PITFALLS IN THE MANAGEMENT OF THE POISONED PATIENT

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INTRODUCTION

Acute poisoning is a common problem worldwide. In the United Kingdom (UK) it accounts for an estimated 10–20% of acute medical admissions and 5–10% of the workload of Accident and Emergency (A&E) departments.[1–4] Episodes of self-poisoning in the UK continue to rise, with the rates being among the highest in Europe.[5–7] The severity of poisoning has decreased over the past decade with the introduction of safer drugs, such as the selective serotonin reuptake inhibitors, but the total number of deaths from poisoning in the UK remains unchanged at more than 3,000 per year.[2] This paper will address common pitfalls in the management of poisoned patients where clinical management could be improved and medicolegal problems avoided.

SUPPORTIVE CARE

Supportive care is the most important aspect of the management of poisoned patients.[8] The majority of patients who present with self-poisoning develop minimal or no clinical effects, and therefore the aim is to identify as early as possible the 5% who will proceed to develop significant clinical features.[9] As a general rule, complete elimination of a drug takes approximately the duration of five half-lives of the drug and so the patient needs to be supported during this phase with monitoring for and treatment of any secondary organ dysfunction or other features that develop.[8]

The management of the airway and breathing in all poisoned patients requires special attention. Failure to ventilate the patient sufficiently early may lead to general deterioration with complications such as pulmonary aspiration.

The mainstay of gut decontamination is the administration of activated charcoal within one hour of a significant ingestion of a toxin that binds to charcoal.[10] Recent studies have shown that, in the UK, as few as 15% of patients are seen in hospital in the first hour after self-poisoning and further delays can occur during triage or while waiting in the A&E department.[11,12] It is important that those who have ingested a potentially serious overdose and have presented within one hour are rapidly identified and 'fast tracked' for administration of activated charcoal.

Multiple-dose activated charcoal (MDAC) increases the elimination of some drugs by interrupting their entero-enteric and entero-hepatic circulation.[13] The dose given is 50 G (1 G/kg in children) of activated charcoal every four hours.[13] Indications for MDAC are shown in Table 1.[13] In addition to these indications, MDAC should be considered seriously in salicylate poisoning (to prevent delayed absorption) until the salicylate level peaks.[8]

TABLE 1
Indications for Multiple-Dose Activated Charcoal.[13]

To increase drug elimination in life-threatening overdose with:

- carbamazepine
- dapsone
- phenobarbitone
- quinine
- theophylline

To prevent delayed absorption in salicylate overdose

Gastric lavage is much less widely used now. Although there have been descriptive case reports of the removal of tablet debris during gastric lavage, no clinical studies have demonstrated that this has any impact on outcome.[14] There is also the possibility that lavage may increase absorption by pushing tablets into the small intestine.[15] It can also result in hypoxia and tachycardia.[14] Gastric lavage should therefore only be considered if it can be carried out within one hour of a life-threatening ingestion and the patient should be monitored closely during the procedure.[14]

Whole bowel irrigation (WBI) with polyethylene glycol is a newer method of gut decontamination and although the current evidence for its use is based on volunteer studies and case reports, in our experience it is under-utilised in the management of poisoned patients. There are published reports describing the use of WBI in poisoning with a number of substances including iron, lithium, latex packets of cocaine in body-packers, lead and sustained-release preparations including verapamil.[16] Whole bowel irrigation is generally well tolerated, and polyethylene glycol is not absorbed and does not result in significant changes in fluid or electrolyte balance.[16] Whole bowel irrigation may be considered in potentially toxic ingestions of the substances listed in Table 2.[16] The dosage of polyethylene glycol used for WBI is 1,500–2,000 mL/hr for adults, 1,000 mL/hr for children of six to twelve years and 500 mL/hr for children six months to six years of age; it should be continued until the rectal

effluent is clear.[16] It can be given orally or via a nasogastric tube, although in practice, in view of the large volumes of polyethylene glycol that need to be administered, a nasogastric tube is almost always required.

TABLE 2
Indications for Whole Bowel Irrigation (WBI).[16]

Indications to WBI:
- Large ingestions of agents not adsorbed to activated charcoal, e.g. lithium, iron
- Body packers, i.e. ingestion of drug-filled packets
- Large ingestions of sustained release or enteric-coated drugs, e.g. calcium channel blockers

Contraindications to WBI:
- Bowel obstruction or ileus
- Significant gastrointestinal haemorrhage
- Haemodynamic instability

A record of the exact weight of patients is important in clinical toxicology: the toxic dose of many compounds is dependent on the body weight, and the dose of some drugs used to treat poisoned patients is weight-dependent (e.g. N-acetylcysteine (NAC) for paracetamol poisoning). Many patients are not weighed, and weight is frequently estimated, often inaccurately.[17] Weighing scales should be standard equipment in all clinical areas treating poisoned patients and all patients presenting after taking an overdose of any substance should have a formal body weight measurement as a standard part of their management.

The psychological aspect of the self-poisoned patient should not be forgotten. An assessment of mental state and the further risk of self-harm should be carried out in all patients who present with self-poisoning, ideally by a psychiatric nurse or psychiatrist.[8] Care for these patients is a multidisciplinary responsibility, and nurses, physicians, psychiatrists and social workers all play key roles in the rehabilitation and future management of the patient.

PARACETAMOL

Paracetamol remains the most common substance taken in overdose in the UK, accounting for 50% of all self-poisoning episodes and 100–200 deaths per year.[4,18] The vast majority of cases of early, lone paracetamol poisoning are asymptomatic at presentation; therefore management is best guided by blood tests as discussed below.[19] Because paracetamol overdose is the commonest form of self-poisoning in the UK, national guidelines have been produced and distributed as a poster in prose format to all A&E departments.[20] In addition, we have recently reviewed this topic and produced an evidence-based flowchart to guide the management of patients presenting with paracetamol poisoning.[21]

1. Risk factors for paracetamol poisoning

A number of factors may increase the risk of hepatotoxicity in patients with paracetamol poisoning and identify them as high risk; these are detailed in Table 3. Surprisingly, these are based on little evidence,[22–8] and yet they have become established and, currently, we support their use. The standard treatment line on the Prescott nomogram is lowered by 50% and treatment line B is used for these 'high risk' patients (Figure 1).[20, 29, 30] Prior to commencing treatment with NAC, a risk assessment should be made to determine whether the patient falls into a high- or low-risk treatment group for paracetamol toxicity; the appropriate treatment line on the nomogram should be followed.[30]

TABLE 3
Risk factors in paracetamol overdose.

- Regular ethanol consumption in excess of currently recommended limits (21 units/week in males; 14 units/week in females)[22, 23]
- Regular use of enzyme-inducing drugs (e.g. phenytoin, carbamazepine, rifampicin, phenobarbitone)[24–6]
- Conditions causing glutathione depletion (e.g. HIV, eating disorders, malnutrition, cystic fibrosis)[27, 28]

2. Early paracetamol poisoning (less than 15 hours post-ingestion)

The decision to use NAC in patients with early paracetamol poisoning is based on the plasma paracetamol concentration plotted on the Prescott nomogram (Figure 1).[30] Blood should be taken for a plasma paracetamol concentration on presentation (or four hours post-ingestion, whichever is later).[30] N-acetylcysteine is an effective, safe antidote and if given within eight to ten hours of paracetamol ingestion provides almost 100% protection against the development of hepatic and renal toxicity.[30] Therefore, in patients who present early, if the result of the plasma paracetamol concentration is available by eight hours post-ingestion, the decision to start NAC can be based directly on the plasma paracetamol concentration. However, in patients who present at more than eight hours after ingestion of a potentially hepatotoxic dose of paracetamol (>150 mg/kg or 75 mg/kg in high-risk patients), NAC should be started on presentation after blood is taken for a plasma paracetamol concentration; the NAC can be stopped if the plasma paracetamol concentration is found on analysis to be well below the relevant treatment line on the Prescott nomogram.[21, 30, 31]

