Clinical Toxicology: Part II. Diagnosis and Management of Uncommon Poisonings

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ABSTRACT

Objective: To review the diagnosis and management of drug overdose and poisonings in a two-part presentation.

Data sources: A review of articles reported on drug overdose and poisonings.

Summary of review: In patients who attempt suicide it is usual for the overdose to be a therapeutic agent, although in the severely mentally disturbed patient the agent may be an unusual poison. As with any overdose, the most important aspects in the management is the maintenance of the patient’s airway, ventilation and circulation, while the toxin is metabolised and excreted. Adsorbents, gastric lavage and haemodialysis or continuous renal replacement therapy and specific antidotes may be beneficial in individual cases.

The diagnosis and management of uncommon poisonings, including pesticides and herbicides (e.g. organophosphates, carbamates, paraquat, chlorophenoxy herbicides), carbon monoxide, cyanide, strychnine, halogenated hydrocarbons, elemental poisons (e.g. iron, arsenic, lead, mercury, selenium, barium, thallium, lithium, sodium, rubidium, cesium), alkaloids (e.g. mushroom, aconite, conium) and cantharidin poisoning along with the miscellaneous poisonings of quinine, chloroquine, isoniazid, thyroxine, cytotoxic agents (e.g. azathioprine, 6-mercaptopurine, colchicine, methotrexate) are discussed in the second part of this presentation on clinical toxicology.

Conclusions: In the critically ill patient who has taken an overdose of a non therapeutic agent, while activated charcoal, continuous renal replacement therapy and specific antidotes may be of benefit, maintenance of the patient’s airway, ventilation and circulation still remain the most important aspects of management. (Critical Care and Resuscitation 2002; 4: 216-230)

Key words: Drug overdose, poison, toxins, coma

Pesticides and herbicides

Organophosphates and carbamates

The organophosphates and carbamates are anticholinesterases which inhibit acetylcholinesterase, thereby prolonging the effects of acetylcholine (ACh). The anticholinesterases can be classified as quaternary amines (e.g. edrophonium), carbamates (e.g. neostigmine, physostigmine, pyridostigmine and carbaryl), and organophosphates.

The quaternary amines attach to the anionic site by electrostatic attachment, competing with ACh for this site (i.e. they provide a competitive block). The carbamates attach to the esteratic site as well as the anionic site of the enzyme. This attachment results in a chemical bonding and hydrolysis of the carbamylated enzyme which lasts for about 1 hr for neostigmine, physostigmine and pyridostigmine, and 6 - 12 hr for carbaryl. The organophosphates phosphorylate the esteratic site of the enzyme. Physostigmine and most organophosphates pass the blood-brain barrier (causing central nervous system effects), whereas neostigmine and pyridostigmine do not.

Anticholinesterases are often used in agriculture as pesticides. They are either organophosphates (e.g. malathion, dimethoate, metasystox, fenthion, parathion,
Organophosphates inactivate cholinesterase by phosphorylating the esteratic site of the enzyme, and unless dephosphorylation by pralidoxime occurs (which needs to be administered within a few hours of the organophosphate ingestion because of an ‘aging’ of the phosphorylated enzyme), new enzyme has to be synthesised before normal synaptic activity can occur (plasma cholinesterase recovers within 3 - 4 weeks, whereas red blood cell cholinesterase may not be fully restored to normal function for several months). Carbamates, on the other hand, combine reversibly with cholinesterase, allowing their effects to persist for only 12 hr or less.

Clinical features. There may be acute, intermediate and delayed sequelae in patients who have anticholinesterase poisoning.

1. Acute cholinergic syndrome. Acute anticholinesterase poisoning may occur from inhalation, skin absorption, or ingestion, with symptoms characteristically beginning after 30 - 60 min and reaching a maximum after 2 - 8 hr. In some cases, symptomatology may be delayed for up to 12 hr, and with dichlorfenthion and fenthion the onset of symptoms may be delayed by up to 2 and 5 days respectively. With fenthion the symptoms may recur after 24 days.

The organophosphate poisoned patient often emits a characteristic odour. The acute clinical picture may be mild, moderate or severe depending upon the quantity of cholinesterase inhibitor ingested. The patient exhibits some or all of the features listed in Table 1. With severe poisoning, multiple organ failure (e.g. respiratory failure, renal failure, hypotension, complete heart block, ventricular tachycardia and ventricular fibrillation) and even a necrotising pancreatitis can develop. While cardiac arrhythmias associated with organophosphate poisoning usually include an initial brief period of sinus tachycardia followed by bradycardia, a rare syndrome of prolonged QT$_c$ interval and sudden death has also been reported in patients from 1 - 15 days after the exposure.

2. Intermediate syndrome. An intermediate syndrome is diagnosed by the onset of motor paralysis developing 1 - 4 days after organophosphate poisoning. It is characterised by an acute respiratory paresis, weakness of proximal limb muscles and muscles supplied by cranial nerves, and depressed tendon

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical features of cholinesterase inhibitor toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organ or system</strong></td>
<td><strong>Muscarinic effects</strong></td>
</tr>
<tr>
<td>Ocular</td>
<td>miosis</td>
</tr>
<tr>
<td></td>
<td>increased lacrimal secretion</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>bradycardia, junctional rhythm</td>
</tr>
<tr>
<td></td>
<td>peripheral vasodilation</td>
</tr>
<tr>
<td>Respiratory</td>
<td>bronchoconstriction</td>
</tr>
<tr>
<td></td>
<td>bronchorrhoea, pulmonary oedema</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>increased tone and motility</td>
</tr>
<tr>
<td></td>
<td>decreased tone of sphincters and increased secretion</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>contraction of detrusor</td>
</tr>
<tr>
<td>Skin</td>
<td>relaxation of trigone and sphincter</td>
</tr>
<tr>
<td></td>
<td>increased sweat production</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Organ or system</strong></th>
<th><strong>Nicotinic effects</strong></th>
<th><strong>Clinical effects</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal</td>
<td>Skeletal muscle, initial stimulation followed by paralysis</td>
<td>fasciculations (eyelids, tongue) followed by weakness and paralysis (i.e. depolarising block)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Sympathetic ganglia initial stimulation followed by paralysis</td>
<td>tachycardia, hypertension (often overridden by parasympathetic effects)</td>
</tr>
<tr>
<td>Central nervous</td>
<td><em>Muscarinic and nicotinic effects</em></td>
<td>bradycardia, hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tremor, anxiety, confusion, seizures, coma</td>
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</tbody>
</table>
reflexes (i.e. a combined pre- and post-synaptic dysfunction of neuromuscular transmission). Patients with the intermediate syndrome may require mechanical ventilation for up to 18 days, before it reverses.\textsuperscript{5} Parathion is the causative agent in up to 75\% of cases.\textsuperscript{6}

