Pesticides

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Abstract

Over 300,000 people die each year from pesticide poisoning. Most deaths result from self-poisoning by ingestion, rather than occupational or accidental exposures, which are typically topical or inhalational. Severe pesticide poisoning is more common in the rural developing world where pesticides are widely used in smallholder agricultural practice and therefore freely available. Significant acute poisoning is much less common in industrialized countries; here it is the long-term effects of low-dose chronic exposure that most concern the population. Organophosphorus (OP) and carbamate insecticide poisoning causes most severe cases and deaths, although the numbers are falling as the most highly toxic compounds are withdrawn from agricultural practice. Severe OP poisoning requires urgent resuscitation and administration of oxygen, atropine and oximes. Paraquat and aluminium phosphide are major problems in some countries, with case fatality usually exceeding 50% and no effective treatments. Newer pesticides that have become widely used over the last 30 years, for example glyphosate and neonicotinoid and phenylpyrazole insecticides, are more selective in their toxicity to pests, resulting in far less human toxicity and few deaths. Poisoning with these pesticides usually requires only careful supportive care.

Keywords Aluminium phosphide; atropine; carbamates neonicotinoids; organochlorine insecticides; organophosphorus insecticides; oximes; paraquat; solvents

Introduction

'Pesticide' is the term used to describe a range of chemicals utilized as insecticides, fungicides, herbicides and rodenticides.[1] Despite the large number of new pesticide classes that have been introduced intro agricultural practice over the last 50 years, most deaths and severe poisonings are still caused by a small number of older compounds. 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, neonicotinoids) cause far fewer deaths.

The potential for occupational exposure is high, particularly in developing countries where climatic conditions militate against the wearing of the recommended protective equipment. However, exposures that occur by inhalation or dermal exposure are usually smaller than those occurring by ingestion; most deaths from pesticide poisoning therefore result from self-harm and intentional ingestion. Most exposures in developed countries are accidental and do not result in harm.

The case fatality for pesticide poisoning in general will fall as newer, safer pesticides are introduced into global agricultural practice and highly toxic pesticides removed.

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Role of solvents and other co-formulants in agricultural pesticide toxicity

Agricultural pesticides are formulated with other compounds to allow their effective use, incorporating, for example, solvents and surfactants. Studies with glyphosate (see below) and the OP insecticide dimethoate[3] indicate that these co-formulants can be toxic in their own right and fully responsible for a pesticide's toxicity, or additive with the active pesticide ingredient. Where the active ingredient itself has low mammalian toxicity, such as flufenoxuron (see below), any human toxicity noted is likely due to co-formulants.

Organophosphorus insecticides

OP insecticides are estimated to cause more than 100,000 deaths and 2 million hospital admissions every year, nearly all in developing countries. In industrialized countries, public concern about these agents focuses on the possible long-term health effects of single or repeated exposures to low concentrations of pesticide (see below). OPs are readily absorbed through the gut, lung and, to a lesser extent, skin.

Mechanisms of toxicity

OP insecticides phosphorylate multiple enzymes and proteins throughout the body. However, the clinical relevance of this process remains unclear for the great majority of targets. Instead, it is inhibition of the synaptic enzyme acetylcholinesterase that is thought to be responsible for toxicity. The speed of onset, severity and duration of toxicity caused by different OPs vary considerably and depend on several factors including their chemical structure. High tissue concentrations and high affinity for acetylcholinesterase increase toxicity.

Reactivation of inhibited enzyme, which curtails toxicity, occurs slowly spontaneously but can be speeded up with an oxime acetylcholinesterase-reactivating drug, such as pralidoxime or obidoxime.[4] Alternatively, the enzyme can become 'aged', a process in which the phosphoryl group deposited on the enzyme changes chemically, preventing both spontaneous and oxime-induced reactivation. The faster aging occurs, the less effective reactivation therapy will be. Recovery then depends on the slow synthesis of new acetylcholinesterase. Aging occurs very quickly for OP insecticides with an *S*-alkyl structure (e.g. profenofos) but relatively more slowly for dimethyl (e.g. dimethoate) and particularly diethyl (e.g. parathion) OP insecticides.