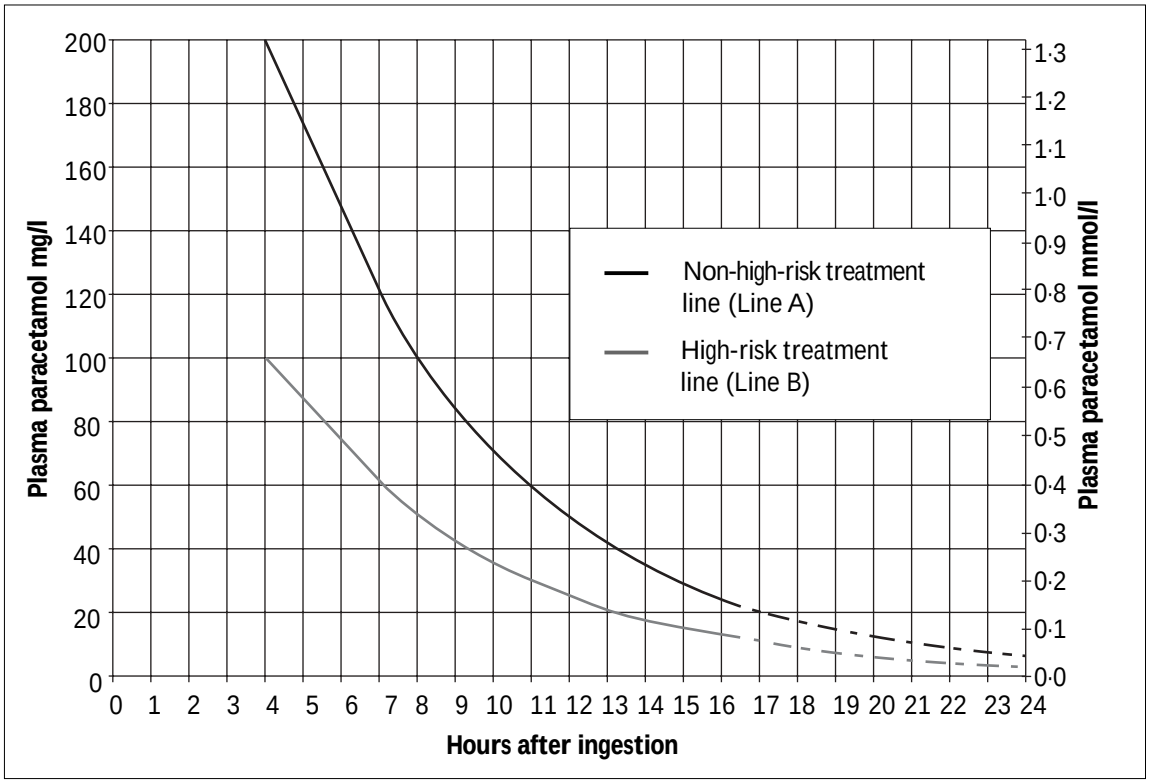

FIGURE 1
The Prescott paracetamol treatment nomogram used in the UK.[30]

3. Late paracetamol poisoning (more than 15 hours post-ingestion)

This group is difficult to manage. In any patient presenting within eight to twenty-four hours of ingestion of a potentially hepatotoxic dose of paracetamol, NAC should be started immediately and blood taken for International Normalised Ratio (INR), liver function tests, serum creatinine and plasma (venous) bicarbonate.[30, 32–7] The decision to continue the infusion will be determined by these blood results, the history and the clinical condition of the patient.[21] While data strongly support the treatment line A (Figure 1) on the Prescott nomogram up to 15 hours,[22] data beyond 15 hours are sparse and extrapolation of the line up to 24 hours amounts to guesswork, although this scheme is commonly used in practice. Furthermore, in late-presenting patients, the detection limit of the plasma paracetamol assay may not be sufficient to distinguish between toxic and non-toxic amounts.[20, 38] Therefore, the plasma paracetamol concentration in late-presenting patients needs to be considered with caution and patients may need to be given NAC on the basis of ingestion of a potentially hepatotoxic dose of paracetamol (150 mg/kg or 75 mg/kg for 'at risk' groups).[21] The maxim to be followed in practice is, 'If in doubt, treat.'[21]

The plasma paracetamol concentration cannot be used to assess patients presenting at more than 24 hours post-ingestion. In these patients, blood should be taken for INR, liver function tests, serum creatinine and plasma venous bicarbonate.[30, 32–7] If the patient is asymptomatic and the blood results are normal he/she may be medically discharged;[38, 39] if not, the National Poisons Information Service (NPIS) should be contacted for management advice.

4. Management of established paracetamol-related hepatotoxicity

Meticulous supportive care is important in these patients[40, 41] and we would advise that a poisons centre or a liver transplant unit should be contacted if there is evidence of hepatotoxicity at any stage or doubt about its management, particularly if markers of severe toxicity shown in Table 4 are present.[42] This ensures that referral takes place before the criteria for liver transplantation are met and that appropriate intensive care support is provided.[42, 43]

5. Staggered paracetamol poisoning

The plasma paracetamol concentration cannot be used to guide management in those patients who have taken a number of doses of paracetamol over a prolonged period of time. A baseline INR, liver function tests, serum creatinine and plasma venous bicarbonate should be taken, but the ingested dose is the most important factor and patients who have ingested more than 150 mg/kg over a 24-hour period (75 mg/kg for high-risk patients) should be treated with NAC.[20, 44–7]

TABLE 4
Markers of severe paracetamol poisoning and indications for referral to a liver unit.[42]

- Progressive coagulopathy, or INR >2 at 24 hours, INR >4 at 48 hours, INR >6 at 72 hours
- Renal impairment (creatinine >200 µmol/L)
- Hypoglycaemia
- Metabolic acidosis (pH <7·3, bicarbonate <18) despite adequate rehydration
- Hypotension despite fluid resuscitation
- Encephalopathy

OPIOIDS

Naloxone has been used as a specific antidote for opioid poisoning since the 1960s.[48] A frequent error in the management of opioid poisoned patients is to administer either excessive or insufficient doses of naloxone. The goal of naloxone treatment is reversal of respiratory depression to a minimum respiratory rate of ten (with adequate respiratory depth and oxygen saturation) and reversal of central nervous system (CNS) depression aiming for a Glasgow Coma Score of 13–14/15.[49] Naloxone can precipitate acute withdrawal syndrome (AWS) in chronic opioid users.[50–6] The agitation, hypertension and tachycardia produced, although rarely life-threatening, may produce significant distress to both the patient and staff. The agitation that results from AWS makes it difficult to monitor the patient and patients in this state may opt to leave the A&E department against medical advice. In addition, vomiting commonly occurs in acute withdrawal and, in a patient who does not regain consciousness immediately after naloxone, this can result in aspiration.

The bolus dose required to reverse the depressant effects of an opioid depends on the quantity of the drug present at the receptor sites and the competitive relationship that exists between the opioid and the antagonist at the receptor site.[57] This is generally between 0·4 mg and 2·0 mg IV, although this should not be given as a single large bolus.[8] We would recommend that 2 mg of naloxone is made up in a 10 ml syringe with saline and given in 100–200 mcg boluses to a maximum of 10 mg, titrated according to the effect produced (see Figure 2).

The half-life of naloxone is between 30 and 100 minutes.[57] Because the duration of action of most opioids exceeds that of naloxone[58, 59] either repeated doses or an intravenous infusion of naloxone are often required. The protocol we recommend is that described by Goldfrank (Figure 2).[60]

CARBON MONOXIDE POISONING

Carbon monoxide remains the commonest cause of death by poisoning in the UK.[2,61] Two areas of particular concern are the clinical assessment of the patient and adequate oxygen therapy.

Patients should have a thorough neurological examination which should include heel–toe walking and other tests of cerebellar function.[8] A carboxyhaemoglobin saturation level is of value in confirming the diagnosis but its level is not indicative of the severity of poisoning.[62, 63] An electrocardiogram (ECG) is essential in any patient with severe poisoning or in those with pre-existing heart disease because arrhythmias and myocardial ischaemia are a common cause of morbidity and mortality in severe carbon monoxide poisoning.[64–70] Arterial blood gas analysis is also required in significant poisoning; oxygen saturation monitors are misleading as they measure both oxyhaemoglobin and carboxyhaemoglobin.[71]

All patients should receive high flow oxygen through a tightly fitting facemask and this should be continued for at least 12 hours. The use of hyperbaric oxygen is controversial and six published randomised trials disagree on its efficacy.[72–7] The trials each have limitations which include either too few patients, inclusion of patients who were exposed to other toxins in fires and different treatment protocols. Until further, well-controlled evidence is available we would recommend hyperbaric oxygen therapy in the groups of patients with carbon monoxide poisoning shown in Table 5.[8]

TABLE 5
Current recommendations for hyperbaric oxygen therapy.[8]

- Any history of unconsciousness
- Carboxyhaemoglobin concentration of >40% at any time
- Presence of any neurological features (especially cerebellar signs)
- Pregnancy
- ECG changes

CARDIOVASCULAR TOXICITY

Cardiovascular toxicity is a common cause of death in severely poisoned patients. The following three areas merit special attention.

1. Arrhythmias associated with poisoning

Arrhythmias associated with poisoning should not in general be treated with anti-arrhythmic agents as a first-line approach.[8] Anti-arrhythmic agents have negative