3. Delayed sequelae. In some cases (due to the phosphorylation of a peripheral nervous tissue esterase),\textsuperscript{4,8} the acute cholinergic phase may be followed by a delayed peripheral polyneuropathy involving the distal muscles of the extremities.\textsuperscript{9} The rapid onset of a distal and symmetrical sensorimotor polyneuropathy (with weakness and ataxia\textsuperscript{10}) is diagnostic, appearing 2 - 5 weeks after the exposure. Chronic neuropsychological functional impairment (e.g. impairment of auditory attention, visual memory, problem solving, motor reaction and dexterity) may also occur after an acute episode of organophosphate poisoning,\textsuperscript{11} and after long-term occupational exposure.\textsuperscript{12}

The red blood cell (true) and plasma (pseudo) cholinesterase levels are reduced markedly with anticholinesterase poisoning and are usually 30 - 50\% of normal levels by the time symptoms appear.\textsuperscript{13} Patients with levels less than 50\% of normal are often symptomatic, although during convalescence the patient may return to normal muscle function with pseudo-cholinesterase levels of only 20\%. Normally, red blood cell cholinesterase levels return to normal after 5 - 7 weeks and pseudocholinesterase levels return to normal after 4 - 6 weeks.\textsuperscript{13}

Treatment. Treatment of organophosphate poisoning usually includes:

1. Resuscitation. Intravenous fluids, intubation ventilation and control of seizures by using benzodiazepines or barbiturates may be required, as well as gastric lavage and oral activated charcoal. Medical and nursing personnel should wear protective clothing and gloves, when dealing with these patients, to avoid contact with the pesticide.

2. Anticholinergic agents (e.g. atropine, glycopyrrolate). These agents reverse the muscarinic symptoms of bradycardia, and excessive gastrointestinal and respiratory secretions. While one study found that 7.5 mg of glycopyrrolate in 200 mL of 0.9\% saline was just as effective as 15 mg of atropine in 100 mL of 0.9\% saline (both of which were infused until the heart rate was > 60 and fasciculations were absent) in the management of organophosphate poisoning,\textsuperscript{14} atropine is usually regarded as the drug of choice and is administered intravenously in 1 - 5 mg amounts every 5 min until excessive secretions are controlled, the pulse rate is greater than 80 beats per min and the pupils are dilated.\textsuperscript{15} Up to 10 - 30 mg of atropine may be required initially, thereafter 1 - 5 mg may be required every 30 min for maintenance. While atropine (unlike glycopyrrolate) crosses the blood-brain barrier and reverses some of the central nervous system (CNS) effects, it is ineffective against the neuromuscular paralysis. In one case of organophosphate poisoning, 19,590 mg of atropine was administered over 24 days, with 2950 mg administered in one 24 hr period.\textsuperscript{16}

3. Cholinesterase reactivators (pralidoxime, obidoxine). Pralidoxime is the agent of choice as high doses of obidoxine are hepatotoxic.\textsuperscript{17} Pralidoxime (PAM) as the chloride, iodide, mesylate or methyl-sulphate salt are all equally effective in reactivating cholinesterase. However, pralidoxime chloride is usually recommended, as it has less side-effects than the iodide salt (repeated asystole has been reported with the administration of pralidoxime iodide\textsuperscript{18}) and can be used in patients who have iodide sensitivity.\textsuperscript{19}

Pralidoxime is most effective in treating the nicotinic symptoms (e.g. muscular fasciculations and paralysis) of certain organophosphate poisonings. It appears to be relatively ineffective against dimefox, dimethoate, methyl diazinon, mipafox and schradan and against carbamates (it may even increase carbamate toxicity because pralidoxime has a weak anticholinesterase activity).\textsuperscript{20} Pralidoxime is an ionised compound and therefore does not cross the blood-brain barrier easily. Accordingly it has minimal beneficial effects against CNS symptoms. It is also only effective if it is administered within 24 hr of the poisoning, as the organophosphate-cholinesterase bond becomes relatively permanent after 48 - 72 hr.

To reach a plasma concentration of 4 mg/L, pralidoxime should be administered as a 1 g intravenous bolus, followed by an infusion of 0.5 g/hr (i.e. 12 g/day).\textsuperscript{21} However, some believe that a plasma concentration of 4 mg/L does not permit the full exploitation of the therapeutic potential of pralidoxime\textsuperscript{22} and so higher doses have been used (e.g. 30 mg/kg followed by 8 mg/kg/hr,\textsuperscript{17} and in children 25 - 50 mg/kg followed by a continuous infusion of 10 - 20 mg/kg/hr).\textsuperscript{23}

Pralidoxime is relatively non toxic, although rapid intravenous administration may be associated with nausea, tachycardia, disturbances of vision, headache, dizziness and weakness due to transient neuromuscular blockade. It has an elimination half-life of 1.2 hr and is normally excreted by the kidneys.\textsuperscript{15}
Nevertheless, some have questioned the effectiveness of pralidoxime, with one stating that ‘PAM has no place’ in the current management of organophosphate poisoning. In one study of 10 cases of organophosphate poisoning, no clinical evidence of reactivation of the phosphorylated cholinesterase was observed, when pralidoxime was used. In another study, the use of pralidoxime (4 g in the first 24 h followed by 1 g daily for 5 days) was not associated with an improvement in outcome. Nevertheless, the doses used in all of these studies may have been insufficient, as other studies have reported beneficial effects from high dose pralidoxime administration.