Clinical features

Acute poisoning is characterized by widespread muscarinic and nicotinic effects caused by inhibition of acetylcholinesterase at autonomic nerve endings and neuromuscular junctions, and in the central nervous system (CNS). Muscarinic symptoms usually first occur in the system through which the pesticide enters (Table 1). Secretory effects (salivation, bronchorrhoea) as well as pinpoint pupils (miosis) are common.

Muscarinic features of organophosphorus and carbamate insecticide 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

Nicotinic effects include profuse sweating, fasciculation, progressive flaccidity and weakness of proximal muscle groups, in particular the neck flexors followed later by the extraocular muscles and muscles of respiration. Respiratory failure is common in severe poisoning[5] and is the major cause of death; it results from a direct effect on central respiratory drive as well as from muscle weakness, bronchospasm and retention of bronchial secretions. In patients with severe poisoning, initial mild excitatory CNS effects (e.g. anxiety, restlessness, dizziness) can be followed by coma and, less commonly, seizures.[6] Severe hypotension is noted with some OP pesticides;[6] tachycardia can result from direct nicotinic effects and also from hypovolaemia and sepsis. Hyperglycaemia and glycosuria are common.

Diagnosis

This is usually made clinically in combination with the characteristic smell of formulated OP insecticides. It is then confirmed by measuring plasma or, preferably, red cell acetylcholinesterase activity to demonstrate inhibition. Clinical management should not await results of these assays.

Management

Initial treatment: the initial aims are to resuscitate and stabilize the patient with support of the airway, ventilation and circulation.[7] Oxygen and intravenous fluids should be given and convulsions controlled with intravenous diazepam. Even in the absence of convulsions, intravenous administration of diazepam (10 milligrams in adults) reduces anxiety and restlessness and can improve outcome. Decontamination of the patient should await patient stabilization with administration of antidotes (see below) as necessary.

Antidotes: the specific antidotes are atropine and oxime reactivators.[8]

Atropine can be used rapidly to block muscarinic effects and improve cardiorespiratory function. It is given intravenously (initially, adult 1–3 milligrams, child 0.02 mg/kg (20 micrograms/kg)) and repeated in doubling doses at 5-minute intervals until bronchorrhoea and bronchospasm are abolished and cardiovascular function restored (systolic blood pressure >80 mmHg, pulse >80 bpm).[7,9] Once these thresholds have been attained, atropine can be continued as a constant infusion to sustain adequate cardiorespiratory function. Patients with severe poisoning may require very large doses of atropine. However, if there is evidence of atropine intoxication (dry mouth, tachycardia, agitation or confusion, dry skin, ileus), the infusion should be stopped temporarily and restarted at around 70% of the previous rate once toxicity has settled. Patients must also be observed carefully for the recurrence of cholinergic features requiring bolus atropine.

Oximes such as pralidoxime and obidoxime (available outside of the UK) reactivate phosphorylated cholinesterases, provided they are not given after enzyme aging has occurred.[4] They can restore muscle power, reduce fasciculations and improve the patient's level of consciousness, but effectiveness is not confirmed.[10] Pralidoxime chloride (or obidoxime) should be given, preferably in a critical care environment, as a loading dose of 30 mg/kg (or obidoxime 250 milligrams) by slow intravenous injection over 30–60 minutes followed by an infusion of 8–10 mg/kg/hour (or obidoxime 32 mg/hour), continued for 2–3 days. If muscle weakness gets worse on stopping oximes, they can be restarted with daily attempts at withdrawal.

Long-term health effects

OP pesticides (particularly those used in sheep dips) are thought by some to be responsible for a long-term debilitating illness with numerous symptoms.[11] Neuromuscular complaints (lethargy, irritability, poor concentration, mood swings, depression, insomnia, paraesthesia, 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, whether at work or in leisure activities; the patient is best able to compile this list. Exclusion of other explanations is an essential component of the assessment.

Clinical examination and extensive investigation often fail to identify any significant abnormality or cause. Subtle impairment of nerve conduction velocities and performance in some neurobehavioural tests has been reported, but their relevance to the symptoms remains unclear. Management focuses on symptom control and psychological support.

Carbamate insecticides

Features and management

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