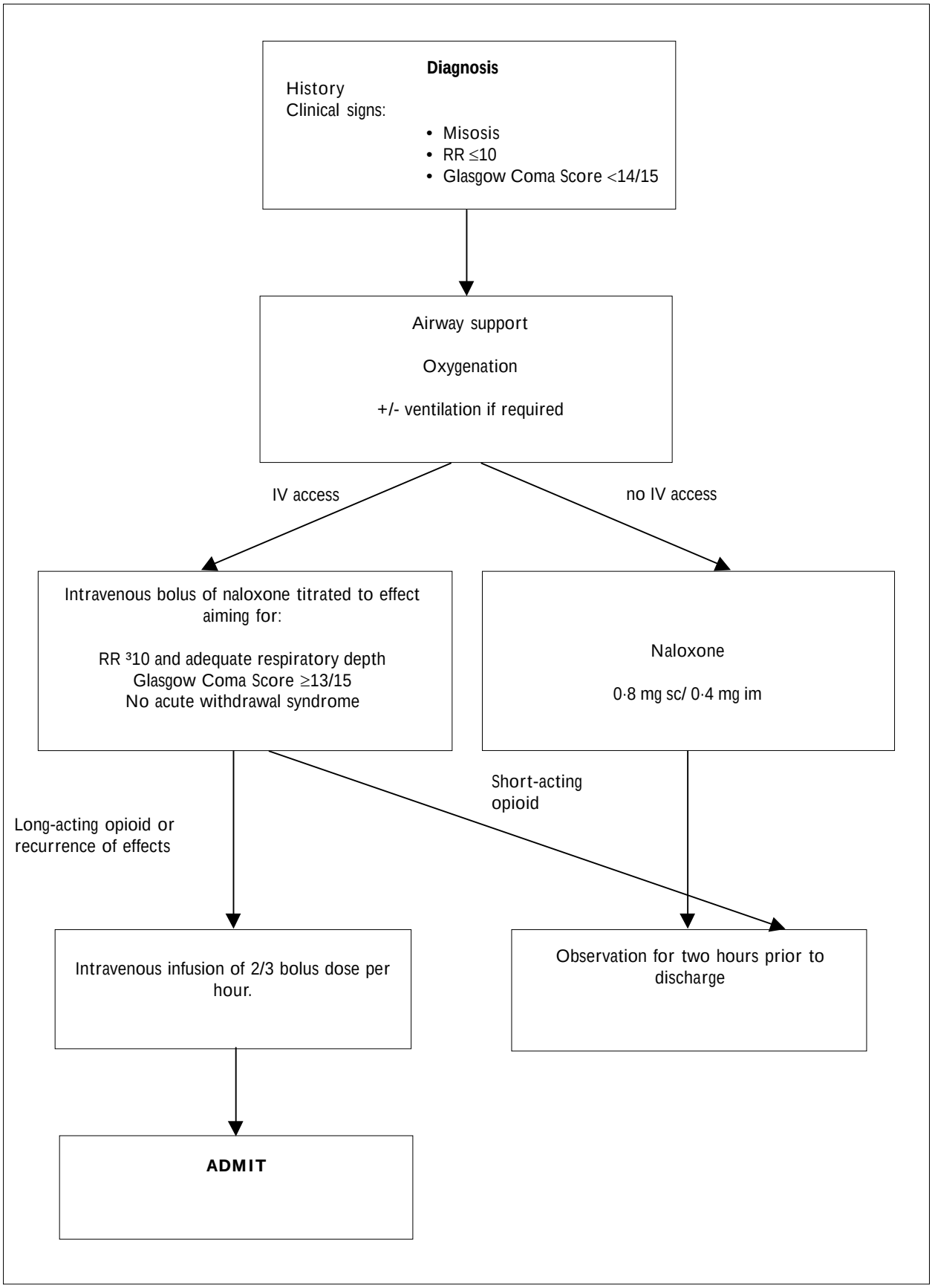

FIGURE 2
Flowchart for the management of opioid overdose.[60]

inotropic and chronotropic effects, and may lead to a deterioration in cardiovascular status, particularly in patients with arrhythmias due to a cardiotoxic agent. One should consider whether or not these drugs are really necessary; for example in poisoning with tricyclic antidepressants, administration of hypertonic sodium bicarbonate should be the first step in arrhythmia management.[8, 78] In other cases antidotes are indicated, e.g. Digibind® is preferable to pacing for brady-arrhythmias or anti-arrhythmic agents/DC cardioversion for tachy-arrhythmias in digoxin poisoning.[79–81]

2. Cocaine-induced acute-coronary syndrome

The pathophysiology of cocaine-induced acute-coronary syndrome is different to that associated with atherosclerotic coronary artery disease; it is due primarily to coronary artery spasm rather than thrombosis and other pathological forms of occlusion.[82–5] Management is therefore based on diazepam, aspirin, and buccal/intravenous nitrates as specific coronary artery vasodilators.[83, 86, 87] Calcium channel antagonists such as verapamil may also be used.[88] In patients with cocaine-induced myocardial infarction the use of thrombolytics is not usually necessary as the underlying aetiology is not thrombosis; the use of thrombolysis can further increase the risk of intracranial haemorrhage associated with cocaine use.[83]

The initial drug of choice in treatment of cocaine-induced hypertension is diazepam, which reduces the central stimulation, tachycardia and hypertension associated with cocaine toxicity. A common error is to give beta-blockers, which may lead to worsening hypertension due to unopposed alpha-stimulation. Hypertension that does not settle with diazepam should be treated with intravenous nitrates.[83]

3. Recovery from cardiac arrest

Some poisoned patients make a good recovery despite prolonged cardiac arrest[89–93] and a common problem is that these patients are not resuscitated for long enough. A case has been reported of a successful outcome after 50 minutes of cardiopulmonary resucitation (CPR) in a patient with a large imipramine overdose.[89] This patient required 400 mmol of sodium bicarbonate in addition to standard adrenaline therapy.[89] Poisoned patients who have developed a cardiac arrest are very different to other patients in the general population, or hospital in-patients who have a cardiac arrest, as they are more often fit young individuals with a better cardiorespiratory reserve.

ACIDOSIS

A metabolic acidosis is very common in poisoning[8] although diabetic ketoacidosis is still missed; a bedside and laboratory assay of glucose should be carried out and urinalysis performed in all acidotic patients.

A patient with a high anion gap metabolic acidosis and high osmolal gap is very likely to be poisoned with ethylene glycol or methanol.[94, 95] The absence of a high anion gap metabolic acidosis does not, however, exclude methanol/ethylene glycol poisoning as the metabolic acidosis is due to the toxic metabolites, and metabolism of methanol/ethylene glycol can take between eight and thirty-six hours.[96, 97] Therefore, patients who present within the first eight to twenty-four hours of poisoning may have a normal blood gas and anion gap, and the diagnosis is usually made on the basis of a raised osmolal gap.[8] The osmolal gap (normal value <10) is the difference between the measures serum osmolality (O_m) and the calculated osmolality (O_c). The formula for calculation of the calculated osmolality is: $O_c = 2(Na^+ + K^+) + \text{urea} + \text{glucose}$. Common toxic causes of an elevated osmolal gap are methanol, ethanol, ethylene glycol and isopropanol.[94] It is important to exclude ethanol as the cause of the elevated osmolal gap and so a serum ethanol concentration should also be measured; 3·7 mg/dL of ethanol approximates to 1 mOsm/L.[98]

Management of methanol/ethylene glycol poisoning involves supportive care together with the use of competitive inhibitors of alcohol dehydrogenase (e.g. ethanol, 4-methylpyrazole) to reduce the formation of their toxic metabolites.[94, 95] In addition, aggressive bicarbonate therapy in patients with a metabolic acidosis decreases CNS transit of both ethylene glycol and methanol, and reduces optic nerve toxicity with methanol.[94, 95] Ethanol remains the antidote of choice in most cases for ingestion of these substances. All patients who have ingested a significant amount of ethylene glycol or methanol should receive a loading dose of ethanol while awaiting confirmatory laboratory results.[94, 95] An infusion should then be commenced in patients with confirmed poisoning (usually on the basis of a history of methanol or ethylene glycol ingestion in association with a raised osmolal gap) aiming for a blood ethanol concentration of 100–150 mg/dL.[94, 95, 99, 100] Ethanol has unpredictable kinetics therefore patients who require an ethanol infusion should have hourly to two-hourly monitoring of blood ethanol concentrations until the serum ethanol concentration is 100–150 mg/dL, and then two to four-hourly monitoring once this concentration is achieved.[8, 94] Patients with severe methanol/ethylene glycol poisoning (e.g. severe, resistant metabolic acidosis, acute renal failure, ocular toxicity with methanol poisoning) may require haemodialysis; the dose of ethanol should be increased in these patients, or ethanol put in the dialysate to maintain a serum ethanol concentration of 100–150 mg/dL.[94, 95]

Sodium bicarbonate is frequently used in the management of poisoned patients and the common indications are summarised in Table 6.[101] It should be titrated to clinical effect and very large doses may be required, for instance in severe tricyclic antidepressant poisoning, where initial boluses of 1–2 mL 8·4% sodium bicarbonate should be

followed by further doses titrated to a pH of 7·45–7·5.[102–4] It is important that drowsy patients are ventilated to prevent the potential carbon dioxide retention that can occur and result in a paradoxical intracellular acidosis in these patients treated with sodium bicarbonate.

RARER OVERDOSES

The most common area of mismanagement in the following, rarer overdoses is failure to recognise the potential severity of poisoning and instigate early appropriate treatment.

