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. azothioprine, 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,

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sarin, soman) or carbamates (e.g. Carbaryl, Baygon).

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.[1] With fenthion the symptoms may recur after 24 days.[1]

   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.[2] 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.[3]
2. *Intermediate syndrome*. An intermediate syndrome is diagnosed by the onset of motor paralysis developing 1 - 4 days after organophosphate poisoning.[4] It is characterised by an acute respiratory paresis, weakness of proximal limb muscles and muscles supplied by cranial nerves, and depressed tendon

Table 1 Clinical features of cholinesterase inhibitor toxicity

Organ or system	*Muscarinic effects*	*Clinical effects*
Ocular	miosis	blurred vision
	increased lacrimal secretion	
Cardiovascular	bradycardia, junctional rhythm	hypotension
	peripheral vasodilation	warm skin
Respiratory	bronchoconstriction	dyspnoea, cough, cyanosis
	bronchorrhoea, pulmonary oedema	crackles, wheezes
Gastrointestinal	increased tone and motility	salivation, vomiting
	decreased tone of sphincters and increased secretion	diarrhoea, abdominal cramps
Genitourinary	contraction of detrusor	urinary incontinence
	relaxation of trigone and sphincter	
Skin	increased sweat production	diaphoresis
Organ or system	*Nicotinic effects*	*Clinical effects*
Musculoskeletal	Skeletal muscle, initial stimulation followed by paralysis	fasciculations (eyelids, tongue) followed by weakness and paralysis (i.e. depolarising block)
Cardiovascular	Sympathetic ganglia	
	initial stimulation	tachycardia, hypertension (often overridden by parasympathetic effects)
	followed by paralysis	bradycardia, hypotension
Central nervous	*Muscarinic and nicotinic effects*	tremor, anxiety, confusion, seizures, coma

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.[5] Parathion is the causative agent in up to 75% of cases.[6]

3. *Delayed sequelae.* In some cases (due to the phosphorylation of a peripheral nervous tissue esterase),[7,8] the acute cholinergic phase may be followed by a delayed peripheral polyneuropathy involving the distal muscles of the extremities.[9] The rapid onset of a distal and symmetrical sensorimotor polyneuropathy (with weakness and ataxia[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,[11] and after long-term occupational exposure.[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.[13] Patients with levels less than 50% of normal are often symptomatic, although during convalescence the patient may return to normal muscle function with pseudocholinesterase 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.[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 faciculations were absent) in the management of organophosphate poisoning,[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.[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.[16]
3. *Cholinesterase reactivators (pralidoxime, obidoxine).* Pralidoxime is the agent of choice as high doses of obidoxime are hepatotoxic.[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[18]) and can be used in patients who have iodide sensitivity.[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).[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).[21] However, some believe that a plasma concentration of 4 mg/L does not permit the full exploitation of the therapeutic potential of pralidoxime,[22] and so higher doses have been used (e.g. 30 mg/kg followed by 8 mg/kg/hr,[17] and in children 25 - 50 mg/kg followed by a continuous infusion of 10 - 20 mg/kg/hr).[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.[15]

Nevertheless, some have questioned the effectiveness of praladoxime,[24,25] with one stating that 'PAM has no place' in the current management of organophosphate poisoning.[18] In one study of 10 cases of organophosphate poisoning, no clinical evidence of reactivation of the phosphorylated cholinesterase was observed, when pralidoxime was used.[26] In another study, the use of pralidoxime (4 g in the first 24 hr followed by 1 g daily for 5 days) was not associated with an improvement in outcome.[27] Nevertheless, the doses used in all of these studies may have been insufficient,[28] as other studies have reported beneficial effects from high dose pralidoxime administration.[17,23,29]

4. *Other therapy*. Replacement of blood volume has been used successfully[3] 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.[30] Magnesium sulphate has also been used to control tachycardia, ventricular arrhythmias and muscle faciculations.[15]

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 hr 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,[31] even against a concentration gradient.[32] The mechanism of toxicity is due to an inhibition of superoxide dismutase, generation of free radicals, and NADH depletion.[33] With severe acute toxicity, paraquat can cause a multisystem 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 hr plasma level predicted using a graph[34] 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).[35]