4. Other therapy. Replacement of blood volume has been used successfully and plasmapheresis (with fresh frozen plasma replacement) may also be of use. In the experimental model, adenosine receptor agonists (5'-N-ethylcarboxamido-adenosine and N6-cyclopentyl adenosine) if given within minutes of organophosphate poisoning, prevent or reduce salivation, seizures and respiratory distress and improve survival. Magnesium sulphate has also been used to control tachycardia, ventricular arrhythmias and muscle fasciculations.

Paraquat

Paraquat is a commonly used herbicide which, on contact with green foliage and in the presence of sunlight, kills plant tissue. It is rendered harmless on contact with soil.

Clinical features. These include, nausea, vomiting, abdominal pain and diarrhoea, and, if concentrated formulations are swallowed, oral and throat ulcerations can occur. Signs of renal and hepatic dysfunction develop within 1 - 3 days, and are usually reversible when treated by conventional means. Pulmonary fibrosis and respiratory failure, on the other hand, is nonreversible and is the common cause of death. The respiratory complications usually appear with pulmonary oedema within 24 h of ingestion, followed after 1 - 2 weeks by a progressive pulmonary fibrosis. The pulmonary tissue is thought to be particularly susceptible because both type I and II alveolar cells actively accumulate paraquat, even against a concentration gradient. The mechanism of toxicity is due to an inhibition of superoxide dismutase, generation of free radicals, and NADH depletion. With severe acute toxicity, paraquat can cause a multisytem failure with lung, kidney and hepatic failure predominating, although cardiac necrosis, adrenal necrosis, and cerebral oedema may also occur.

Poisoning may be mild (usually less than 20 mg paraquat ion per kg or less than 7.5 mL of 20% paraquat concentrate) presenting with oral irritation, and gastric upset only and is associated with complete recovery; moderate (between 20 - 40 mg paraquat ion per kg or 7.5 - 15 mL of 20% paraquat concentrate) with renal, hepatic and pulmonary failure and often leading to death within 2 - 3 weeks; or severe (usually greater than 40 mg paraquat ion per kg or more than 15 mL of 20% paraquat concentrate) with pulmonary, renal and hepatic failure leading to death within a few days.

Plasma paraquat levels peak at 0.5 - 2 hours after ingestion, with the probability of survival predicted for the 4 - 12 h plasma level predicted using a graph or at any specified time using the equation: exp (logit)/[1 + exp(logit)], where logit = 0.58 - 2.33 x log (plasma paraquat) - 1.15 x log (hr since ingestion).

However, when plasma levels cannot be performed a urinary sodium dithionate test with a ‘navy blue’ or ‘dark blue’ reaction generally indicates significant paraquat poisoning with a subsequent poor prognosis. A colourless or light blue reaction generally indicates mild poisoning.

Treatment. Without appropriate treatment, the mortality after ingestion of paraquat varies from 87 - 100%. An injection of as little as 1 mL subcutaneously has been fatal. The estimated fatal dose in humans may be as low as 4 mg/kg, although the LD50 in an adult human is normally about 3 - 5 g (i.e. 10 - 15 mL of the 20% concentrate). Apart from gastric lavage and supportive management, the specific binder ‘Fuller’s earth’ (calcium montmorillonite) should be administered. As only 5 - 10% of paraquat is absorbed in 24 h, Fuller’s earth is given orally as soon as possible (e.g. 1 litre of a 30% solution - 300 g suspended in 1 litre of water - followed by 200 mL of 20% mannitol). This is followed 2-hourly by a 15% solution (1000 mL of water with 150 g of Fuller’s earth), followed by 200 mg of 20% mannitol, every 4 h to induce a catharsis, and it is repeated until the stools are seen to contain Fuller’s earth. If Fuller’s earth is unavailable, experimentally activated charcoal appears to be just as effective. If purgation is not achieved within 4-6 hours then gastrointestinal decontamination should be discontinued.

During purgation the patients fluid and electrolyte status needs to be closely monitored (Fuller’s earth may also cause hypercalcaemia and faecoliths with bowel obstruction or perforation). To reduce the toxicity of paraquat, oxygen administration is delayed as long as possible. Haemodialysis, peritoneal dialysis and haemoperfusion are all ineffective for paraquat removal, although haemodialysis may be required to manage renal failure. Also large doses of vitamin C and vitamin E as antioxidants have not yet been confirmed to be helpful and other antidotes including superoxide
dismutase, selenium, niacin, N-acetylcysteine, corticosteroids, immunosuppressive agents and radiotherapy, have not yet been shown to be effective in limiting the lung injury. 31

Lung transplantation has been used successfully to manage a patient with progressive respiratory failure 6 weeks after paraquat poisoning. 44 In another case report, a patient who ingested 160 mg/kg of paraquat, was treated with early digestive decontamination, haemodialysis, antioxidant treatment with desferrioxamine (100 mg/kg) for 24 hr and N-acetylcysteine (a loading dose of 150 mg/kg followed by 300mg/kg/day for 21 days), with a successful outcome. 35

In one study of patients with moderate to severe poisoning (determined by a dark blue reaction to sodium dithionite added to a specimen of the patient’s urine under alkaline conditions), cyclophosphamide 1 g intravenously for two days with methyl prednisolone 1 g daily for three days, reduced the mortality compared to a historical control group. 46 This study was followed up with a prospective randomised trial of intravenous cyclophosphamide (15 mg/kg infused over 2 hr for two days) and methyprednisolone (1 g infused over 2 hr for daily three days) in 50 patients with moderate to severe paraquat poisoning (this was associated with, oral activated charcoal two courses of charcoal haemoperfusion 8-hourly and dexamethasone 10 mg 8-hourly for 14 days) reducing the mortality from 57% to 18% (although mortality was not reduced in the group with severe poisoning). 38

However, another study using high dose dexamethasone and cyclophosphamide showed no reduction in mortality. 37

**Chlorophenoxy herbicides (e.g. 2,4-dichlorophenoxyacetic acid)**

While muscle weakness and peripheral neuropathy have been reported with occupational exposure, the toxicology of an acute ingestion parallels that of salicylic acid.

**Clinical features.** These include nausea, vomiting, abdominal pain, hypotension, pyrexia, diaphoresis, fatigue, thirst, anxiety, agitation, hyperventilation, tachycardia, slurred speech, acidosis, hypoglycaemia, drowsiness and coma.