TABLE 6
Indications for use of sodium bicarbonate in poisoned patients.[101]

- Severe metabolic acidosis associated with methanol, ethylene glycol, cyanide, salicylates
- Urinary alkalinisation to enhance elimination of salicylate (and less commonly for phenobarbitone, chlorpropamide and some pesticides, e.g. 2,4D) or prevent renal deposition of myoglobin after severe rhabdomyolysis
- Cardiotoxicity caused by tricyclic antidepressants, dextropropoxyphene, flecanide, quinidine, procainamide, disopyramide, phenothiazines, chloroquine

Chloroquine

The mortality rate in published studies of chloroquine overdose is between 12–35%, among the highest in clinical toxicology.[105,106] Ingestion of more than 5 g of chloroquine is probably the most accurate predictor of a fatal outcome; death is usually due to cardiotoxicity.[107] The window of opportunity for treatment is short: the interval between ingestion and onset of symptoms is usually between one to three hours, with death within 12 hours.[108] Studies have suggested that early management of severe chloroquine intoxication may have a cardioprotective effect and reduce the fatality rate.[109, 110] Chloroquine blood concentrations are not required for the institution of treatment. Clinical features, which primarily involve the cardiovascular and CNS, are more important. Activated charcoal should be given to patients presenting within one hour of ingestion of more than 15 mg/kg chloroquine.[111] It is essential to intubate and ventilate early in the course of chloroquine poisoning if arrhythmias, hypotension, seizures or significant CNS depression are present. Anti-arrhythmic agents should be avoided if possible as they may precipitate further arrhythmias. Intravenous sodium bicarbonate is the treatment of choice for arrhythmias[109, 112] and should be used in patients with widened QRS and QT_C intervals (1–2 ml/kg 8·4% sodium bicarbonate repeated as necessary aiming for a pH of 7·45–7·5). Overdrive pacing is the treatment of choice for ventricular tachycardia or torsade de pointes.[113] Inotropes may also be necessary for hypotension unresponsive to a fluid challenge.[113, 114] Plasma potassium should be monitored, although hypokalaemia may have a protective effect and should not be aggressively corrected in the early stages of poisoning as there is no total body deficit of potassium and attempted early correction can worsen cardiotoxicity.[115] If hypokalaemia persists beyond eight hours, potassium should be replaced cautiously.[115] High dose diazepam has been reported to have a specific cardioprotective action in severe chloroquine poisoning.[113, 116] It is recommended that after intubation 2 mg/kg of intravenous diazepam should be given over 30 minutes and then 1 to 2 mg/kg for two to four days.[113,116] Continuous and aggressive cardiorespiratory support appears to be the most critical factor in survival.

Salicylate

Salicylate poisoning is much less common than ten years ago[4] and for this reason doctors may fail to recognise its severity or treat such patients optimally. Delay in diagnosis was associated with a mortality of 15% compared to a much lower rate in those patients in whom early diagnosis and initiation of therapy was made.[118] We have recently reviewed the management of salicylate poisoning and proposed a management flowchart.[119] The clinical effects of salicylate poisoning are shown in Table 7.[120–5] Children and the elderly may suffer toxicity with lower ingested doses and at relatively lower plasma salicylate concentrations.

There is no antidote to salicylate poisoning, and management is directed towards preventing further absorption and enhancing elimination of the drug in patients with features of moderate or severe intoxication.[119] The use of MDAC is controversial in salicylate overdose.[126–9] We advocate its use, to prevent delayed absorption, until the salicylate level has peaked, which can be as late as 12–18 hours post-ingestion.[8]

The plasma salicylate concentration should be determined on admission provided that the patient is more than four hours post-ingestion.[119] As salicylates can delay gastric emptying and may form concretions in the stomach resulting in delayed absorption, the plasma salicylate concentration should be repeated every three to four hours to ensure the concentration does not continue to rise.[119] The plasma salicylate concentration correlates very roughly with toxicity[124,130] (see Table 7) although the presence of symptoms and signs and the degree of acidosis should be considered when interpreting the plasma salicylate concentration and deciding on further management.[124, 131] Metabolic acidosis is a particularly important negative predictor as it increases the CNS transit of salicylate and decreases salicylate renal elimination. After ingestion of enteric-coated preparations, plasma salicylate concentrations on admission are unreliable guides to the severity of

TABLE 7
Clinical features of salicylate poisoning.

	Dose ingested	Salicylate concentration		Clinical features
		Adults	Children/Elderly	
Mild	>150 mg/kg	300–600 mg/L	250–450 mg/L	Lethargy, nausea, vomiting, tinnitus, dizziness
Moderate	>250 mg/kg	600–800 mg/L	450–700 mg/L	Mild features and tachypnoea, sweating, hyperpyrexia, dehydration, restlessness
Severe	>500 mg/kg	>800 mg/L	>700 mg/L	Moderate features and metabolic acidosis, hypotension, CNS features (e.g. coma, seizures), renal failure

poisoning as levels may not peak until more than 12–18 hours after ingestion.[132–4]

Patients with salicylate poisoning are often dehydrated because of vomiting, hyperventilation and sweating; rehydration is therefore an important aspect of management. Patients with severe salicylate poisoning are also at risk of pulmonary oedema, however, and it is important not to cause fluid overload; in the elderly or those with cardiac disease a central line may be necessary to guide rehydration.[8]

Urinary alkalinisation is an effective method of increasing salicylate elimination and is indicated in patients with moderate salicylate poisoning (see Table 7).[125] In adults this is achieved by administering 1L of 1·26% sodium bicarbonate over three to four hours and regularly checking the urinary pH with indicator paper aiming for a urinary pH 7·5–8·5; an increase in the infusion rate or bolus of 8·4% sodium bicarbonate may be required if an alkaline urine is not achieved as patients can have a significant base deficit.[119] The plasma potassium should be monitored as the serum potassium can fall precipitously once adequate urinary alkalinisation is achieved and also it is very difficult to produce an alkaline urine if the patient is hypokalemic.[119] We would therefore recommend adding 20–40 mmol potassium to each litre of intravenous fluid administered.

Haemodialysis reduces both the mortality and morbidity of poisoning, and, as well as being effective at increasing salicylate clearance it also corrects acid-base and fluid balance abnormalities.[121] It should be considered if the patient has a metabolic acidosis resistant to correction with 8·4% sodium bicarbonate, especially if the pH is <7·2, the salicylate concentration is >800 mg/L in adults or 700 mg/L in children or elderly, or the patient has features of severe poisoning (see Table 7).[120–5] It is important that alkalinisation is still achieved in those salicylate-poisoned patients undergoing haemodialysis in order to reduce plasma levels quickly, prevent acidaemia and promote elimination of as much salicylate as possible via the kidneys.[123]

Theophylline

Severe theophylline poisoning (ingestion of more than 3 g in adults or 40 mg/kg in children) is associated with a high mortality.[8] Theophylline is most commonly used in sustained release formulations leading to delayed absorption in overdose and delayed onset of toxicity, as late as 12–24 hours post-ingestion.[135]

A system has been proposed for grading the severity of theophylline intoxication and is shown in Table 8.[136] Plasma theophylline concentrations can help confirm ingestion and may be of value in deciding upon elimination methods, but in the vast majority of poisoned patients they do not aid management.[8] Management is most appropriately guided by the severity on the Sessler grading scheme (Table 8),[136] bearing in mind that delayed effects occur in overdoses with sustained-release preparations.

All patients with theophylline poisoning should receive MDAC.[13, 137, 138] Vomiting, which may be profuse, occurs in overdose in more than 70% of patients.[139–41] It may respond to metoclopramide but is more likely to be controlled by a $5HT_3$-receptor antagonist such as ondansetron.[142] All patients should have cardiac monitoring. Sinus or supraventricular arrhythmias not causing haemodynamic compromise are best left untreated.[138] In non-asthmatic patients, symptomatic supraventricular tachycardia should be treated with propranolol (0·01–0·03 mg/kg IV) or esmolol (25–50 µg/kg), repeated according to response.[143, 144] Asthmatic patients should be treated with verapamil or cautiously treated with esmolol (short half-life and relative beta 1 selectivity).[145–7] Ventricular arrhythmias are treated with DC cardioversion or magnesium sulphate.[8] Convulsions

TABLE 8
Grading scheme for patients with theophylline intoxication.[136]

Severity grade	Clinical features
1	Vomiting, abdominal pain, diarrhoea, anxiety, tremor, sinus tachycardia >120 bpm, plasma potassium 2·5–3·5 mmol/L
2	Haematemesis, disorientation, supra-ventricular tachycardia, frequent ectopics, mean arterial blood pressure at least 60 mmHg but unresponsive to standard therapy, plasma potassium <2·5 mmol/L, arterial pH <7·2 or >7·6, rhabdomyolysis
3	Non-repetitive seizure, sustained ventricular tachycardia, mean arterial blood pressure <60 mmHg and unresponsive to standard therapy
4	Recurrent seizures, ventricular fibrillation, cardiac arrest

should be treated with intravenous diazepam; if these are resistant to treatment, the patient should be intubated and ventilated.[137] Plasma potassium concentration should be monitored frequently (every one to two hours in severely poisoned patients) as hypokalaemia is a potentially life-threatening consequence of theophylline poisoning.[137] The blood glucose should be checked, as hyperglycaemia is also common.[138]

It is likely that MDAC is almost as effective as charcoal haemoperfusion in the management of severe theophylline poisoning.[148] If MDAC is not possible, however, e.g. paralytic ileus, charcoal haemoperfusion should be considered in patients with severe (grade 3 and 4) poisoning.[148, 149]

Iron

The clinical course of iron poisoning may be divided into four stages.[150, 151] During the initial 30 minutes to several hours after ingestion, the corrosive effects of iron result in gastrointestinal upset leading to nausea and vomiting, abdominal pain and diarrhoea. In severe cases gastrointestinal haemorrhage and shock can occur. The second phase, during which the clinical effects usually abate, lasts from six to twenty-four hours after ingestion. This phase can be deceptively reassuring as the asymptomatic patient during this phase can still go on to develop severe toxicity. Phase three occurs from 12–48 hours after ingestion and may include severe lethargy, coma, convulsions, gastrointestinal haemorrhage, shock, metabolic acidosis, hepatic failure with hypoglycaemia, coagulopathy, pulmonary oedema and renal failure. Phase four occurs between two and five weeks if the patient survives. Scarring from the initial corrosive damage can result in small bowel strictures and pyloric stenosis.