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.[36,37] A colourless or light blue reaction generally indicates mild poisoning.[38]

Treatment. Without appropriate treatment, the mortality after ingestion of paraquat varies from 87 - 100%.[39] An injection of as little as 1 mL subcutaneously has been fatal.[40] The estimated fatal dose in humans may be as low as 4 mg/kg, although the LD_{50} in an adult human is normally about 3 - 5 g (i.e. 10 - 15 mL of the 20% concentrate).[31] 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 hr 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.[41] 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 carefully 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.[39] Haemodialysis, peritoneal dialysis and haemoperfusion are all ineffective for paraquat removal,[42,43] 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[33] 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.[45]

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 daily for two days) and methyprednisolone (1 g infused over 2 hr daily for 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.[47]

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. rhabdomyolysis 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 carboxhaemoglobin 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]

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,[56,59] and administration of oxygen by facemask for 6 hr is all that is required.[58] 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.[60] 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 was associated with a worse outcome, leading the authors to conclude that CO should not be used for CO poisoning.[61]

N-acetylcysteine administration, as outlined for paracetamol overdosage, has also been used to reduce the incidence of post hypoxic neurological sequelae.[62,63]

Cyanide poisoning

Cyanide combines with the cytochrome oxidase 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 μmol/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;[64] 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.[64]

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.[64-66]

   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,[67] 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.[68] Intravenous administration of 5 g of hydroxocobalamin (3.714 mmol) in 100 mL of water has been used empiric-ally in patients with suspected cyanide poisoning, using a plasma cyanocobalamin (measured shortly after the infusion) at or near 300 μ mol/L as an indication for a further 5 g of hydroxocobalamin.[69]
2. *Methaemoglobin forming agents and thiosulphate.* Sodium or amyl nitrite can produce methaemoglobin (i.e. change Fe^{2+} to 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. $NaNO_2$ 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 thio-cyanate.
   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.[70]

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.[64]

Nevertheless, if the patient is drowsy, stuporous or in coma, then blood levels for cyanide should be taken and hydroxocobalamin or cobalt edetate administered.[71]

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.[72]

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 P_{450} mixed function oxidase system),[77,78] standard therapy requires the administration of intravenous N-acetylcysteine (which facilitates the detoxification of the active intermediates of CCl_4 produced by P_{450} 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 μ mol/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, melaena 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 haemoconcentration 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.[70] 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-desferioxamine complex should be reserved for patients who have renal failure.

Arsenic, lead, mercury

Arsenic causes toxicity by combining with sulphydryl (-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 (Meé's lines) on the nailplate, hyperpigmentation, palmar and plantar hyperkeratosis, garlic halitosis, pancytopaenia 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. Selenium is found bound to plasma protein and in red blood cells. The treatment is largely symptomatic.[94]

Group IA alkali metals (lithium, rubidium, cesium)

Lithium. Lithium metabolism (and toxicity) is described in part I.

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

Cesium. Cesium chloride has been used for cancer, depression, schizophrenia and prophylaxis against radioactive cesium exposure.[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.[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,[100] and in large doses (1 - 2 mmol/kg) ventricular tachycardia is observed in the experimental model.[101] Prolonged QT_c 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.[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 vasoconstriction 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),[103] also occurs with severe overdosage and may be exacerbated by catecholamine therapy.[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.[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.[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).[108] Methaemoglobinaemia may occur with overdoses of dapsone or primaquine.[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).[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.[111,112] There is little correlation between severity of intoxication and isoniazid blood levels.[113] Acute administration of pyridoxine is relatively safe. In one individual, 52 g of pyridoxine was tolerated without

adverse effects.[110]

Thyroxine overdosage

The half-life of thyroxine (T_4) is 7 days, and overdoses of up to 10 mg are usually well tolerated.[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_4, plasmapheresis has been recommended,[116] although in one patient who ingested 6 mg of thyroxine, plasmapheresis was of no significant pharmacokinetic or clinical benefit.[117]

Cytotoxic agents

Overdosage of azathioprine or 6-mercaptopurine are often without clinical effect and therefore aggressive treatment is usually not warranted.[118] Vincristine overdosage is treated with folinic acid and plasmapheresis.[119] Colchicine overdosage 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.[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).[121]

