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Poisoning

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Pesticides

Michael Eddleston

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Abstract

300,000 people die each year from pesticide self-poisoning in the rural developing world where pesticides are widely used in smallholder agricultural practice. Significant acute poisoning is much less common in industrialized countries and it is the long-term effects of low-dose chronic exposure that most concern the population. Organophosphorus and carbamate insecticides cause most acute fatalities; severe poisoning requires urgent resuscitation and administration of oxygen, atropine and oximes. The incidence of organochlorine poisoning will decrease as more of this environmentally persistent class are banned. Paraquat and aluminium phosphide are major problems in particular countries with extremely high fatality ratios of over 60%. No effective treatments are available. Chlorphenoxyacetate herbicides and superwarfarin rodenticides cause fewer deaths; other pesticides are generally less toxic and require only supportive care.

Keywords aluminium phosphide; atropine; carbamates; chlorphenoxyacetate herbicides; organochlorine insecticides; organophosphorus insecticides; oximes; paraquat; superwarfarins

'Pesticide' is the term used to describe a range of chemicals used as insecticides, fungicides, herbicides, and rodenticides.¹ Despite the large number of new chemicals that have been introduced as pesticides, their contribution to clinical toxicology continues to be dominated by a small number that have been available for many years. Organophosphorus (OP) and carbamate insecticides and the herbicide paraquat are the most important; the rodenticide aluminium phosphide is a major problem in parts of rural Asia.² Newer agents (e.g. pyrethroids, glyphosate) are generally less toxic.

The potential for occupational exposure is high, particularly in developing countries where climatic conditions militate against the wearing of recommended protective equipment. However, many pesticides are relatively less toxic by inhalation or dermal exposure and most pesticide deaths result from intentional self-poisoning.

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Organophosphorus insecticides

OP pesticides are believed to cause tens of thousands of deaths and many more clinical poisonings every year, nearly all in developing countries. In developed countries, public concern about these agents focuses on the possible long-term health consequences of single or repeated exposure to comparatively low concentrations of pesticide (see below). OPs are readily absorbed through the gut, respiratory tract, and to a lesser extent the skin.

Mechanism of toxicity: the OPs used as insecticides or military nerve agents inhibit acetylcholinesterase by phosphorylating a serine at the active site (NB. not every compound with an OP structure is an anti-cholinesterase). The speed of onset, severity, and duration of toxicity caused by different OPs vary considerably and depend on several factors. High tissue concentrations and high affinity for acetylcholinesterase increase toxicity. Dephosphorylation of the inhibited enzyme, which reactivates the enzyme, occurs very slowly spontaneously but can be speeded up with a cholinesterase reactivating drug, such as pralidoxime or obidoxime.³ Instead of reactivating, inhibited enzyme can also become 'aged', a process in which the phosphoryl group bound to the enzyme changes chemically, preventing both spontaneous and oxime-induced reactivation. The faster ageing occurs, the less effective reactivation therapy will be. Once ageing occurs, recovery depends on the slow synthesis of new acetylcholinesterase.

Clinical features – acute poisoning is characterized by widespread muscarinic and nicotinic effects caused by inhibition of acetylcholinesterase at peripheral nerve endings, in ganglia, and in the brain. The earliest muscarinic symptoms usually occur in the system through which the pesticide enters (Table 1) and secretory effects (salivation, bronchorrhoea) are often seen. Pinpoint pupils and profuse sweating are common. The nicotinic effects of poisoning include fasciculation, progressive flaccidity, and weakness of proximal muscle groups, in particular the neck flexors but later extra-ocular muscles and muscles of respiration. Respiratory failure is common in severe poisoning⁴ and is a poor prognostic sign, but results as much from a direct effect on respiratory drive as from muscle weakness, bronchospasm and retention of bronchial secretions. In patients with severe poisoning, initial mild excitatory effects on the brain (e.g. anxiety, restlessness, dizziness) are followed by impairment of consciousness and, less commonly, seizures.⁵ Severe hypotension is noted with some OP pesticides⁵; tachycardia can result from direct nicotinic effects but also from hypovolaemia and sepsis. Various cardiac arrhythmias have been described. Hyperglycaemia and glycosuria are common.