It is important when assessing the ingested dose of iron that the elemental content of different iron preparations is considered (see Table 9).[152] Undissolved iron tablets are radiopaque, and an abdominal X-ray (AXR) should be taken in all patients to determine the need for gut decontamination.[151] However the absence of radiopaque material on AXR does not exclude iron ingestion.[151] If any tablets are visible on the AXR, whole bowel irrigation should be undertaken.[153]

TABLE 9
Elemental iron content of iron preparations in the UK.[153]

Iron preparation	Usual dosage	Amount of elemental iron
Ferrous fumarate	200 mg	65 mg
Ferrous gluconate	300 mg	35 mg
Ferrous succinate	100 mg	35 mg
Ferrous sulphate	200 mg	60 mg
Ferrous sulphate (dried)	300 mg	60–5 mg

Blood should be taken four hours after ingestion for determination of the serum iron concentration.[154] If desferrioxamine is to be given before four hours for severe poisoning, blood should be taken for determination of the serum iron level just prior to its administration as once desferrioxamine has been given colorimetric assay methods may underestimate the amount of free serum iron.[155, 156] A blood level taken more than six to eight hours after ingestion may underestimate the amount of free iron because of distribution into the tissues.[154] For sustained-release preparations an initial serum concentration should be checked at four hours and again two to four hours later.[8] The serum iron concentration should not be interpreted in isolation but in the context of the patients clinical condition and an accurate history of the ingested dose. Measurement of the total iron binding capacity is of no value in the management of these patients.[157]

There have been no controlled studies looking at the use of desferrioxamine in iron poisoning;[158] we would, however, recommend its use in patients with hypotension, shock, severe lethargy, coma or convulsions or a serum iron level >90 mmol/L.[8] Patients with a serum iron concentration of 55–90 mmol/L should be observed for 24–48 hours post-ingestion. They do not require chelation therapy unless they develop symptoms, or have haematemesis or melaena.[8] The recommended initial dose of desferrioxamine is 15 mg/kg/hour, reduced after two to four hours up to a maximum of 80 mg/kg in 24

hours.[159] More rapid infusion rates can cause hypotension,[160] and there is a risk of pulmonary complications such as ARDS with doses of more than 80 mg/kg/24hrs.[151, 160, 161] Chelation with desferrioxamine should be continued until the urine has returned to a normal colour, symptoms have abated and all radiopacities have disappeared.[8, 161] Haemodialysis or haemofiltration may be required to remove the iron-desferrioxamine complex in patients with renal failure.[8, 161]

CYANIDE

Although rare, acute cyanide poisoning requires immediate action as it produces its effects, which include metabolic acidosis and CNS, cardiac and respiratory depression, rapidly.[19] The immediate diagnosis of cyanide poisoning is difficult despite improvements in blood cyanide detection methods.[162–4] This poses a therapeutic dilemma for the clinician who must rapidly decide whether to administer specific antidotes, some of which are themselves toxic.[165, 166] The blood cyanide concentration is considered the gold standard in confirmation of acute cyanide poisoning; they are, however, rarely of use in emergency management because they cannot be carried out rapidly enough to guide treatment.[167] A sample should be taken before antidote administration for cyanide quantification at a later stage.

Many patients suffering from smoke inhalation or burns may also have cyanide toxicity and may present with a lactic acidosis not responding to oxygen administration.[19, 167] A recent study has shown that immediate and serial measurements of plasma lactate concentrations are useful in assessing the severity of cyanide poisoning in patients in whom the diagnosis is strongly suspected on a clinical basis.[19, 166] In burn victims without severe burns, a plasma lactate concentration of >90 mg/dL (10 mmol/L) is a sensitive and specific indicator of cyanide intoxication.[168]

Decontamination is an important aspect of management; it is vital that medical staff treating the patient do not become poisoned.[8, 169] If hydrogen cyanide gas or liquid cyanide is involved, protective clothing and breathing apparatus is necessary and if the patient is intubated a closed circuit should be used.[8, 169] In cyanide salt exposure, contaminated clothing should be removed and placed in sealed bags, and the skin washed with soapy water.[8, 169]

Meticulous supportive care is important in the management of cyanide poisoning. All patients should receive high-flow oxygen,[170] and comatose patients will require intubation.[171] Patients who present with an established metabolic acidosis should be treated with 1–2 ml of 8·4% sodium bicarbonate to correct the acidosis.[172]

The other aspect of the management of cyanide poisoning is the use of antidotes. Dicobalt edetate can be associated with severe adverse effects including cardiotoxicity, facial and laryngeal oedema, bronchospasm and rashes.[173–5] These effects are more likely to occur if it is administered in the absence of cyanide ions or if the drug is injected too rapidly. It should therefore be used only if the diagnosis of cyanide poisoning is certain and the patient has severe clinical features;[8] adrenaline and facilities for intubation should be available. If the diagnosis is uncertain or dicobalt edetate is unavailable, the patient should be treated with a combination of intravenous sodium thiosulphate and sodium nitrite.[176–8] Hydroxocobalamin (at a dose of 5 g for an adult[179, 180]) is a newer cyanide antidote and is both effective and well tolerated.[180, 181] Currently the concentrated form of hydroxocobalamin is not widely available in the UK.

DECLARTION OF INTERESTS

AL Jones is a scientific advisor for GlaxoSmithKline on analgesics; PI Dargan has acted as a scientific advisor to GlaxoSmithKline and received funding to attend scientific meetings. The Medical Toxicology Unit at the National Poisons Information Service is supported by AstraZeneca-Novartis, Boots Healthcare and Bass Breweries.

REFERENCES

1 Greaves I, Goodacre S, Grout P. Management of drug overdose in accident and emergency departments in the United Kingdom. *J Accident Emerg Med* 1996; **13:**46–8.

2 Flanagan RJ, Rooney C. Recording acute poisoning deaths. *Forensic Sci Int* 2002; **128(1–2):**3–19.

3 Ramsay LE, Freestone S, Silas JH. Drug-related acute medical admissions. *Hum Toxicol* 1982; **1(4):**379–86.

4 Townsend E, Hawton K, Harriss L *et al*. Substances used in deliberate self-poisoning 1985–1997: trends and associations with age, gender, repetition and suicide intent. *Soc Psychiatry Psychiatr Epidemiol* 2001; **36:**228–34.

5 Hawton K, Fagg J. Deliberate self-poisoning and self-injury in adolescents: a study of characteristics and trends in Oxford, 1976–89. *Br J Psychiatry* 1997; **171(12):**556–60.

6 Schmidtke A, Bille-Brahe U, Deleo D *et al*. Attempted suicide in Europe: rates, trends, and sociodemographic characteristics of suicide attempters during the period 1989–1992. Results of the WHO/EURO multicentre study on parasuicide. *Acta Psychiatrica Scandinavica*1996; **93:**327–38.

7 Michel K, Ballinari P, Bille-Brahe U *et al*. Methods used for parasuicide: results of the WHO/EURO Multicentre Study on Parasuicide. *Soc Psychiatry Psychiatr Epidemiol* 2000; **35(4):**156–63.

8 Jones AL, Dargan PI. *Churchill's Pocketbook of Toxicology*. Edinburgh: Churchill Livingston, Harcourt; 2001.

9 Litovitz TL, Klein-Schwartz W, Rogers CJ Jr *et al*. 2001 Annual Report of the American Association of Poison Control Centres Toxic Exposure Surveillance System. *Am J Emerg Med* 2002; **20:**391–452.

10 American Academy of Clinical Toxicology; European Association of Poison Control Centres and Clinical Toxicologists. Position statement: Single-dose activated charcoal. *Clin Tox* 1997; **35(7):**721–41.