**Treatment.** Apart from gastric lavage, repeated oral activated charcoal and haemodialysis, treatment is largely supportive. Intravenous glucose and alkaline diuresis to enhance renal excretion have also been used. 48

**Carbon monoxide**

Carbon monoxide combines with haemoglobin with an affinity which is 200 - 250 times greater than that of oxygen (carbon monoxide combines with the haem iron at the same site as oxygen) and shifts the oxygen-haemoglobin dissociation curve to the left. Both abnormalities are responsible for tissue hypoxia (although reperfusion injury and lipid peroxidation may also be responsible for tissue injury caused by carbon monoxide). 49 Normally, nonsmokers have a carboxyhaemoglobin level between 1 - 2% and smokers have a carboxyhaemoglobin level between 5 - 7%. While carbon monoxide may also combine to cytochrome oxidase, the affinity of cytochrome oxidase for oxygen is 8 times greater than that for carbon monoxide. 50

**Clinical features.** Symptoms may not be related to carboxyhaemoglobin levels, although in general, carboxyhaemoglobin concentrations less than 10% are usually not associated with symptoms. Patients with carboxyhaemoglobin levels of 20% or greater usually have a headache and dyspnoea, and have difficulty in concentrating. At levels of 30 - 40%, there are signs of irritability, nausea, confusion, tachypnoea, chest pain, ST segment depression, AV conduction block and ventricular dysrhythmias. Concentrations from 40 - 60% may be associated with seizures, coma, and death. The cherry-red discolouration of the skin and mucus membranes is not commonly found. There is also an increased incidence of pressure injury (e.g. rhadomyolysis with renal failure 51 and dermal blistering has also been reported 52 ) in patients with carbon monoxide poisoning.

Delayed complications of a diffuse cerebral demyelination causing gradual neurological deterioration with apathy, apraxia, gait disturbances, incontinence, movement disorders (parkinsonism, choreoathetosis), hallucinations, seizures, cortical blindness, dementia and coma beginning 1 - 40 days after the initial hypoxic insult, may occur in 2 - 10% of patients. 53,54

**Treatment.** The elimination half-life of carboxyhaemoglobin decreases from 350 min to 90 min when the patient breathes 100% oxygen (increasing when normocarbia is maintained). 55 Hyperbaric oxygen at twice atmospheric pressure (2 atm) decreases the elimination half-life further to 30 min. 56,57

If the patient is unconscious, then intubation and ventilation with 100% oxygen is performed. If there is a hyperbaric facility close by, administration of hyperbaric oxygen (2 atm for 2 hr) is often used for patients who were initially unconscious (i.e. unable to be roused by rescue staff), 56,58 which is usually associated with an initial carbon monoxide level greater than 40%. 57 As the foetus is unduly sensitive to carbon monoxide toxicity, carbon monoxide poisoning and pregnancy is often used as an indication for hyperbaric oxygen therapy. 49,49
If the patient has not suffered any impairment of consciousness, hyperbaric oxygen (in comparison to continuous oxygen by face mask) is not associated with an improved outcome, and administration of oxygen by facemask for 6 hr is all that is required. One study of 50 patients with acute carbon monoxide poisoning were enrolled in a trial of hyperbaric oxygen compared with normobaric oxygen delivered in a hyperbaric chamber (a true sham control). This study revealed no difference in persistent or delayed neuropsychological sequelae between treatment groups. In a recent randomised, controlled study of 191 patients with CO poisoning, hyperbaric oxygen (compared with continuous oxygen by face mask) was of no benefit, and in a subgroup of patients with severe carbon monoxide poisoning associated with a worse outcome, leading the authors to conclude that CO should not be used for CO poisoning.

N-acetylcysteine administration, as outlined for paracetamol overdosage, has also been used to reduce the incidence of post hypoxic neurological sequelae.

**Cyanide poisoning**

Cyanide combines with the cytochrome oxidase $\text{Fe}^{3+}$, paralysing cellular respiration. In adults the lethal dose of hydrocyanic acid is 50 mg, while that of an ingested cyanide salt is 250 mg, both of which may be associated with blood cyanide levels of 0.25 - 0.30 mg/100 mL (96 - 115 $\mu$mol/L). Cyanide poisoning may also occur in patients with amygdalin toxicity (a cyanogenic glycoside found in the kernels of apricots, peaches and plums). When amygdalin is taken by mouth it can be hydrolysed to benzaldehyde and cyanide by beta-glucosidases.

**Clinical features.** If large quantities of cyanide are ingested or inhaled, there is often a rapid demise (usually within 1 - 15 min), which is preceded by rapid respiration, vomiting, hypotension, agitation, coma and convulsions.

The patient often has a characteristic smell of bitter almonds. With moderate doses, death usually occurs within 4 hr. The body's natural detoxification mechanisms will normally inactivate 50% of absorbed cyanide within 1 hr; thus if there are no signs of cyanide toxicity within the first 1 - 3 hr of exposure to cyanide, it is unlikely that cyanide toxicity will occur.

**Treatment.** Apart from supportive measures (e.g. removing clothing and washing skin contaminated with cyanide), specific measures include:

1. **Chelating agents.** Dicobalt edetate has a higher affinity for cyanide ions than cytochrome oxidase, and will form cobalt cyanide complexes that are stable and nontoxic. Approximately 300 mg is infused slowly intravenously followed by 50 mL of 50% dextrose. This is followed by a further 300 mg of cobalt edetate (if no adverse response occurs with the first dose). As this agent commonly produces angio-oedema (particularly in the absence of cyanide), it should only be used when definite evidence of cyanide toxicity exists.

Hydroxocobalamin is also a specific cyanide antidote acting by combining with the cyanide ion on a molar basis to form the nontoxic cyanocobalamin. While hydroxocobalamin is nontoxic and believed to be a more effective agent for cyanide toxicity than dicobalt edetate, 3 litres (or 3000 ampoules of the presently marketed hydroxocobalamin solution) will be required to achieve the dose of 50 mg/kg required for adults. Intravenous administration of 5 g of hydroxocobalamin (3.714 mmol) in 100 mL of water has been used empirically in patients with suspected cyanide poisoning, using a plasma cyanocobalamin (measured shortly after the infusion) at or near 300 $\mu$mol/L as an indication for a further 5 g of hydroxocobalamin.