Diagnosis – can be confirmed retrospectively by measuring plasma or, preferably, RBC acetylcholinesterase activity. These activities may be reduced by 30–50% in asymptomatic patients, in whom no treatment is indicated. RBC acetylcholinesterase activity is often reduced to 10–20% in moderate poisoning, and to less than 10% in severe poisoning. Clinical management should not wait for results of these assays.

Management

Initial treatment – aims to resuscitate and stabilize the patient with support of the airway, ventilation, and circulation.^{6,7} Administer oxygen and i.v. fluids. Convulsions should be suppressed with intravenous diazepam; even in the absence of convulsions,

Muscarinic features of organophosphate and carbamate poisoning

Eye

- Miosis
- Blurred vision
- Eye pain

Ingestion

- Hypersalivation
- Nausea
- Vomiting
- Abdominal cramps
- Diarrhoea
- Tenesmus

Inhalation

- Cough
- Expectoration of frothy secretions
- Chest tightness and wheeze
- Pulmonary oedema

Table 1

administration of diazepam, 5–10 mg i.v. in adults, reduces anxiety and restlessness and may improve outcome. Decontamination of the patient should take place only once the patient has been stabilized with administration of antidotes (see below) as necessary.

Antidotes – the specific antidotes for OP pesticide poisoning are atropine and oxime cholinesterase reactivators.⁸

Atropine can be used to block muscarinic effects and thereby improve cardiorespiratory function. It should be given intravenously (initially, adult 1–3 mg, child 0.02 mg/kg) and repeated in doubling doses at five minute intervals until bronchorrhoea and bronchospasm are abolished and cardiovascular function restored (blood pressure > 80 mmHg, pulse > 80 bpm).⁹ Once attained, continue atropine as a constant infusion to sustain cardiorespiratory function. Patients with severe poisoning may require very large doses of atropine. However, if there is evidence of atropine intoxication (dry mouth, tachycardia, dry skin, ileus), then too much atropine has been given.

Oximes such as pralidoxime mesylate (P2S), pralidoxime chloride, and obidoxime reactivate phosphorylated cholinesterases, provided they are not given after ageing has already occurred. They may restore muscle power, reduce fasciculations and convulsions, and improve the patient's consciousness level. Pralidoxime chloride should be given as a loading dose of 30 mg/kg by slow intravenous injection over 30 mins followed by an infusion of 8–10 mg/kg/hr, continued until atropine has not been required for 12–24 hrs.

Long-term health effects – OP pesticides (particularly those in sheep dips and nerve gases) are thought by some to be responsible for long-term debilitating illness with numerous symptoms. Neuromuscular complaints (lethargy, irritability, poor concentration, mood swings, depression, insomnia, paraesthesiae, muscle aches and pains) predominate. A few affected individuals are so disabled that they become housebound and their quality of life is extremely poor. Assessment and management of such patients is difficult.

A detailed history is required to establish the time relationship between symptoms and pesticide exposure, the frequency and duration of exposure, and all the pesticides (and their solvents) and other chemicals to which the patient has been exposed, at work and in leisure activities; the patient is best able to compile this list. Exclusion of other explanations is an essential component of the assessment. Often, however, clinical examination and extensive investigation fail to identify any significant abnormality or cause. Subtle impairment of nerve conduction velocities and performance in some neurobehavioural tests have been reported, but their relevance to the symptoms remains unclear.

Carbamate insecticides

Carbamate insecticides act in the same manner as OP insecticides and the features of poisoning are similar. However, carbamate poisoning is generally less severe and of shorter duration because carbamate-inhibited acetylcholinesterase is reactivated comparatively rapidly.

Management – resuscitation and supportive measures should be implemented as necessary. Oxygen, fluids, and atropine should be given as necessary; oximes are seldom needed.

Organochlorine insecticides

These insecticides have generally been replaced in agricultural practice by OP pesticides. More recently, concerns about long-term environmental persistence has led to worldwide bans. However, some organochlorines are still used in some countries; severe poisoning with endosulfan results in status epilepticus that may not respond to any treatment. First-line treatment is benzodiazepines, followed by phenobarbital and then general anaesthesia as required.

Paraquat

Paraquat poisoning is common in parts of Asia, Pacific, and the Caribbean. It is often fatal despite strenuous therapeutic endeavours. Deaths almost always result from deliberate ingestion; a few have occurred after accidental percutaneous absorption.