11 Thakore S, Murphy N. The potential role of prehospital

administration of activated charcoal. *Emerg Med J* 2002; **19:**63–5.
12 Karim A, Ivatts S, Dargan PI *et al*. How feasible is it to conform to the European guidelines on the administration of activated charcoal within one hour of overdose? *Emerg Med J* 2001; **18:**390–2.
13 American Academy of Clinical Toxicology; European Association of Poison Control Centres and Clinical Toxicologists. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. *Clin Tox* 1999; **37(6):**731–51.
14 Saetta JP, March S, Gaunt ME *et al*. Gastric emptying procedures in the self poisoned patient: are we forcing gastric content beyond the pylorus? *J R Soc Med* 1991; **84:**274–6.
15 American Academy of Clinical Toxicology and European Association of Poisons Centres. Position statement: Gastric lavage. *Clin Tox*1997; **35(7):**711–19.
16 American Academy of Clinical Toxicology and European Association of Poisons Centres. Position statement: Whole bowel irrigation. *Clin Tox* 1997; **35:**735–62.
17 Dargan PI, Shin GY, Jones AL. How well do doctors and nurses estimate the weight of patients? *J Toxicol Clin Toxicol* 2001; **39:**567–8.
18 Hawton K, Townsend E, Deeks J *et al*. Effects of legislation restricting pack sizes of paracetamol and salicylate on self-poisoning in the UK: before and after study. *BMJ* 2001; **322:**1203–7.
19 Parfitt A, Henry JA. Troublesome toxins. *Emerg Med J* 2002; **19:**192–3.
20 NPIS. Management of acute paracetamol poisoning. Guidelines agreed by the UK National Poisons Information Service 1998. Supplied to the Accident and Emergency Centres in the UK by the Paracetamol Information Centre in collaboration with the British Association for Accident and Emergency Medicine.
21 Wallace CI, Dargan PI, Jones AL. Paracetamol overdose: an evidence-based flowchart to guide management. *Emerg Med J* 2002; **19:**202–5.
22 Prescott LF. Paracetamol, alcohol and the liver. *Br J Clin Pharmacol* 2000; **49:**291–301.
23 Bray GP, Mowat C, Muir DF *et al*. The effect of chronic alcohol intake on prognosis and outcome in paracetamol overdose. *Hum Exp Toxicol* 1991; **10:**435–8.
24 Wright N, Prescott LF. Potentiation by previous drug therapy of hepatotoxicity following paracetamol overdose. *Scott Med J* 1973; **18:**56–8.
25 Smith JA, Hine ID, Beck P *et al*. Paracetamol toxicity: is enzyme induction important? *Hum Exp Toxicol* 1986; **5:**383–5.
26 Minton N, Henry JA, Frankel RJ. Fatal paracetamol poisoning in an epileptic. *Hum Exp Toxicol* 1988; **7:**33–4.
27 Whitcomb DC, Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol use. *JAMA* 1994; **272:**1845–50.
28 Buhl R, Jaffe HA, Holroyd KA *et al*. Systemic glutathione deficiency in symptom-free HIV-seropositive individuals. *Lancet* 1989; **ii:**1294–8.
29 Routledge PA, Vale JA, Bateman DN *et al*. Paracetamol (acetaminophen) poisoning. *BMJ* 1998; **317:**1609–10.
30 Prescott LF, Illingworth RN, Critchley JA *et al*. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. *BMJ* 1979; **2:**1098–100.
31 Jones AL. Mechanism of action of N-acetylcysteine in the treatment of early and late acetaminophen poisoning: a critical review. *J Toxicol Clin Tox* 1998; **36:**277–85.
32 Singer AJ, Carracio TR, Mofenson HC. The temporal profile of increased transaminase levels in patients with acetaminophen induced liver dysfunction. *Ann Emerg Med* 1995; **26:**49–53.
33 Harrison PM, O'Grady JG, Keays RT *et al*. Serial prothrombin time as a prognostic indicator in paracetamol induced fulminant hepatic failure. *BMJ*; **301:**964–6.
34 Record CO, Iles RA, Cohen RD *et al*. Acid-base and metabolic disturbances in fulminant hepatic failure. *Gut* 1975; **16:**144–9.
35 Blantz RC. Acetaminophen, acute and chronic effects on renal function. *Am J Kidney Dis* 1996; **28(1 Suppl 1):**S3–6.
36 Eguia L, Materson BJ. Acetaminophen-related acute renal failure without fulminant liver failure. *Pharmacotherapy* 1997; **17:**363–70.
37 Prescott LF, Proudfoot AT, Creegan RJ. Paracetamol induced renal failure in the absence of fulminant liver damage. *BMJ* 1992; **284:**421–2.
38 Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. *Lancet* 1995; **346:**547–52.
39 Prescott LF, Critchley JA. The treatment of acetaminophen poisoning. *Ann Rev Pharmacol Toxicol* 1983; **23:**87–101.
40 Fellay M, Kehtari R. Insuffisance hepatique fulminante et subfulminante. *Rev Med Suisse Romande* 1996; **116:**483–91.
41 Makin AJ, Wendon J, Williams R. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987–93). *Gastroenterology* 1995; **109:**1907–16.
42 Makin A, Williams R. The current management of paracetamol overdosage. *Br J Clin Pharmacol* 1994; **48:**144–8.
43 O'Grady JG, Wendon J, Tan KC *et al*. Liver transplantation after paracetamol overdose. *BMJ* 1991; **303:**221–3.
44 Wendel A, Jaeschke H, Gloger M. Drug induced lipid peroxidation in mice – protection against paracetamol induced liver necrosis by intravenous liposomally entrapped glutathione. *Biochem Pharmacol* 1982; **31:**3601–5.
45 Prescott LF. *Paracetamol (acetaminophen). A critical bibliographic review*. London: Taylor and Francis; 1996.
46 Linden CH, Rumack BH. Acetaminophen overdose. *Emerg Clin North Am* 1984; **2:**103.
47 Henretig FM, Selbst SM, Forrest C *et al*. Repeated acetaminophen overdosing causing hepatotoxicity in children: clinical reports and literature review. *Clin Pediatr* 1989; **28:**525–8.
48 Sadove MS, Balagot RC, Hatano S *et al*. Study of a narcotic antagonist – n-allyl-noroxymorphone. *JAMA* 1963; **183:**666–8.
49 Allen SC. Problems with naloxone (letter). *BMJ* 1975; **3:**434.
50 Wikler A, Fraser HF, Isbell H. N-allylnormorphone: effects of single doses and precipitation of acute 'abstinence syndromes' during addiction to morphine, methadone or heroin in man (post-addicts). *J Pharmacol Exp Ther* 1953; **109:**8–20.
51 Evans LEJ, Roscoe P, Swainson CP *et al*. Treatment of drug overdosage with naloxone, a specific narcotic antagonist. *Lancet* 1973; **i:**452–5.
52 Buchwald A. Naloxone use: side effects may occur (letter). *Ann Emerg Med* 1988; **17:**765.
53 Popper C, Kelen GD, Cunningham G. Naloxone hazard in a drug abuser. *Lancet* 1989; **2(8666):**446.
54 Gibbs J, Newson T, Williams J *et al*. Naloxone hazard in infant of opioid abuser (letter). *Lancet* 1989; **2(8655):**159.
55 Gaddis G, Watson WA. Naloxone–associated patient violence: an overlooked toxicity? *Ann Pharmacotherapy*