2. **Methaemoglobin forming agents and thiosulphate.** Sodium or amyl nitrite can produce methaemoglobin (i.e. change $\text{Fe}^{2+}$ to $\text{Fe}^{3+}$) which has the capacity to provide an alternative sink for the cyanide ion. The methaemoglobin level aimed for in treatment of cyanide toxicity is 25%, which may be achieved by:

   a. $\text{NaNO}_2$ 0.3 g intravenously over 20 min and sodium thiosulphate 12.5 g intravenously over 10 min. The latter is administered to provide sulphur for the formation of the nontoxic thiocyanate.

   b. Amyl nitrite inhalation for 5 min (which may require 2 - 3 amyl nitrate ampoules) has also been recommended. However, it is now not used as it does not achieve adequate levels of methaemoglobin.

While there may be some evidence to support the use of all agents, in general, if cyanide toxicity is suspected and the patient is conscious and oriented, then observation for 2 hr may be all that is required, particularly as natural detoxification mechanisms will inactivate 50% of absorbed cyanide within 1 hr of exposure.

Nevertheless, if the patient is drowsy, stuporous or in coma, then blood levels for cyanide should be taken and hydroxocobalamin or cobalt edetate administered.

**Strychnine**

Strychnine is an alkaloid extracted from the seeds of the Strychnos nuxvomica vine. It is rapidly absorbed from the gastrointestinal tract, metabolised in the liver and has a plasma half life of approximately 10 hr.
Strychnine produces a receptor block of the post synaptic inhibitory neurone neurotransmitter, glycine (tetanus toxin acts at the same neurone, although it prevents the release of the neurotransmitter, glycine). The fatal dose of strychnine is 15 - 30 mg.

**Clinical features.** Usually within a few minutes of ingestion of strychnine the patient develops increased muscle tone, extensor muscle spasms, seizures and respiratory paralysis. Lactic acidosis, hyperthermia and rhabdomyolysis may develop due to continuous seizures.72

**Treatment.** Management is largely supportive consisting of gastric lavage followed by repeated oral activated charcoal to reduce further absorption of the toxin,73 and diazepam or phenobarbitone sedation to control muscle spasms. Uncontrolled muscle spasms require relaxation, intubation and mechanical ventilation. Because both detoxification and excretion for strychnine are rapid the prognosis is good for a patient that can be supported over 6 - 12 hr.74,75 Acute chemical pancreatitis has also been described with non fatal strychnine poisoning.76

**Halogenated hydrocarbons**

**Methyl chloride, methyl bromide and methyl iodide**

These agents are used as refrigerants and as fumigants. Methyl chloride and bromide are gases at room temperature, whereas methyl iodide is a volatile liquid.

**Clinical features.** These include dizziness, headache, nausea, vomiting, abdominal pain, blurred vision, vertigo, weakness, paralysis, drowsiness, pulmonary oedema, anuria, coma, seizures, hypotension and death.

**Treatment.** Apart from gastric lavage and repeated oral activated charcoal, the treatment is largely supportive.

**Trichlorethylene, 1,1,1-trichloroethane, tetrachloroethylene**

All these agents have predominantly anaesthetic effects.

**Carbon tetrachloride**

Carbon tetrachloride is used as an industrial solvent. The fatal adult dose (by inhalation or ingestion) is 3 - 5 mL.

**Clinical features.** The clinical features include, vomiting, abdominal pain, diarrhoea, ataxia, confusion, drowsiness and coma. Hepatorenal failure usually occurs within 48 hr, although it may be delayed up to 2 weeks after the exposure.

**Treatment.** While hyperbaric oxygen has been used to treat carbon tetrachloride toxicity (which acts by inhibiting the P450 mixed function oxidase system),77,78 standard therapy requires the administration of intravenous N-acetylcysteine (which facilitates the detoxification of the active intermediates of CCl₄ produced by P₄₅₀ mixed function oxidase system)79 in a therapeutic regimen outlined for paracetamol toxicity.80 As carbon tetrachloride may still be detectable 10 days after ingestion, the N-acetylcysteine is continued or followed by 5 days of oral methionine 4 g a day.

**Elemental poisons**

**Acute iron poisoning**

The majority of iron preparations are either sulphate (20% elemental iron), gluconate (12% elemental iron) or fumarate (33% elemental iron) compounds. Nontoxic ingestions are defined as those less than 20 mg of elemental iron per kilogram (< 1.5 g/70 kg), mild toxicity is defined as 20 - 60 mg of elemental iron per kilogram (1.5 - 4.0 g/70 kg) and severe toxicity is defined as > 60 mg elemental iron per kilogram (i.e. > 4.0 g/70 kg). A serum iron level of greater than 60 µmol/L (350 µg/100 mL) is generally considered to be associated with toxicity (i.e. gastrointestinal, renal, hepatic and cardiac failure).81

**Clinical features.** Acute iron poisoning is often a paediatric problem. The clinical features are due to the direct corrosive properties of iron and are often divided into four stages:

1. During the first 6 hr after ingestion, vomiting, diarrhoea, melena and abdominal pain often occur which may progress to haemorrhagic gastritis, intestinal necrosis, perforation and peritonitis. The blood pressure falls initially as the intravascular fluid leaks into the interstitial space and haemocoencentration occurs.
2. At 6 - 24 hr after ingestion, the patient often appears to be improving and the severity of the toxicity may be underestimated.
3. At 12 - 24 hr after ingestion, signs of systemic toxicity may appear with metabolic acidosis, fever, coma, seizures, bleeding disorders, hepatic failure, renal failure and shock.
4. Several weeks after the ingestion, intestinal scarring and obstruction may occur.

**Treatment.** Apart from supportive measures, desferrioxamine (an iron-specific chelating agent, 1 g of which will bind with 85 mg of elemental iron) is used. It can be administered both orally, to bind with iron in the gastrointestinal tract and decrease its absorption, and intravenously to bind with free iron to form a soluble complex which is readily excreted via the kidneys.