Clinical features – the initial features of poisoning include nausea, vomiting and abdominal pain. Doses greater than 20 ml of the 20% solution cause death from multiorgan failure (including coma, metabolic acidosis, pulmonary oedema and myocardial depression) within a few hours. The clinical picture in patients who have ingested smaller doses and survive for 3–4 days is dominated by severe, painful ulceration of the lips, tongue, pharynx and larynx, leading to dysphagia, cough, dysphonia, and inability to clear saliva and other secretions. Acute renal failure is common by 4–5 days after ingestion and liver damage may occur. Increasing breathlessness and pulmonary opacities herald almost certain death within a few days or weeks as extensive and progressive pulmonary fibrosis develops.

Diagnosis is for the most part clinical, although outcome can be predicted with reasonable confidence within a few hours of ingestion, by relating plasma paraquat concentration to the time elapsed in hours.

Management – many treatments for paraquat poisoning have been advocated.¹⁰ Gastric lavage may be considered if the patient presents within 1 hour of ingestion, but there is no evidence that it

is of value if oesophageal perforation has occurred. It is customary to give activated charcoal or Fuller's Earth, 50–100 g, although in most cases peak plasma concentrations of the poison are attained before the patient reaches hospital and efficacy is unlikely. Whole-bowel irrigation is distressing and ineffective, and forced diuresis, haemodialysis and haemoperfusion do not seem to remove paraquat sufficiently rapidly to affect the outcome.

Pharmacological interventions (e.g. corticosteroids, superoxide dismutase), surgical approaches (lung transplantation) and radiotherapy to the diseased lungs have not been shown to be effective, although there are reports that pulse immunosuppression with methylprednisolone and cyclophosphamide can treat the lung fibrosis.¹¹ Further trials are required.

If the plasma concentration clearly indicates a fatal outcome, it is probably more humane for the doctor to accept the inevitable and keep the patient comfortable rather than attempt measures with a negligible likelihood of success. In each case, however, expert advice should be sought from a poisons information service.

Aluminium phosphide

Aluminium phosphide is a rodenticide and fumigant used to protect grain. It has the highest case fatality proportion of any pesticide – usually more than 65% of people who ingest the pesticide die.¹² On contact with water in the stomach, phosphine gas is liberated which has direct toxic effects on multiple organs. Death results from cardiogenic shock and hypotension. Management requires resuscitation and supportive care. As yet, there is no good evidence that any proposed intervention offers clinical benefit, including magnesium sulphate.¹³

Chlorphenoxyacetate herbicides

Acute severe poisoning with chlorphenoxyacetates such as 2,4-D and MCPA is uncommon and almost always follows ingestion.

Clinical features include a burning sensation in the mouth and throat, nausea and vomiting followed in severe cases by sweating, hyperventilation, and coma, which may be prolonged.¹⁴ Acute myositis with pain, fasciculation, myotonia, weakness and myoglobinuria have been reported.

Management involves resuscitation and supportive care. Gastric decontamination is of unknown effectiveness. There are no antidotes but, theoretically, urine alkalization may enhance renal elimination of these weak acids and improve outcome in severe poisoning. It is achieved by infusion of isotonic sodium bicarbonate to raise urine pH to as close to 8 as possible. Frequent monitoring of urine pH is essential. Unfortunately, no trials have yet been performed to assess effectiveness.

Anticoagulants

Warfarin has been used in mouse and rat baits for many years, but the emergence of resistant strains of animals has led to the introduction of 'superwarfarins'. These include brodifacoum, bromodialone, chlorophacinone, coumatetralyl, difenacoum and flocoumafen, single doses of which are followed by an anticoagulant effect lasting weeks or months.

Clinical features – symptoms are unlikely to occur after accidental ingestion of warfarin-containing baits by children, because

very large amounts would have to be eaten for them to ingest a significant amount of anticoagulant. Large ingestions of superwarfarins are also needed to produce haemorrhagic complications. When there is concern about the amount involved, prothrombin time ratio or INR can be measured after about 24 hours.

Management – most patients will require only vitamin K until clotting returns to normal. However, whole blood and fresh-frozen plasma or clotting factor concentrates may be required in severe acute haemorrhage.

Other pesticides

The majority of other pesticides are less dangerous to humans and supportive measures are all that most require. The case fatality for pesticide poisoning in general will fall as newer, safer pesticides are introduced into global agricultural practice. ♦

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