Mushroom poisoning

Of the 2000 species of mushrooms, approximately 50 are poisonous to humans, with the genus *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).[122]

The non life-threatening mushroom poisonings usually resolve within 6 hr and require symptomatic treatment only.[122]

Life-threatening mushroom poisoning may occur with:

a. *Gyromitrin esculenta poisoning*. Clinical features associated with *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.[123]
b. *Amanita phalloides poisoning.* The symptoms and signs specific of *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).[124] Pancreatitis may also occur.[125] Death occurs in up to 50% of cases and commonly occurs with ingestion of 3 or more mushrooms (i.e. 50 g)

Clinical features. There are three phases of the 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.

Treatment.[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 amanitin is tightly bound to plasma proteins. In one study, plasmapheresis was associated with a reduction in mortality from 80 to 12%.[127]
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.[128,129]

Aconite poisoning

Aconite alkaloids (e.g. aconitine, mesaconitine, hypaconitine) 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.[130] 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 flecainide, amiodarone, lignocaine, atropine, mexiletine, procainamide and phenytoin have been published.[131] Cardiopulmonary bypass and ventricular assist devices have been used for refractory cardiac arrest.[132,133] Aconite cardiotoxicity usually resolves within 24 hr.

Coniine (hemlock) poisoning

Conium alkaloids are responsible for hemlock (Conium maculatum) poisoning.[134] The pharmacological effects include nicotinic receptor stimulation then paralysis.

Clinical features. Symptoms include nausea, vomiting, lethargy, drowsyness, 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.

Cantharidin ('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 cantharidin poisoning should be suspected in any patient presenting with unexplained haematuria or with gastrointestinal haemorrhage.[135] Cantharadin acts as a protein phosphatase inhibitor.[136]

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 abnorm-alities are less commonly seen.[137]

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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REFERENCES

1. Merrill DG, Mihm FG. Prolonged toxicity of organophosphate poisoning. Crit Care Med 1982;10:550-551.
2. Panieri E, Krige JE, Bornman PC, Linton DM. Severe necrotizing pancreatitis caused by organophosphate poisoning. J Clin Gastroenterol 1997;25:463-465.
3. Roth A, Zellinger I, Arad M, Atsmon J. Organophosphates and the heart. Chest 1993;103:576-582.
4. Senanayake N, Karalliedde L. Neurotoxic effects of organophosphorous insecticides. N Engl J Med 1987;316:761-763.
5. de Bleecker J, van den Neucker K, Colardyn F. Intermediate syndrome in organophosphorus poisoning: a prospective study. Crit Care Med 1993;21:1706-1711.
6. Leon-s Fidias E, Pradilla G, Vesga E. Neurological effects of organophosphate pesticides. BMJ 1996;313:690-691.
7. Johnson MK. Delayed neuropathy caused by some organophosphate esters. Toxicology 1975;3:289-316.
8. Davies JE. Changing profile of pesticide poisoning. N Engl J Med 1987;316:807-808.
9. Karalliedde L, Senanayake N. Organophosphorous insecticide poisoning. Br J Anaesth 1989;63:736-750.