Gastric lavage is performed using a desferrioxamine solution (e.g. 2 g in 1 litre of water). After the lavage is
completed, 5 g of desferrioxamine in 50 mL of water is left in the stomach. If mild iron toxicity is suspected then desferrioxamine is infused at 5 mg/kg/hr (350 mg/70kg/hr) for 16 hours.90 If severe iron toxicity is suspected then desferrioxamine is infused at 15 mg/kg/hr (1000 mg/70kg/hr) for no longer than 24 hr (i.e. up to a maximum of 24 g/70 kg) as an infusion of desferrioxamine for longer periods may cause acute respiratory distress syndrome.82 Plasmapheresis, to remove the iron-desferrioxamine complex should be reserved for patients who have renal failure.

Arsenic, lead, mercury
Arsenic causes toxicity by combining with sulphhydryl (-SH) enzymes and interfering with cellular metabolism.

Clinical features.
1. Acute arsenic ingestion may produce a severe gastroenteritis with nausea, vomiting, diarrhoea (which may be watery or bloody) and severe abdominal pain. The patient develops shock from fluid loss, haemolysis, coma, seizures and if death does not intervene, renal and hepatic failure occur within 1 - 3 days. With lesser doses, a neurological form of the disease is prominent with headaches, dizziness, chills, cramps, and variable paralysis which may develop over a period of several weeks. Cardiac failure and arrhythmias may also be prominent. Inhalation of arsenic dusts may cause acute pulmonary oedema. Chronic arsenic toxicity may cause white transverse bands (Méé’s lines) on the nailplate, hyperpigmentation, palmar and plantar hyperkeratosis, garlic halitosis, pancytopenia and abnormal red blood cell morphology (e.g. anisocytosis, poikilocytosis, and basophilic stippling).83 Numerous multicentric superficial basal cell carcinomas may also be a feature.84

2. Acute mercury or lead poisoning may produce a severe gastroenteritis with nausea, vomiting, bloody or watery diarrhoea and abdominal pain. The patient may develop shock from fluid loss. An abdominal X-ray may reveal the radiopaque lead arsenate or mercury material.

Treatment. Apart from gastric lavage, treatment is largely symptomatic. The water soluble and non toxic chelating agent 2,3-dimercaptosuccinic acid (DMSA – Succimer) may also be used to increase the excretion of the heavy metal,85 and may be administered either orally or intravenously at 30 mg/kg for five days then 20 mg/kg for the following two weeks.86 Dimercaprol 3 mg/kg (200 mg/70 kg) as an intramuscular injection 4-hourly for 2 days then 2 mg/kg (150 mg/70 kg) 12-hourly may be used to hasten excretion of arsenic, lead or mercury if DMSA is not available. Treatment for up to 10 days may be necessary. If renal failure exists then haemodialysis will be necessary to remove the dimercaprol. For lead poisoning, the additional treatment of calcium edetate 50 - 75 mg/kg (3500 - 5000 mg/70 kg), infused over 1 hr for 5 days (every 2 g of calcium edetate should be diluted with 200 mL of 0.9% saline) may be included with DMSA.87

Barium
The absorbable salts of barium are carbonate, hydroxide and chloride, which have all been used as pesticides. Barium reduces the membrane permeability to potassium by blocking potassium channels,88 and it can also initiate or potentiate synaptic transmission, by causing release of acetylcholine. The lethal dose of absorbed barium is approximately 1 g.

Clinical features. These include vomiting, diarrhoea, muscle fasciculations, weakness, cardiac failure, arrhythmias, coma and seizures. The characteristic biochemical abnormality is severe and resistant hypokalaemia.89

Treatment. Apart from gastric lavage, treatment is largely supportive, using endotracheal intubation and mechanical ventilation if respiratory failure intervenes. Sodium sulphate 30 g orally and repeated after an hour, has been used in an attempt to form an insoluble barium sulphate from the barium not yet absorbed. Haemodialysis shortens the half-life of barium and is used in severe barium poisoning.90 Intravenous magnesium and potassium chloride are used to correct hypomagnesaemia and hypokalaemia, respectively.

Thallium
The fatal dose is approximately 1 g of absorbed thallium.

Clinical features. These include abdominal pain, nausea, vomiting, loss of hair, pains in the extremities, cerebellar ataxia, mental impairment, flaccid paraparesis, hypertension, sinus tachycardia, and ventricular tachycardia which occur from 1 - 10 days after ingestion.

Treatment. This is largely supportive, although oral Prussian blue (i.e. potassium ferrihexacyanoferrate, 5 g in 50 mL of 15% mannitol solution, orally four times a day, to form insoluble complexes in the gut lumen, with thallium ions exchanging for potassium ions in the molecular lattices) and haemodialysis are effective in clearing thallium, reducing the elimination half-life from 8 to 1.4 days.91-93

Selenium
Acute selenium poisoning may produce (within hours), hepatic necrosis, haemolysis, acute cardiomyopathy, seizures and red pigmentation of viscera. With
chronic poisoning, nausea, ‘garlic’ breath odour, vomiting, diarrhoea, alopecia and red pigmentation of nails, hair and teeth may occur. The treatment is largely symptomatic.\textsuperscript{94}

**Group 1A alkali metals (lithium, rubidium, cesium)**

- **Rubidium.**
  - Rubidium chloride has been used as an antidepressant,\textsuperscript{95} however its long half life (i.e. 30 - 60 days)\textsuperscript{96} and experimental epileptogenicity (particularly in the presence of hypokalaemia,\textsuperscript{97} which may be caused by a rubidium induced kaluresis),\textsuperscript{98} have limited its use.

- **Cesium.**
  - Cesium chloride has been used for cancer, depression, schizophrenia and prophylaxis against radioactive cesium exposure.\textsuperscript{99} While oral doses up to 6 g/day maintain elevated cesium blood levels for more than a year, it appears to be largely non toxic in doses up to 6 g/day (0.5 mmol/kg/day) for 36 days in the normal individual.\textsuperscript{100} However, mild symptoms of diarrhoea and tingling of the mouth, hands and feet (particularly in the presence of a low potassium diet) have been described,\textsuperscript{100} and in large doses (1 - 2 mmol/kg) ventricular tachycardia is observed in the experimental model.\textsuperscript{101} Prolonged QT, and torsade de pointes have been described (that ceased when the cesium tablets were discontinued) in a patient taking 1 g of oral cesium chloride 8-hourly.\textsuperscript{102}

  As both rubidium and cesium toxicities are exacerbated by hypokalaemia, treatment of these disorders requires potassium therapy.

