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EDITORIAL

The pathophysiology of organophosphorus pesticide self-poisoning is not so simple

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The paper by Aardema and colleagues in this issue of the *Netherlands Journal of Medicine* illustrates well the problems that clinicians face with organophosphorus pesticide self-poisoning.[1] Yet the toxicological literature's image of this poisoning is beguilingly simple.[2-5] Ingestion of an organophosphorus pesticide results in inhibition of acetylcholinesterase. The resulting build up of acetylcholine causes overstimulation of cholinergic synapses in the autonomic nervous system, central nervous system and neuromuscular junction, producing the acute cholinergic crisis. Patients die from respiratory failure during this crisis, or from a delayed respiratory failure called the intermediate syndrome. Atropine and oximes treat the poisoning.

However, organophosphorus pesticide poisoning in reality is much more complicated than this. The clinical syndrome and cause of death vary according to the precise pesticide ingested.[6] The consequences of aspiration often dominate the clinical picture and treatments do not work so well.[7] As a result, the case fatality may reach 40% in even the best Western intensive care units with parathion poisoning.[8,9]

Organophosphorus pesticide poisoning is a major problem in the developing world where health care is often distant. Many patients in such regions die before they reach health care;[10,11] patient B in Aardema's paper would never have survived to hospital. Patients having a respiratory arrest at home, away from a doctor capable of intubating them, are unlikely to survive.

There seem to be two major factors that affect whether a person ingesting a substantial dose will survive to hospital admission. The first is the speed of action of the pesticide ingested. Some are active poisons and do not require any conversion to effectively inhibit acetylcholinesterase. Others are pro-poisons, or thions, requiring activation by cytochrome P450s in the gut wall and liver to become active. But this conversion may be very fast – parathion can be converted to paraoxon and cause a person to become unconscious in just 10 to 20 minutes.[9] Other thions take longer to work; for example, dimethoate is both slowly converted to its active oxon, omethoate, and a slow inhibitor of acetylcholinesterase.[12] As a consequence, severe poisoning develops over several hours, often allowing a person to survive to hospital admission.[6] Of note, thion pesticides should not all be considered as slower poisons compared with oxon pesticides as there is much variation in speed of activation between thions.

A second little mentioned factor is the solvent in which the pesticide is formulated.[6] In animal studies, we have found that a very large dose of dimethoate containing 40% cyclohexanone and 5% xylene causes apnoea after just five to ten minutes (Eddleston & Clutton, unpublished), well before clinically significant acetylcholinesterase inhibition occurs. By contrast, a similar dose of chlorpyrifos, formulated in 60% naphtha, caused no such respiratory depression. No rules seem to be available concerning the solvents used for organophosphorus pesticides. Generic manufacturers of pesticides for the Asian market tend to formulate the pesticide in 40% xylene; by contrast, branded products from the large international companies vary markedly.

The solvent used for a particular pesticide may well therefore affect the likelihood of prehospital respiratory arrest. This seems to be an area that needs careful research. We do not yet know whether solvents are responsible for early deaths; if they are, it will be valuable to identify a number of safer solvents for pesticide manufacturers.

A fall in Glasgow Coma Scale (GCS) before hospital presentation markedly increases the risk of aspiration. Multiple case series from intensive care units across Asia report that the majority of late deaths are due to aspiration

pneumonia.[13-15] However, the pathophysiological processes leading to these deaths are unclear. In particular, the effects on the lung of blood-borne organophosphorus pesticide (rather than aspirated pesticide) in human poisoning are not known; a study in dogs by Lainee and colleagues[16] reported that an intravenous dose of the organophosphorus nerve agent VX caused breakdown of the alveolar epithelial/endothelial barrier and an inflammatory/exudative infiltrate into the lungs within two hours. Such an effect may well be sufficient to initiate the acute respiratory distress syndrome (ARDS).

The incidence of ARDS in humans with pesticide poisoning after aspiration or as an effect of the absorbed pesticide is not known. Cases of ARDS have been reported after organophosphorus poisoning.[17-22] Perhaps ARDS is the common underlying pathology that explains the large number of deaths after organophosphorus aspiration? Distinguishing ARDS from aspiration pneumonia will be important since treatment is quite different.

The best way for treating poisoned patients is not yet clear.[23] The use of atropine is not contentious. A doubling dose of atropine to ensure rapid atropinisation followed by an infusion titrated to clinical features seems sensible.[24] By contrast, the administration of oximes, such as pralidoxime or obidoxime, is contentious. Their use is recommended by the WHO.[25] However, as discussed by Aardema and colleagues, the evidence for clinical benefit is weak and the subject of much debate.

What is clear is that aged acetylcholinesterase cannot be reactivated by oximes.[26] This reaction occurs quickly in poisoning with fat insoluble dimethyl compounds such as dimethoate, so that oximes are totally ineffective by 12 hours.[27,28] Getting oximes in early in such poisoning is therefore essential if any benefit is to occur. This may be why Pawar and colleagues saw a benefit from the high-dose oxime used in their study for patients presenting within two to three hours.[29,30]

Poisoning with diethyl organophosphorus pesticides such as parathion can respond to oximes for several days, as long as sufficient oxime is given to compete with the pesticide remaining in the blood and the oxime is continued for long enough.[26,31] However, fat soluble pesticides, such as fenthion (whether dimethyl or diethyl), may benefit from oximes for many weeks. After absorption, the pesticide is stored in fat. Over time, perhaps up to several weeks after ingestion, the pesticide is released into the blood and freshly inhibits acetylcholinesterase causing recurrent cholinergic crises.[32] Since this is a new reaction, ageing starts afresh and oximes should remain effective for as long as atropine is required.

The rational use of oximes is complicated,[30] especially when the pesticide ingested is not known. Some patients will not benefit. However, at present, it seems safest to follow the WHO's guideline to give oximes to all patients[25] and to continue them until atropine is no longer required. Perhaps in the future we will have more selective guidelines. However, such guidelines will always be based on knowing the ingested pesticide and this is something that is not always certain even when the pesticide bottle is brought. Where oximes are not available or where patients ingest dimethyl pesticides and present after ten hours, excellent intensive nursing care and ventilation may well be able to compensate for not using oximes.

Treating organophosphorus pesticide poisoned patients will always be messy. The early and sudden onset of symptoms will often mean that clinicians are caring for patients whose predominant pathology (aspiration pneumonia or ARDS, or anoxic brain damage) does not respond to the specific antidotes. Organophosphorus treatment is likely to remain ineffective for a significant proportion of patients as long as fast acting, highly toxic, pesticides are used in agricultural practice. Changing use from the most toxic pesticides to less toxic pesticides has had a remarkable effect in Sri Lanka where the overall suicide rate has fallen by 50% over ten years since such legislation was passed.[33] The introduction of similar legislation across Asia would have a great effect on regional and therefore global suicide rates.

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