10. Cherniack MG. Organophosphorous esters and polyneuropathy. Ann Intern Med 1986;104:264-266.
11. Rosenstock L, Keifer M, Daniell WE, McConnell R, Claypoole K, and the Pesticide Health Effects Study Group. Chronic central nervous system effects of acute organophosphate pesticide intoxication. Lancet 1991;338:223-227.
12 . Stephens R, Spurgeon A, Calvert IA, et al. Neuropsychological effects of long-term exposure to organophosphates in sheep dip. Lancet 1995;345:1135-1139.
13. Nelson TC, Burritt MF. Pesticide poisoning, succinylcholine-induced apnea, and pseudocholinesterase. Mayo Clin Proc 1986;61:750-752.
14. Bardin PG, Van Eeden SF. Organophosphate poisoning: grading the severity and comparing treatment between atropine and glycopyrrolate. Crit Care Med 1990;18:956-960.
15. Karalliedde L. Organophosphorus poisoning and anaesthesia. Anaesthesia 1999;54:1073-1088.
16. Golsousidis H, Kokkas V. Use of 19,590 mg of atropine during 24 days of treatment, after a case of unusually severe parathion poisoning. Human Toxicol 1985;4:339-340.
17. Balali-Mood M, Shariat M. Treatment of organophosphate poisoning. Experience of nerve agents and acute pesticide poisoning on the effects of oximes. J Physiol Paris 1998;92:375-378.
18. Scott RJ. Repeated asystole following PAM in organophosphate self-poisoning. Anaesth Intens Care 1986;14:458-460.
19. Ellin RI, Wills JH. Oximes antagonistic to inhibitors of cholinesterase II. J Pharm Sci 1964;53:1143-1150.
20. Taylor P. Anticholinesterase agents. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. The pharmacological basis of therapeutics. New York: MacMillan, 1985;110-129.
21. Thompson DF, Thompson GD, Greenwood RB, Trammel HL. Therapeutic dosing of pralidoxime chloride. Drug Intell Clin Pharm 1987;21:590-593.
22. Worek F, Backer M, Thiermann H, et al. Reappraisal of indications and limitations of oxime therapy in organophosphate poisoning. Hum Exp Toxicol 1997;16:466-472.
23. Schexnayder S, James LP, Kearns GL, Farrar HC. The pharmacokinetics of continuous infusion pralidoxime in children with organophosphate poisoning. J Toxicol Clin Toxicol 1998;36:549-555.
24. Johnson S, Peter JV, Thomas K, Jeyaseelan L, Cherian AM. Evaluation of two treatment regimens of pralidoxime (1gm single bolus dose vs. 12 gm infusion) in the management of organophosphorus poisoning. J Assoc Physicians India 1996;44:529-531.
25. Cherian AM, Peter JV, Samuel J, et al. Effectiveness of P2AM in the treatment of organophosphorus poisoning. A randomised, double blind placebo controlled clinical trial. J Assoc Physicians India 1997;45:22-24.
26. Genandran A. Organophosphate insecticide poisoning and its management. Anaesth Intens Care 1974;4:361-368.
27. de Silva HJ, Wijewickrema R, Senanayake N. Does pralidoxime affect outcome of management in acute organophosphorus poisoning. Lancet 1992;339:1136-1138.
28. Johnson MK, Vale JA, Marrs TC, Meredith TJ. Pralidoxime for organophosphorous poisoning. Lancet 1992;340:64.
29. Tush GM, Anstead MI. Pralidoxime continuous infusion in the treatment of organophosphate poisoning. Ann Pharmacother 1997;31:441-444.
30. van Helden HP, Groen B, Moor E, Westerink BH, Bruijnzeel PL. New generic approach to the treatment of organophosphate poisoning: adenosine receptor mediated inhibition of ACh-release. Drug Chem Toxicol 1998;21 Suppl 1:171-181.
31. Pond SM. Manifestations and management of paraquat poisoning. Med J Aust 1990;152:256-259.
32. Rose MS, Smith LL, Wyat I. Evidence for energy-dependent accumulation of paraquat into rat lung. Nature 1974;252:314-315.
33. Yasaka T, Okudaira K, Fujito H, Matsumoto J, Ohya I, Miyamoto Y. Further studies of lipid peroxidation in human paraquat poisoning. Arch Intern Med 1986;146:681-685.
34. Hart TB, Nevitt A, Whitehead A. A new statistical approach to the prognostic significance of plasma paraquat concentrations. Lancet 1984;ii:1222-1223.
35. Jones AL, Elton R, Flanagan R. Multiple logistic regression analysis of plasma paraquat concentrations as a predictor of outcome in 375 cases of paraquat poisoning. QJM 1999;92:573-578.
36. Scherrmann JM, Houze P, Bismuth C, Bourdon R. Prognostic value of plasma and urine paraquat concentration. Hum Toxicol 1987;6:91-93.
37. Braithwaite RA. Emergency analysis of paraquat in biological fluids. Hum Toxicol 1987;6:83-86.
38. Lin JL, Leu ML, Liu YC, Chen GH. A prospective clinical trial of pulse therapy with glucocorticoid and cyclophosphamide in moderate to severe paraquat-poisoned patients. Am J Respir Crit Care Med 1999;159:357-360.
39. Fairshter RD. Paraquat toxicity and lipid peroxidation. Arch Intern Med 1981;141:1121-1123.
40. Almog CH, Tal E. Death from paraquat after subcutaneous injection. Br Med J 1967;3:721.
41. Idid SZ, Lee CY. Effects of Fuller's Earth and activated charcoal on oral absorption of paraquat in rabbits. Clin Exp Pharmacol Physiol 1996;23:679-681.
42. Mascie-Taylor BH, Thompson J, Davison AM. Haemoperfusion ineffective for paraquat removal in life-threatening poisoning. Lancet 1983;i:1376-1377.
43. van de Vyver FL, van de Sande J, Verpooten GA, de Broe ME, van den Heede M, Heyndrickx A. Haemoperfusion ineffective for paraquat removal in life-threatening poisoning. Lancet 1983;ii:173.
44. Licker M, Schweizer A, Hohn L, Morel DR, Spiliopoulos A. Single lung transplantation for adult

