vomiting
Liver biochemistry tests	Alanine aminotransferase increases with liver injury
Coagulation screen	Prothrombin time increases when liver synthetic function is impaired
Urea and electrolytes	Creatinine increase, which can indicate impending renal failure; hypokalaemia resulting from paracetamol-induced kaliuresis
Paracetamol	Detectable concentrations indicate delayed clearance and increased risk of liver damage

Table 3

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Multiple-dose activated charcoal

Multiple doses of oral activated charcoal can be effective in enhancing gastrointestinal drug elimination by interfering with enterohepatic recirculation, distinct from an effect on initial drug absorption. Key examples of where multiple dose therapy can be effective include carbamazepine, theophylline, quinine and aspirin. Treatment can be administered orally or via a nasogastric tube every 4 hours, and should be avoided in patients at risk of lung aspiration.

Haemodialysis

Haemodialysis is an effective means of clearing certain drugs and chemicals from the body, and allows correction of acid–base and electrolyte disturbances if these fail to respond to conventional treatments. The extent to which haemodialysis might be effective depends on the physiochemical and pharmacokinetic properties of the specific drug. Comparatively few data are available on clinical outcomes after haemodialysis in poisoned patients. Specific examples of where haemodialysis is established include severe poisoning by ethylene glycol, methanol, lithium and aspirin.

Haemodialysis is capable of enhancing the clearance of certain antidotes. For example, the frequency of fomepizole administration needs to be increased during haemodialysis, and the rate of administration of acetylcysteine needs to be increased by as much as 100% to achieve the same blood concentrations.

Haemofiltration techniques may be more readily accessible in clinical practice and are, for example, widely available within critical care departments. It is important to recognize that haemofiltration techniques can be less effective for removing drugs than haemodialysis and can be less appropriate than haemodialysis in some severely poisoned patients.

Intralipid

Intralipid (Baxter, Cambridge, UK) is a lipid-rich formulation used to provide intravenous calorific and nutritional support. It is capable of rapidly reversing the life-threatening cardiotoxicity seen after systemic exposure to local anaesthetic agents (e.g. lidocaine), and is included in resuscitation guidelines. Its mechanisms of action may include movement of drugs from the tissues to equilibrate in a larger circulating lipid pool (so-called 'lipid sink'), and restoration of carnitine-linked metabolic pathways within cardiomyocytes.[5]

There has been interest in the possibility that lipid administration might also be effective in reversing severe, life-threatening cardiotoxicity from lipid-soluble non-anaesthetic agents, but published case reports are contradictory. Despite the lack of robust outcome data, intravenous lipid administration can be considered in the setting of life-threatening cardiotoxicity where conventional treatments have been unsuccessful. A registry to collect outcome data from clinical cases has been established (http://www.lipidrescue.org).

A typical administration regimen for Intralipid 20% is 1.5 ml/kg bolus followed by an infusion at 0.25 ml/kg per minute for 1 hour, with one or two repeated boluses if asystole persists, and an increased rate of infusion depending on blood pressure response. Recognized adverse effects include local vein irritation, acute pancreatitis and electrolyte disturbances.

Outdated techniques in clinical toxicology

A number of historical methods applied in clinical toxicology have now been abandoned. For example, vomiting induced by syrup of ipecacuanha fails to minimize toxicity from ingested agents and increases the risk of upper gastrointestinal perforation and aspiration pneumonia. Forced diuresis including administration of excessive fluid volumes, intravenous bicarbonate or diuretics offers no benefit over normal hydration status, and poses risks of fluid overload and electrolyte imbalance. Gastric lavage was once widely applied to poisoned patients but offers little benefit and can paradoxically enhance the rate and extent of drug absorption. Its only role is limited to specific circumstances where appropriately skilled staff are available and patients present within 1 hour of a life-threatening ingestion of certain agents such as lithium.

Psychosocial assessment

Alongside the medical toxicological effects that require treatment, there should also be consideration of patients' psychosocial needs. Psychiatric illness is uncommon – <10% of patients who present to hospital after self-harm – and assessment by a trained psychiatrist rather than a general physician allows more sensitive detection of psychiatric illness. Only around 5% of intentional overdoses are motivated by suicidal intent, most cases instead representing an impulsive act or intense frustration. A number of general sources of support are available for patients and carers (e.g. http://www.mind.org.uk).

Sources of specialist clinical toxicology support

Clinical toxicologists have expertise in managing poisoned patients, although in the UK such specialists are currently available in only a small number of hospitals, in contrast to other medical specialties. The National Poisons Information Service provides clinical management advice regarding poisoned patients via TOXBASE, an internet-based resource that is freely available to registered healthcare professionals in the UK. It is supported by a telephone service that provides clinical management advice and is available 24 hours per day. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 36-year-old woman presented to the emergency department 3 hours after drinking a bottle of white wine and an intentional overdose involving unknown quantities of ibuprofen, tramadol, fluoxetine and propranolol.

Investigations

- Resting electrocardiogram (ECG) showed heart rate of 74 beats/minute, QRS duration of 98 ms and QT interval of 498 ms

What action would be most appropriate as a result of these findings?

A. Insertion of a pacing wire
B. Intravenous administration of magnesium
C. Oral administration of activated charcoal
D. Intravenous administration of sodium bicarbonate 8.4%
E. Intravenous administration of calcium gluconate

Question 2

A 66-year-old man was admitted 40 minutes after an intentional overdose involving citalopram, mirtazapine, gliclazide and possibly other drugs.
On clinical examination, he was alert and orientated, with a Glasgow Coma Scale score of 15, heart rate 88 beats/minute, and blood pressure 138/70 mmHg

What is the most appropriate immediate treatment?

A. Oral activated charcoal
B. Intravenous acetylcysteine
C. Intravenous sodium bicarbonate
D. Haemodialysis
E. Intravenous infusion of dextrose 5%

Question 3

A 28-year-old woman presented to the emergency department having been found collapsed in the street. There was no information on previous health problems or medications.
On clinical examination, she had a reduced conscious level (responding to voice), and there was a strong odour of alcohol. Her heart rate was 124 beats/minute, and blood pressure 154/86 mmHg. Both pupils measured 8 mm and constricted in response to light. Limb reflexes were very brisk and symmetrical throughout the upper and lower limbs, and there were three or four beats of myoclonus at both ankles.

Investigations

- Resting ECG showed sinus tachycardia with QRS duration of 76 ms and QT interval of 494 ms

Ingestion of which of the following drugs would best explain these findings?

A. Amitriptyline
B. Citalopram
C. Fexofenadine
D. Tramadol
E. Zopiclone

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