**Miscellaneous poisonings**

- **Quinine and chloroquine.**
  - Quinine is used as an antimalarial agent and to treat nocturnal cramps. It is also present in tonic water. Chloroquine is used to treat malaria, rheumatoid arthritis and systemic lupus erythematosus.

  **Clinical features.**
  1. **Quinine overdose.** The clinical features of a quinine overdose includes cinchonism (headache, vertigo, tinnitus, deafness, nausea and vomiting), hypotension, drowsiness, blurred vision, sudden loss of vision (which may occur 24 hr after the overdose, and may be due to retinal artery vasospasm or a direct retinal toxic effect of quinine), coma, seizures and cardiac arrhythmias.
  2. **Chloroquine overdose.** The clinical features of a chloroquine overdose include nausea, vomiting, sedation, coma, seizures, visual problems, cardiac arrhythmia, hypotension and shock. Hypokalaemia, due to a potassium compartmental shift (by inhibiting the potassium exit from cells),\textsuperscript{103} also occurs with severe overdosage and may be exacerbated by catecholamine therapy.\textsuperscript{104} Death can occur with doses of chloroquine base above 30 mg/kg (e.g. 15 tablets in an adult) and doses above 5 g are commonly associated with a fatal outcome. Most deaths occur from 1 to 3 hr after ingestion. Despite the elimination half-life of chloroquine of 6 to 14 days, the toxic effects rarely last beyond 24 hr.\textsuperscript{105}

  **Treatment.** Apart from gastric lavage and repeated oral activated charcoal, treatment is largely supportive. While stellate ganglion block has been recommended to prevent quinine amblyopia, it does not reduce the incidence of visual defects associated with quinine overdosage and therefore is no longer recommended.\textsuperscript{106,107}

  Hypotension is managed using standard therapy of intravenous infusions followed by intravenous calcium chloride (10 mL of 10% calcium chloride over 5 min) and inotropic support. Right heart catheter monitoring may also be required. In patients who have taken 5 g or more of chloroquine, one study reported a decrease in mortality from 91 to 9% by immediate endotracheal intubation, mechanical ventilation, diazepam (2 mg/kg, i.e. 140 mg/70 kg over 30 min and continuing at 1 - 2 mg/kg/min for 1 - 4 days) and a continuous infusion of adrenaline (0.25 µg/kg/min, i.e. 15 µg/70 kg/min and increasing in increments of 0.25 µg/kg/min until the systolic blood pressure was 100 mmHg or greater).\textsuperscript{108} Methaemoglobinemia may occur with overdoses of dapsone or primaquine.\textsuperscript{109}

- **Isoniazid.**
  - An acute ingestion of more than 6 g of isoniazid is associated with severe toxicity, due to an inhibition of the enzyme pyridoxal-5-phosphate causing a CNS depletion of gamma-aminobutyric acid (GABA).\textsuperscript{110}

  **Clinical features.** Symptoms and signs usually develop within 30 min to 2 hr after ingestion, beginning with nausea, vomiting, blurred vision, visual abnormalities (coloured lights, spots), dizziness, ataxia and slurred speech, which are followed by stupor, coma and seizures. Seizures usually occur if more than 6 g have been ingested. Hyperpyrexia, metabolic acidosis, hyperkalaemia, rhabdomyolysis and renal failure may also occur.

  **Treatment.** This consists of pyridoxine, 1 g intravenously for every gram of isoniazid ingested, or, if the amount of isoniazid ingested is unknown, 5 g intravenously at 15 min intervals, until the seizures are controlled.\textsuperscript{111,112} There is little correlation between severity of intoxication and isoniazid blood levels.\textsuperscript{113} Acute administration of pyridoxine is relatively safe. In one individual, 52 g of pyridoxine was tolerated without...
adverse effects.\textsuperscript{110}

\textbf{Thyroxine overdose}

The half-life of thyroxine (T\textsubscript{4}) is 7 days, and overdoses of up to 10 mg are usually well tolerated.\textsuperscript{114,115} With massive overdoses (i.e. 20 - 1200 mg) signs of thyrotoxicosis develop within 3 days (e.g. nervousness, insomnia, tachycardia, heat intolerance, fever, arthralgia, weakness and diarrhoea), cardiac arrhythmias, delirium and coma develops after 7 - 10 days. Treatment usually consists of oral activated charcoal only. If symptoms of hyperthyroidism appear, propranolol 120 - 180 mg/day and hydrocortisone 100 mg daily may be used. With severely elevated levels of T\textsubscript{4}, plasmapheresis has been recommended,\textsuperscript{116} although in one patient who ingested 6 mg of thyroxine, plasmapheresis was of no significant pharmacokinetic or clinical benefit.\textsuperscript{117}

\textbf{Cytotoxic agents}

Overdose of azathioprine or 6-mercaptopurine are often without clinical effect and therefore aggressive treatment is usually not warranted.\textsuperscript{118} Vincristine overdose is treated with folinic acid and plasmapheresis.\textsuperscript{119} Colchicine overdose is usually associated with a high mortality (due to irreversible shock and cardiac arrhythmias) and treatment is often limited to supportive measures. Recently, colchicine-specific Fab fragments (6.4 g intravenously in a patient who ingested 60 mg of colchicine) were used successfully in the management of life threatening colchicine poisoning.\textsuperscript{120} Methotrexate poisoning is treated with folinic acid (60 mg 12-hourly for the first 24 hr, then 15 mg 6-hourly for 5 to 7 days). Haemoperfusion may be warranted if methotrexate poisoning is association with renal failure. Methotrexate neurotoxicity (due to a neural adenosine effect) may be reduced by using the adenosine blocker aminophylline (2.5 mg/kg, i.v. over 6 hours).\textsuperscript{121}

\textbf{Mushroom poisoning}

Of the 2000 species of mushrooms, approximately 50 are poisonous to humans, with the genus \textit{Amanita} being responsible for more than 90% of deaths. The various species of mushroom poisonings produce either a mild non life-threatening clinical disorder or a severe life-threatening disorder.