respiratory distress syndrome after paraquat poisoning. Thorax 1998;53:620-621.
45. Lheureux P, Leduc D, Vanbinst R, Askenasi R. Survival in a case of massive paraquat ingestion. Chest 1995;107:285-289.
46. Lin J-L, Wei M-C, Liu Y-C. Pulse therapy with cyclophosphamide and methylprednisolone in patients with moderate to severe paraquat poisoning: a preliminary report. Thorax 1996;51:661-663.
47. Perriens JH, Benimadho S, Kiauw IL, Wisse J, Chee H. High-dose cyclophosphamide and dexamethasone in paraquat poisoning: a prospective study. Hum Exp Toxicol 1992;11:129-134.
48. Flanagan RJ, Meredith TJ, Ruprah M, Onyon LJ, Liddle A. Alkaline diuresis for acute poisoning with chlorophenoxy herbicides and ioxynil. Lancet 1990;335:454-458.
49. Ernst A, Zibrak JD. Carbon monoxide poisoning. N Engl J Med 1998;339:1603-1608.
50. Ball EG, Strittmatter CF, Cooper O. The reaction of cytochrome oxidase with carbon monoxide. J. Biol Chem 1951;193:635-647.
51. Florkowski CM, Rossi ML, Carey MP, Poulton K, Dickson GR, Ferner RE. Rhabdomyolysis and acute renal failure following carbon monoxide poisoning: two case reports with muscle histopathology and enzyme activities. J Toxicol Clin Toxicol 1992;30:443-454.
52. Nagy R, Greer KE, Harman LE Jr. Cutaneous manifestations of acute carbon monoxide poisoning. Cutis 1979;24:381-383.
53. Choi IS. Delayed neurologic sequelae in carbon monoxide intoxication. Arch Neurol 1983;40:433-435.
54. Adams RD, Victor M. Principles of neurology. New York: McGraw-Hill;1985:699.
55. Takeuchi A, Vesely A, Rucker J, et al. A simple "new" method to accelerate clearance of carbon monoxide. Am J Respir Crit Care Med. 2000;161:1816-1819.
56. Raphael J-C, Elkharrat D, Jars-Guincestre et al. Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. Lancet 1989;ii:414-419.
57. Meredith T, Vale A. Carbon monoxide poisoning. Br J Med 1988;296:77-79.
58. Ilano AL, Raffin TA. Management of carbon monoxide poisoning. Chest 1990;97:165-169.
59. Raphael JC, Elkharrat D, Chastang C, Jars MC, Vercken JB, Gajdos Ph. Isobaric (IBO) versus hyperbaric (HBO) in acute carbon monoxide poisoning (CMP) results of 2 randomised trials. Intensive Care Med 1988;14 (suppl 1):289.
60. Weaver LK, Hopkins RO, Larson-Lohr V, Howe S, Haberstock D. Double-blind, controlled, prospective, randomized clinical trial (RCT) in patients with acute carbon monoxide poisoning: outcome of patients treated with normobaric oxygen or hyperbaric oxygen (HBO2) - an interim report. Undersea Hyperb Med 1995;22:Suppl:14.abstract.
61. Scheinkestel CD, Bailey M, Myles PS, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. Med J Aust 1999;170:203-210.
62. Flanagan RJ, Meredith TJ. Use of N-acetylcysteine in clinical toxicology. Am J Med 1991;91(suppl 3C):131S-139S.
63. Howard RJMW, Blake DR, Pall H, Williams A, Green ID. Allopurinol/N-acetylcysteine for carbon monoxide poisoning. Lancet 1987;ii:628-629.
64. Bryson DD. Cyanide poisoning. Lancet 1978;i:92.
65. McKiernan MJ. Emergency treatment of cyanide poisoning. Lancet 1980;ii:86.
66. Dodds C, McKnight C. Cyanide toxicity after immersion and the hazards of dicobalt edetate. Br J Med 1985;291:785-786.
67. Riou B, Berdeaux A, Pussard E, Giudicelli J-F. Comparison of the hemodymamic effects of hydroxocobalamin and cobalt edetate at equipotent cyanide antidotal doses in conscious dogs. Intensive Care Med 1993;19:26-32.
68. Nicholson DP. The immediate management of overdose. Med Clin N Amer 1983;67:1279-1293.
69. Houeto P, Hoffman JR, Imbert M, Levillain P, Baud FJ. Relation of blood cyanide to plasma cyanocobalamin concentration after a fixed dose of hydroxocobalamin in cyanide poisoning. Lancet 1995;346;346:605-608.
70. Meredith T, Caisley J, Volans. ABC of poisoning. Emergency drugs: agents used in the treatment of poisoning. Br Med J 1984;289:742-748.
71. Naughton M. Acute cyanide poisoning. Anaesth Intens Care 1974;4:351-356.
72. Burn DJ, Tomson CRV, Seviour J, Dale G. Strychnine poisoning as an unusual cause of convulsions. Postgrad Med 1989;65:563-664.
73. Smith BA. Strychnine poisoning. J Emerg Med 1990;8:321-325.
74. Boyd RE, Brennan PT, Deng J-F, Rochester DF, Spyker DA. Strychnine poisoning. Recovery from profound lactic acidosis, hyperthermia and rhabdomyolysis. Am J Med 1983;74:507-512.
75. Van Heerden PV, Edibam C, Augustson B, Thompson WR, Power BM. Strychnine poisoning - alive and well in Australia! Anaesth Intens Care 1993;21:876-878.
76. Hernandez AF, Pomares J, Schiaffino S, Pla A, Villanueva E. Acute chemical pancreatitis associated with nonfatal strychnine poisoning. J Toxicol Clin Toxicol 1998;36:67-71.
77. Truss CD, Killenberg PG. Treatment of carbon tetrachloride poisioning with hyperbaric oxygen. Gastroenterology 1982;82:767-769.
78. Burk RF, Reiter R, Lane JM. Hyperbaric oxygen protection against carbon tetrachloride hepatotoxicity in the rat. Gastroenterology 1986;90:812-818.
79. Editorial. Paracetamol toxicity. Lancet 1975;ii:1189-1191.
80. Ruprah M, Mant TGK, Flanagan RJ. Acute carbon tetrachloride poisoning in 19 patients: implications for diagnosis and treatment. Lancet 1985;i:1027-1029.
81. Engle JP, Polin KS, Stile IL. Acute iron intoxication: treatment controversies. Drug Intell Clin Pharm 1987;21:153-159.
82. Tenenbeim M, Kowalski S, Sienko A, Bowden DH, Adamson IYR. Pulmonary toxic effects of continuous