1992; **26:**196–7.
56 Martin WR. Naloxone: diagnosis and treatment. *Ann Intern Med* 1976; **85:**765–8.
57 Fishman J, Roffwarg H, Hellman L. Disposition of naloxone in normal and narcotic dependent men. *J Pharmacol Exp Ther* 1973; **187:**575–80.
58 Lasagna L. The clinical evaluation of morphine and its substitutes as analgesics. *Pharmacol Rev* 1964; **16:**47–83.
59 Murphree HB. Clinical pharmacology of potent analgesics. *Clin Pharmacol Ther* 1962; **3:**473–504.
60 Goldfrank L, Weisman RS, Errick, JK *et al*. A dosing nomogram for continuous infusion intravenous naloxone. *Ann Emerg Med* 1986; **566:**91–5.
61 Wilson RC, Saunders PJ, Smith G. An epidemiological study of acute carbon monoxide poisoning in the West Midlands. *Occup Env Med* 1998; **55:**723–8.
62 Gorman DF, Clayton D, Gilligan JE *et al*. A longitudinal study of 100 consecutive admissions for carbon monoxide poisoning to the Royal Adelaide Hospital. *Anaesth Intensive Care* 1992; **20:**311–16.
63 Thom SR, Keim LW. Carbon monoxide poisoning: a review of epidemiology, pathophysiology, clinical findings, and treatment options including hyperbaric oxygen therapy. *Clin Toxicol* 1989; **27:**141–56
64 Yanir Y, Shupak A, Abramovich A *et al*. Cardiogenic shock complicating acute carbon monoxide poisoning despite neurological and metabolic recovery. *Ann Emerg Med* 2002; **40:**420–4.
65 Ernst A, Zibrak JD. Carbon monoxide poisoning. *N Engl J Med* 1998; **339:**1603–8.
66 Miro O, Casademont J, Barrientos A *et al*. Mitochondrial cytochrome oxidase inhibition during acute carbon monoxide poisoning. *Pharmacol Toxicol* 1998; **82:**199–202.
67 Diltoer MW, Colle IO, Hubloue I *et al*. Reversible cardiac failure in an adolescent after prolonged exposure to carbon monoxide. *Eur J Emerg Med* 1995; **2:**231–5.
68 Tritapepe L, Macchiarelli G, Rocco M *et al*. Functional and ultrastructural evidence of myocardial stunning after acute carbon monoxide poisoning. *Crit Care Med* 1998; **26:**797–801.
69 McMeekin JD, Finegan BA. Reversible myocardial dysfunction following carbon monoxide poisoning. *Can J Cardiol* 1987; **3:**118–21.
70 Kubat K, Zboril M. Determination of serum lactic acid and the acid-base equilibrium in carbon monoxide poisoning. *Vnitr Lek* 1995; **45:**545–8.
71 Buckley RG, Aks SE, Ashom JL *et al*. The pulse oximetry gap in carbon monoxide intoxication. *Ann Emerg Med* 1994; **24:**252–5.
72 Ducasse JL, Celsius P, Marc-Vergnes JP. Non-comatose patients with acute carbon monoxide poisoning: hyperbaric or normobaric oxygenation? *Undersea Hyperb Med* 1995; **22:**1–9.
73 Mathieu D, Wattel F, Mathieu-Nolf M. Randomised prospective study comparing the effect of hyperbaric oxygen versus 12 hours non-hyperbaric oxygen in non-comatose CO poisoned patients: results of the interim analysis. *Undersea Hyperb Med* 1996; **23:**7–8.
74 Raphael J-C, Elkarrat D, Jars-Guincestre MC *et al*. Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. *Lancet* 1989; **ii:**414–19.
75 Scheinkestel CD, Biley M, Myles PS *et al*. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled trial. *Med J Aust* 1999; **170:**203–10.
76 Thom SR, Tber RL, Mendiguren I, Clark JM *et al*. Delayed neuropsychologic sequelae after carbon monoxide poisoning: prevention by treatment with hyperbaric oxygen. *Ann Emerg Med* 1995; **25:**474–80.
77 Weaver LK, Hopkins RO, Chan KJ *et al*. Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med* 2002; **347(14):**1057–67.
78 Jones AL. Recent advances in the management of poisoning. *Ther Drug Monit* 2002; **24:**150–5.
79 Taboulet P, Baud FJ, Bismuth C. Clinical features and management of digitalis poisoning rationale for immunotherapy. *J Toxicol Clin Toxicol* 1993; **31:**247–60.
80 Smolarz A, Roesch E, Lenz E *et al.* Digoxin specific antibody (Fab) fragments in 34 cases ofsevere digitalis intoxication. *J Toxicol Clin Toxicol* 1985; **23:**327–40.
81 Taboulet P, Baud FJ, Bismuth C *et al.* Acute digitalis intoxication – is pacing still appropriate? *J Toxicol Clin Toxicol* 1993; **31:**261–73.
82 Lange RA, Hillis LD. Medical progress: cardiovascular complications of cocaine use. *N Engl J Med* 2001; **345(5):**351–8.
83 Stouffer GA, Sheahan RG, Lenihan DJ *et al*. Cocaine-associated chest pain. *Amer J Med Sci* 2002; **324(1):**37–44.
84 Beckman KJ, Parker RB, Hariman RJ *et al*. Hemodynamic and electrophysiological actions of cocaine. *Circulation* 1991; **83:**1799–807.
85 Flores ED, Lange RA, Cigarroa RG *et al*. Effect of cocaine on coronary artery dimensions in atherosclerotic coronary artery disease: enhanced vasoconstriction at sites of significant stenoses. *J Am Coll Cardiol* 1990; **16:**74–9.
86 Brogan WC, Lange RA, Kim AS *et al*. Alleviation of cocaine-induced coronary vasoconstriction by nitroglycerin. *J Am Coll Cardiol* 1991; **18:**581–6.
87 Hollander JE, Hoffman RS, Gennis P *et al*. Nitroglycerin in the treatment of cocaine associated chest pain – clinical safety and efficacy. *Clin Toxicol* 1994; **32:**243–56.
88 Negus BH, Willard JE, Hillis LD *et al*. Alleviation of cocaine-induced coronary vasoconstriction with intravenous verapamil. *Am J Cardiol* 1994; **73:**510–13.
89. Sandeman DJ, Alahakoon TI, Bentley SC. Tricyclic poisoning – successful management of ventricular fibrillation following massive overdose of imipramine. *Anaesth Intensive Care* 1997; **25(5):**542–5.
90 Evans JS, Oram MP. Neurological recovery after prolonged verapamil-induced cardiac arrest. *Anaesth Intensive Care* 1999; **27(6):** 653–5.
91 Cordova S, Lee R. Fixed dilated pupils in the ICU: another recoverable cause. *Anaesth Intensive Care* 2000; **28(1):**91–3.
92 Christiaens F, Lessire H, Dellers I *et al*. Successful prolonged cardiopulmonary resuscitation after a combined intoxication with a tricyclic antidepressant, a benzodiazepine and a neuroleptic. *Eur J Emerg Med* 2000; **7(3):**229–36.
93 European Resuscitation Council. Part 8: advanced challenges in resuscitation. Section 2: toxicology in ECC. *Resuscitation* 2000; **46(1–3):**261–6.
94 American Academy of Clinical Toxicology. Practice guidelines on the treatment of methanol poisoning. *Clin Toxicol* 2002; **40(4):**415–46.
95 Brent J. Current management of ethylene glycol poisoning. *Drugs* 2001; **61(7):**979–88.
96 McMartin KE, Ambre JJ, Tephly TR *et al*. Methanol poisoning in human subjects. Role for formic acid accumulation in the metabolic acidosis. *Am J Med* 1980; **68:**414–18.

97 Shanangian S, Ash KO. Formic and lactic acidosis in a fatal case of methanol intoxication. *Clin Chem* 1986; **32:**395–7.

98 Purssell RA, Pudek M, Brubacher J, Abu-Laban RB. Derivation and validation of a formula to calculate the contribution of ethanol to the osmolal gap. *Ann Emerg Med* 2001; **38:**653–9.

99 Jacobsen D, McMartin KE. Methanol and ethylene glycol poisonings. Mechanism of toxicity, clinical course, diagnosis and treatment. *Med Toxicol* 1986; **1:**309–34.

100 Kowalczuk M, Halvosen S, Ovrebo S *et al*. Ethanol treatment in ethylene glycol poisoned patients. *Vet Hum Toxicol* 1998; **4:**225–8.

101 Olsen KR, editor. *Poisoning and drug overdose*. Stamford, CN: Appleton and Lange; 1999.

102 McCabe JL, Cobaugh DJ, Menegazzi JJ *et al.* Experimental tricyclic antidepressant toxicity: a randomized, controlled comparison of hypertonic saline solution, sodium bicarbonate, and hyperventilation. *Ann Emerg Med* 1998; **32:**329–33.

103 Blackman K, Brown SG, Wilkes GJ. Plasma alkalinisation for tricyclic antidepressant toxicity: a systemic review. *Emerg Med* (Fremantle) 2001; **13:**204–10.

104 Hoffman JR, Votey SR, Bayer M *et al*. Effect of hypertonic sodium bicarbonate in the treatment of moderate-to-severe tricyclic antidepressant overdose. *Am J Emerg Med* 1993; **11:**336–41.

105 Burg F. Intoxications volontaires par la chloroquine. *These Medecine*. Strasbourg: Universite Louis Pasteur; 1976.

106 Conso F. Death from acute poisoning in man. *Vet and Hum Toxicol* 1979; **21:**68–9.

107 Goldfrank LR, editor. *Goldfrank's Toxicologic Emergencies*. 6th ed. Stamford, CN: Appleton and Lange; 1998; 745.

108 Vitris M, Aubert M. Intoxications a la chloroquine: notre experience a propos de 80 cas. *Dakar Medical* 1983; **28:**593–602.

109 Clemessy JL, Taboulet P, Hoffman JR *et al*. Treatment of acute chloroquine poisoning: a 5-year experience. *Crit Care Med* 1996; **24:**1189–95.

110 Riou B, Rimailho A, Galliot M *et al*. Protective cardiovascular effects of diazepam in experimental acute chloroquine poisoning. *Intensive Care Med* 1998; **14:**610–16.

111 Neuvonen PJ, Kivisto KT, Laine K *et al*. Prevention of chloroquine absorption by activated charcoal. *Hum Exp Toxicol* 1992; **11:**117–20.

112 Jaeger A, Raguin O, Liegeon MN. Acute poisoning by Class 1 antiarrhythmic agents and by chloroquine. *Rev Prat* 1997; **47:**748–53.

113 Jaeger A, Sauder P, Kopferschmitt J *et al*. Clinical features and management of poisoning due to antimalarialdrugs. *Med Tox* 1987; **2:**242–73.

114 Clemessy JL, Favier C, Borron SW *et al*. Hypokalaemia related to acute chloroquine ingestion. *Lancet* 1995; **346:**877–80.

115 Bouvier AM, Bertrand D, Timsit JF *et al*. Intoxications massives et prolongees par la nivaquine: effets du diazepam. Reanimation Soins Intensifs, *Medicine d'Urgence* 1986; **2:**265.

116 Riou B, Barriot P, Rimailho A *et al*. Treatment of severe chloroquine poisoning. *New Engl J Med* 1988; **318:**1–6.

117 Bateman DN, Dyson EH. Quinine toxicity. *Adv Drug React Ac Pois Rev* 1986; **5(4):**215–33.

118 Dargan PI, Wallace CI, Jones AL. An evidence-based flowchart to guide the management of acute salicylate (aspirin) overdose. *Emerg Med J* 2002; **19:**206–9.

119 Brenner BE, Simon RR. Management of salicylate intoxication. *Drugs* 1982; **24:**335–40.

120 Temple AR. Acute and chronic effects of aspirin toxicity and their treatment. *Arch Intern Med* 1981; **141:**364–9.

121 Chapman BJ, Proudfoot AT. Adult salicylate poisoning: deaths and outcome in patients with high salicylate concentrations. *Q J Med* 1989; **72:**699–707.

122 Higgins RM, Connolly JO, Hendry BM. Alkalinisation and hemodialysis in severe salicylate poisoning: comparison of elimination techniques in the same patient. *Clin Nephrol* 1998; **50:**178–83.

123 Proudfoot AT. Toxicity of salicylates. *Am J Med* 1983; **75:**99–103.

124 Prescott LF, Balali-Mood M, Critchley JA *et al*. Diuresis or urinary alkalinisation for salicylate poisoning? *BMJ (Clin Res Ed)* 1982; **285:**1383–6.

125 Hillman RJ, Prescott LF. Treatment of salicylate poisoning with repeated oral charcoal. *BMJ (Clin Res Ed)* 1985; **291:**1472.