The non life-threatening mushroom poisonings usually present within 2 hr of ingestion (c.f. life-threatening mushroom poisoning where symptoms occur 6 - 12 hr after ingestion) with clinical features of, a) nausea, vomiting, diarrhoea and colic (with mush-rooms that contain an enteric toxin), b) excess secretions (with mushrooms that contain muscarine alkaloids), c) ataxia, narcosis and hallucinations (with mushrooms that contain GABA agonists or atropine alkaloids), d) mood elevation, disorientation and hallucinations (with mushrooms that contain psilocybin) or, e) flushing, paraesthesias, nausea, vomiting, tachycardia, hypotension and sweating, following the ingestion of alcohol (with mushrooms that produce a disulfiram effect due to coprine).\textsuperscript{122}

The non life-threatening mushroom poisonings usually resolve within 6 hr and require symptomatic treatment only.\textsuperscript{122}

Life-threatening mushroom poisoning may occur with:

a. \textit{Gyromitrin esculenta} poisoning. Clinical features associated with \textit{Gyromitrin esculenta} poisoning include nausea, vomiting, watery or bloody diarrhoea, abdominal pain, and muscle cramps, which occurs 6 - 12 hr after ingestion and which are thought to be due to the poison monomethylhydrazine. The patient may progress to liver failure, seizures, coma and death in 15 - 40% cases. Treatment requires standard cardiovascular and respiratory support as well as intravenous pyridoxine hydrochloride 25 mg/kg. The pyridoxine is repeated and titrated to neurological symptoms, and may require up to 20 g/day.\textsuperscript{123}

b. \textit{Amanita phalloides} poisoning. The symptoms and signs specific of \textit{Amanita phalloides} poisoning are gastrointestinal irritability due to the toxin phalloidin, and hepatic, renal and cerebral damage due to the toxin alpha-amanitin (which inhibits RNA polymerase II and is not inactivated by cooking, freezing or drying).\textsuperscript{124} Pancreatitis may also occur.\textsuperscript{125} Death occurs in up to 50% of cases and commonly occurs with ingestion of 3 or more mushrooms (i.e. 50 g)

\textit{Clinical features.} There are three phases of the \textit{Amanita phalloides} poisoning:

1. The first stage is heralded by crampy abdominal pain, nausea, vomiting and watery diarrhoea which often occurs 6 - 24 hr after ingestion.
2. The second stage of biochemical hepatic and renal failure occurs 24 - 48 hr after ingestion and may occur after resolution of the gastrointestinal disorder. The patient may feel relatively well although the biochemical tests reveal grossly elevated transaminase and bilirubin levels, prolonged prothrombin time and elevation of the serum creatinine and urea.
3. The third stage is heralded with encephalopathy which begins with the progressive hepatic and renal failure.

\textit{Treatment}.\textsuperscript{125,126} This consists of gastric lavage followed by repeated oral activated charcoal. However,
as patients often present 6 - 8 hr after ingestion, measures to reduce the gastrointestinal absorption may be of limited use.
a. *Penicillin G* (300,000 - 1,000,000 u/kg/day for three days) should be administered as it has a specific antitoxin effect and enhances urinary excretion.
b. *Silymarin* (an extract of milk thistle) at 20 - 50 mg/kg/day for four days (each infusion lasting 2 hr) is also administered.
c. *Plasmapheresis* may also be effective because aminitin is tightly bound to plasma proteins. In one study, plasmapheresis was associated with a reduction in mortality from 80 to 12%.
d. *Hepatic transplantation* should be considered in the event of irreversible hepatic failure occurring.
e. *N-acetylcysteine* infusions have also been used successfully in case studies.

**Aconite poisoning**

Aconite alkaloids (e.g. aconitine, mesaconitine, hyaconitine) are found in many Chinese herbs. The alkaloids are sodium channel activators and have widespread effects on the excitable membranes of cardiac, neural and muscle tissues. Ventricular tachycardia and fibrillation are caused by the enhancement of a transmembrane inward sodium current during the plateau phase of the myocardial action potential which prolongs repolarisation and induces after-depolarisations with triggered automaticity. Stimulation of the vagal medullary centre may also cause bradycardia and sinus arrest.

*Clinical features.* Symptoms include dizziness, nausea, vomiting, diarrhoea, paraesthesia, and palpitations which usually follow within 30 - 60 minutes of aconite alkaloid ingestion. The signs include hypotension, diaphoresis, shock, ventricular tachycardia and ventricular fibrillation.

*Treatment.* This initially consists of gastric lavage followed by oral activated charcoal. The ideal therapy for aconite-induced arrhythmias is unknown, although anecdotal reports of resolution of the arrhythmias using flecaïnide, amiodarone, lignocaine, mexiletine, procainamide and phenytoïn have been published. Cardiopulmonary bypass and ventricular assist devices have been used for refractory cardiac arrest. Aconite cardiotoxicity usually resolves within 24 hr.

**Conine (hemlock) poisoning**

Conium alkaloids are responsible for hemlock (Conium maculatum) poisoning. The pharmacological effects include nicotinic receptor stimulation then paralysis.

*Clinical features.* Symptoms include nausea, vomiting, lethargy, drowsiness, narcosis, weakness and muscle pain which usually follow within 10 - 60 minutes of the alkaloid ingestion. The signs include flaccidity, paralysis, diaphoresis, bradycardia, hypotension, rhabdomyolysis and shock.

*Treatment.* This consists of gastric lavage followed by oral activated charcoal. Cardiovascular, respiratory and renal failure are all managed using standard principles.

**Cantharadin (‘Spanish fly’) poisoning**

The availability of ‘Spanish fly’ in some cultures, its dubious reputation as an aphrodisiac, and the fact that ingestion is frequently inadvertent, mean cantharadin poisoning should be suspected in any patient presenting with unexplained haematuria or with gastrointestinal haemorrhage. Cantharadin acts as a protein phosphatase inhibitor.

*Clinical features.* Symptoms include burning of the mouth, dysphagia, nausea, vomiting, haematemesis, gross haematuria, dysuria, ascending weakness (Guillain-Barré like syndrome), cranial nerve palsies and fixed dilated pupils. Priapism, seizures, and cardiac abnormalities are less commonly seen.

*Treatment.* This consists of gastric lavage followed by oral activated charcoal. Cardiovascular, respiratory and renal failure are all managed using standard principles.

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