desferrioxamine administration in acute iron poisoning. Lancet 1992;339:699-701.
83. Navarro B, Sayas M-J, Atienza A, León P. An unhappily married man with thick soles. Lancet 1996;347:1596.
84. Goldstein GD, Dunn MI. Nailing down arsenic intoxication. Chest 1989;96:670-671.
85. Aposhian HV, Maiorino RM, Gonzalez-Ramirez D, et al. Mobilization of heavy metals by newer, therapeutically useful chelating agents. Toxicology 1995;97:23-38.
86. Muckter H, Liebl B, Reichl FX, Hunder G, Walther U, Fichtl B. Are we ready to replace dimercaprol (BAL) as an arsenic antidote? Hum Exp Toxicol 1997;16:460-465.
87. Tandon SK, Singh S, Jain VK. Efficacy of combined chelation in lead intoxication. Chem Res Toxicol 1994;7:585-589.
88. Tannen RL. Potassium disorders. In Kokko JP, Tannen RL (eds). Fluids and Electrolytes. WB Saunders Co, Philadelphia, 1986, pp 150-228.
89. Phelan DM, Hagley SR, Guerin MD. Is hypokalaemia the cause of paralysis in barium poisoning. Br Med J 1984;289:882.
90. Schorn ThF, Olbricht Ch, Schuler A, et al. Barium carbonate intoxication. Intensive Care Med 1991;17:60-62.
91. Wainwright AP, Kox WJ, House IM, Henry JA, Heaton R, Seed WA. Clinical features and therapy of acute thallium poisoning. Q J Med 1988;69:939-944.
92. Moore D, House I, Dixon A. Thallium poisoning. Br Med J 1993;306:1527-1529.
93. Malbrain ML, Lambrecht GL, Zandijk E, et al. Treatment of severe thallium intoxication. J Toxicol Clin Toxicol 1997;35:97-100.
94. Ruta DA, Haider S. Attempted murder by selenium poisoning. Br Med J 1989;299:316-317.
95. Placidi G, Lenzi A, Lazzerini F, Dell'Osso L, Cassano GB, Akiskal HS. Exploration of the clinical profile of rubidium chloride in depression: a systematic open trial. J Clin Psychopharmacol 1988;8:184-188.
96. Tuoni M, Marchitiello M, Paternoster G, et al. Renal tolerance of rubidium chloride: short term clinical evaluation. J Clin Pharmacol 1987;27:503-507.
97. Meltzer HL, Lieberman KW. Chronic ingestion of rubidium without toxicity: implications for human therapy. Experientia 1971;27:672-674.
98. Beck FX, Dorge A, Giebisch G, Thurau K. Studies on the mechanism of rubidium-induced kaliuresis. Kidney Int 1989;36:175-182.
99. Braverman ER, Sohler A, Pfeiffer CC. Cesium chloride: preventive medicine for radioactive cesium exposure? Med Hypotheses 1988;26:93-95.
100. Neulieb R. Effect of oral intake of cesium chloride: a single case report. Pharmacol Biochem Behav 1984;21 (Suppl 1):15-16.
101. Murakawa Y, Sezaki K, Yamashita T, Kanese Y, Omata M. Three-dimensional activation sequence of cesium-induced ventricular arrhythmias. Am J Physiol 1997;273(3 Pt 2):H1377-H1385.