126 Kirshenbaum LA, Mathews SC, Sitar DS *et al*. Does multiple-dose activated charcoal therapy enhance salicylate excretion? *Arch Intern Med* 1990; **150:**1281–3.

127 Barone JA, Raia JJ, Chain Y. Evaluation of the effects of multiple-dose activated charcoal on the absorption of orally administered salicylates in a simulated toxic ingestion model. *Ann Emerg Med* 1988; **17:**34–7.

128 Done AK. Salicylate intoxication: significance of measurements of salicylate in blood in cases of acute intoxication. *Pediatrics* 1960; **26:**800–7.

129 Thisted B, Krantz T, Stroom J *et al*. Acute salicylate self-poisoning in 177 consecutive patients treated in the ICU. *Acta Anaesthesiol Scand* 1987; **31:**312–16.

130 Todd PJ, Sills JA, Harris F *et al*. Problems with overdoses of sustained-release aspirin. *Lancet* 1981; **1(8232):**777.

131 Kwong TC, Laczin J, Baum J. Self-poisoning with enteric-coated aspirin. *Am J Clin Pathol* 1983; **80:**888–90.

132 Wortzman DJ, Grunfeld A. Delayed absorption following enteric-coated aspirin overdose. *Ann Emerg Med* 1987; **16:**434–6.

133 Henderson A, Wright DM, Pond SM. Management of theophylline overdose patients in the intensive care unit. *Anaesth Intensive Care* 1992; **20(1):**56–62.

134 Sessler CN. Theophylline toxicity: clinical features of 116 cases. *Am J Med* 1990; **88:**567–76.

135 Gaudreault P, Wason S, Lovejoy Jr FH. Acute pediatric theophylline overdose: a summary of 28 cases. *Journal of Pediatrics* 1983; **102:**474–6.

136 Sessler CN, Glauser FL, Cooper KR. Treatment of theophylline toxicity with oral activated charcoal. *Chest* 1985; **87:**325–9.

137 Sessler CN, Glauser FL, Cooper KR. Treatment of theophylline toxicity with oral activated charcoal. *Chest* 1985; **87:**325–9.

138 Minton NA, Henry JA. Treatment of theophylline overdose. *Am J Emerg Med* 1996; **14:**606–12.

139 Brown SGA, Prentice DA. Ondansetron in the treatment of theophylline overdose. *Med J Austr* 1992; **156:**512.

140 Sage TA, Jones WN, Clark RF. Ondansetron in the treatment of intractable nausea associated with theophylline toxicity. *Ann Pharmacother* 1993; **27:**584–5.

141 Vestal RE, Eiriksson Jr CE, Musser B *et al*. Effect of intravenous aminophylline onplasma levels of catecholamines and related cardiovascular and metabolic responses in man. *Circulation* 1983; **67:**162–71.

142 Kearney TE, Manoguerra AS, Curtis GP *et al*. Theophylline toxicity and the beta-adrenergic system. *Ann Intern Med* 1985; **102:**766–9.
143 Biberstein MP, Fiegler MG, Ward DM. Use of beta-blockade and hemoperfusion for acute theophylline poisoning. *West J Med* 1984; **141:**485–90.
144 Amin DA, Henry JA. Propranolol administration in theophylline intoxication. *Lancet* 1985; **1:**520–1.
145 Seneff M, Scott J, Friedman B *et al*. Acute theophylline toxicity and the use of esmolol to reverse cardiovascular instability. *Ann Emerg Med* 1990; **19:**671–3.
146 Vanden Hoek T, Murphy C, Aks S *et al*. The use of esmolol to reverse unstable supraventricular tachycardia in a theophylline toxic patient. *Vet Hum Toxicol* 1991; **33:**390.
147 Levine JH, Michael JR, Guarnieri T. Treatment of multifocal atrial tachycardia with verapamil. *N Engl J Med* 1985; **312:**21–5.
148 Heath A, Knudsen K. Role of extracorporeal drug removal in acute theophylline poisoning. *Med Toxicol* 1987; **2:**294–308.
149 Park GD, Spector R, Roberts RJ *et al*. Use of hemoperfusion for the treatment of theophylline intoxication. *Am J Med* 1983; **74:**961–6.
150 Covey TJ. Ferrous sulphate poisoning: a review, case summaries, and therapeutic regimen. *J Pediatr* 1964; **64:**218–26.
151 Mehta M. Acute iron poisoning. *Indian J Pediatr* 1997; **64:**485–93.
152 *British National Formulary.* Great Britain: Scottish Executive Health Department; 2001; 44, 444.
153 Tenenbein M. Whole bowel irrigation in iron poisoning. *J Pediatr* 1987; **111:**142–5.
154 Fine JS. Iron poisoning. *Curr Probl Pediatr* 2000; **30(3):**70–90
155 Helfer RE, Rodgerson DO. The effect of deferoxamine on the determination of serum iron and iron-binding capacity. *J Pediatr* 1996; **68:**804–6.
156 Gervitz NR, Wasserman LR. The measurement of iron and iron-binding capacity in plasma containing deferioxamine. *J Pediatr* 1966; **68:**802.
157 Siff JE, Meldon SW, Tomassoni AJ. Usefulness of the total iron binding capacity in the evaluation and treatment of acute iron overdose. *Ann Emerg Med* 1999; **33:**73–6.
158 Tenenbein M. Benefits of parenteral deferoxamine for acute iron poisoning. *Clin Tox* 1996; **34(5):**485–9
159 Westluin WF. Deferoxamine as a chelating agent. *J Toxicol Clin Toxicol* 1971; **4:**597–602.
160 Howland MA. Risks of parenteral deferoxamine for acute iron poisoning. *J Toxicol Clin Toxicol* 1996; **339:**699–701.
161 Banner W, Vernon DD, Ward RM *et al*. Continuous haemofiltration in experimental iron intoxication. *Crit Care Med* 1989; **17:**1187–90.
162 Lundquist P, Sorbo B. Rapid determination of toxic cyanide concentrations in blood. *Clin Chem* 1989; **35:**617–19.
163 Laforge M, Buneaux F, Houeto P *et al*. A rapid spectrophotometric blood cyanide determination applicable to emergency toxicology. *J Anal Toxicol* 1994; **8:**173–5.
164 Vesey CJ, McAllister H, Langford RM. A simple rapid and sensitive semimicro method for the measurement of cyanide in blood. *Ann Clin Biochem* 1999; **26:**755–8.
165 Berlin Jr CM. The treatment of cyanide poisoning in children. *Pediatrics* 1970; **46:**793–6.
166 Dodds C, McKnight C. Cyanide toxicity after immersion and hazards of dicobalt edetate. *BMJ* 1985; **291:**785–6.
167 Baud FJ, Boron SW, Megarbane B *et al*. Value of lactic acidosis in the assessment of the severity of acute cyanide poisoning. *Crit Care Med* 2002; **30(9):**2044–50.
168 Baud FJ, Barriot P, Toffis V *et al*. Elevated blood cyanide concentrations in victims of smoke inhalation. *N Engl J Med* 1991; **325:**1761–6.
169 George C, Ramsay K, Rochester M *et al*. Facilities for chemical decontamination in accident and emergency departments in the United Kingdom. *Emerg Med J* 2002; **19:**453–7.
170 Graham DL, Laman D, Theodore J *et al*. Acute cyanide poisoning complicated by lactic acidosis and pulmonary oedema. *Arch Intern Med* 1977; **137:**1051–5.
171 Prien T. Toxic smoke compounds and inhalation injury – a review. *Burns* 1988; **14:**451–60.
172 Hall AH, Rumack BH. Clinical toxicology of cyanide. *Ann Emerg Med* 1986; **15:**1067–74.
173 Dodds C, McKnight C. Cyanide toxicity after immersion and the hazards of dicobalt edetate. *BMJ* 1985; **291:**785–6.
174 Pronczuk de Garbino JP, Bismuth C. Propositions therapeutiques actuelles en cas d'intoxication par les cyanures. *Toxicol Eur Res* 1981; **3:**69–76.
175 Davison V. Cyanide poisoning: kelocyanor – a new treatment. *Occup Health* 1969; **21:**306–8.
176 Hall AH, Rumack BH. Hydroxocobalamin, sodium thiosulphate as a cyanide antidote. *J Emerg Med* 1987; **5:**115–21.
177 Johnson WS, Hall AH, Rumack BH. Cyanide poisoning successfully treated without 'therapeutic methaemoglobin levels'. *Am J Emerg Med* 1989; **7:**437–40.
178 Kirk MA, Gerace R, Kulig KW. Cyanide and methaemoglobin kinetics in smoke inhalation victims treated with the cyanide antidote kit. *Ann Emerg Med* 1993; **22:**1413–18.
179 Houeto P, Borron SW, Sandouk P *et al*. Pharmacokinetics of hydroxocobalamin in smoke inhalation victims. *J Toxicol Clin Toxicol* 1996; **34:**397–404.
180 Houeto P, Hoffman JR, Imbert M *et al*. Relation of blood cyanide to plasma cyanocobalamin concentration after a fixed dose of hydroxocobalamin in cyanide poisoning. *Lancet* 1995; **346:**605–8.
181 Beasley DM, Glass WI. Cyanide poisoning: pathophysiology and treatment recommendations. *Occup Med* 1998; **48:**427–31.