102. Pinter A, Dorian P, Newman D. Cesium-induced torsade de pointes. N Engl J Med 2002;346:383-384.
103. Bradberry SM, Vale JA. Disturbances of potassium homeostasis in poisoning. J Toxicol Clin Toxicol 1995;33:295-310.
104. Clemessy J-L, Favier C, Borron SW, Hantson PE, Vicaut E, Baud FJ. Hypokalaemia related to acute chloroquine ingestion. Lancet 1995;346:877-880.
105. Meeran K, Jacobs MG. Chloroquine poisoning. Rapidly fatal without treatment. Br Med J 1993;307:49-50.
106. Boland M, Volans G. ABC of poisoning. Miscellaneous drugs. Br Med J 1984;289:1361-1364.
107. Boland ME, Roper SMB, Henry JA. Complications of quinine poisoning. Lancet 1985;i:384-385.
108. Riou B, Barriot P, Rimalho A, Baud FJ. Treatment of severe chloroquine poisoning. N Engl J Med 1988;318:1-6.
109. Boland M, Volans G. ABC of poisoning. Miscellaneous drugs. Br Med J 1984;289:1361-1364.
110. Wason S, Lacouture PG, Lovejoy FH Jr. Single high-dose pyridoxine treatment for isoniazid overdose. JAMA 1981;246:1102-1104.
111. Brown CV. Acute isoniazid poisoning. Am Rev Resp Dis 1972;105:206-215.
112. Mant T, Cochrane M, Henry J. ABC of poisoning. Respiratory drugs. Br Med J 1984;289:1133-1135.
113. Alvarez FG, Guntupalli KK. Isoniazid overdose: four case reports and review of the literature. Intensive Care Med 1995;21:641-644.
114. Nystrom E, Lindstedt G, Lundberg PA. Minor signs and symptoms of toxicity in a young woman in spite of a massive thyroxin ingestion. Acta Med Scand 1980;207:135-136.
115. Ratnaike S, Campbell DG, Melick RA. Thyroxine overdosage. Aust NZ J Med 1986;16:514.
116. Binimelis J, Bassas L, Marruecos L, et al. Massive thyroxine intoxication: evaluation of plasma extraction. Intensive Care Med 1987;13:33-38.
117. Henderson A, Hickman P, Ward G, Pond SM. Lack of efficacy of plasmapheresis in a patient overdosed with thyroxine. Anaesth Intens Care 1994;22:463-464.
118. Hendrick D, Mirkin BL. Metabolic disposition and toxicity of 6-mercaptopurine after massive overdose. Lancet 1984;i:277.
119. Pierga J-Y, Beuzeboc P, Dorval T, Palangie T, Pouillart P. Favourable outcome after plasmapheresis for vincristine overdose. Lancet 1992;340:185.
120. Baud FJ, Sabouraud A, Vicaut E, et al. Treatment of severe colchicine overdose with colchicine-specific Fab fragments. N Engl J Med 1995;332:642-645.
121. Bernini JC, Fort DW, Griener JC, Kane BJ, Chappell WB, Kamen BA. Aminophylline for methotrexate-induced nephrotoxicity. Lancet 1995;345:544-547.
122. Barbato MP. Poisoning from accidental ingestion of mushrooms. Med J Aust 1993;158:842-847.
123. Hanrahan JP, Gordon MA. Mushroom poisoning. Case reports and a review of therapy. JAMA 1984;251:1057-1061.

124. Trim GM, Lepp H, Hall MJ, et al. Poisoning by Amanita phalloides ("deathcap") muchrooms in the Australian Capital Territory. Med J Aust 1999;171:247-249.
125. Klein AS, Hart J, Brems JJ, Goldstein L, Lewin K, Busuttil RW. Amanita poisoning: treatment and the role of liver transplantation. Am J Med 1989;86:187-193.
126. Cole FM. Amanita phalloides in Victoria. Med J Aust 1993;158:849-850.
127. Mercuriali F, Sirchia G. Plasma exchange for mushroom poisoning. Transfusion 1977;17:644-646.
128. Montanini S, Sinardi D, Pratico C, Sinardi AU, Trimarchi G. Use of acetylcysteine as the life-saving antidote in Amanita phalloides (death cap) poisoning. Case report on 11 patients. Arzneimittelforschung 1999;49:1044-1047.
129. Boyer JC, Hernandez F, Estorc J, De La Coussaye JE, Bali JP. Management of maternal Amanita Phylloides poisoning during the first trimester of pregnancy: a case report and a review of the literature. Clin Chem 2001;47:971-974.
130. Pepper K, Trautwein W. The effect of aconitine on the membrane current in cardiac muscle. Pfluggers Archiv 1967;296:328-336.
131. Tai Y-T, But PP-H, Young K, Lau CP. Cardiotoxicity after accidental herb-induced aconite poisoning. Lancet 1992;340:1254-1256.
132. Fatovich DM. Aconite: a lethal Chinese herb. Ann Emerg Med 1992;21:309-311.
133. Fitzpatrick AJ, Crawford M, Allan RM, Wolfenden H. Aconite poisoning managed with a ventricular assist device. Anaesth Intens Care 1994;22:714-717.
134. Drummer OH, Roberts AN, Bedford PJ, Crump KL, Phelan MH. Three deaths from hemlock poisoning. Med J Aust 1995;162:592-593.
135. Zouvanis M, Feldman C, Smith C, Promnitz DA, James S, Seftel H. Renal and neuromuscular respiratory failure--is this a syndrome associated with cantharidin poisoning? S Afr Med J 1994;84(11 Suppl):814-816.
136. Knapp J, Boknik P, Luss I, et al. The protein phosphatase inhibitor cantharidin alters vascular endothelial cell permeability. J Pharmacol Exp Ther 1999;289:1480-1486.
137. Karras DJ, Farrell SE, Harrigan RA, Henretig FM, Gealt L. Poisoning from "Spanish fly" (cantharidin). Am J Emerg Med 1996;14:478-483.