

## TREATING PESTICIDE POISONED PATIENTS IN THE TROPICS

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### LA PRISE EN CHARGE DES INTOXICATIONS AUX PESTICIDES EN ZONE TROPICALE

**RÉSUMÉ** • L'intoxication aux pesticides constitue un problème majeur de santé sous les tropiques, entraînant le décès de près de 350 000 individus chaque année. Les intoxications aux organophosphorés et aux carbamates se distinguent non seulement par leur fréquence et gravité mais aussi par la possibilité de les traiter avec des antidotes spécifiques. Ces malades doivent bénéficier en premier lieu de réanimation suivie de recherche systématique des signes de syndrome cholinergique justifiant l'injection d'atropine. En effet, le traitement à l'atropine à double dose doit être instauré sans délai afin de rétablir la stabilité fonctionnelle cardiorespiratoire aussi rapidement que possible. Bien que les oximes soient préconisées uniquement dans les intoxications aux organophosphorés, l'expérience actuelle semble démontrer leur intérêt dans tout syndrome cholinergique hormis dans le cas des insecticides carbamates. L'utilité des autres antidotes n'est pas prouvée. Les insecticides organochlorés, l'herbicide paraquat et le fumigène phosphure d'aluminium peuvent être à l'origine d'intoxications pour lesquelles il n'existe pas d'antidote spécifique. Heureusement la majorité de ces intoxications implique l'ingestion de pesticides qui sont, soit peu toxiques pour l'homme, soit en quantité trop faible pour provoquer des manifestations cliniques. La possibilité de manifestations différées après l'ingestion des organophosphorés peut imposer une période d'observation en milieu hospitalier, qui se termine en général par un retour à domicile après 24 à 48h. Il est urgent de mener des études cliniques et expérimentales afin de mieux comprendre l'intoxication aux pesticides et d'améliorer la prise en charge.

**MOTS-CLÉS** • Pesticides organophosphorés - Carbamates - Atropine.

**ABSTRACT** • Pesticide poisoning is a major clinical problem in the tropics, killing as many as 350,000 people every year. Organophosphorus and carbamate insecticides are the major problem because they are both common causes of severe poisoning and treatable with specific antidotes. Pesticide poisoned patients should first be resuscitated; thereafter the next question is whether they show features of the cholinergic syndrome and therefore require atropine. Atropine should be given rapidly, in doubling doses, to ensure that cardiorespiratory stability is restored as soon as possible. Although oximes are only expected to benefit some organophosphorus poisoned patients, current evidence suggests they should be given to all patients with the cholinergic syndrome who have not definitely been exposed to a carbamate insecticide. The usefulness of other antidotes is unclear. Organochlorine insecticides, the herbicide paraquat, and the fumigant aluminium phosphide are responsible for most other severe pesticide poisonings but specific antidotes are not available. Many patients will have ingested pesticides of low human toxicity or too low a dose of a toxic pesticide to show clinical features. A few others will have ingested OP pesticides with slow onset of signs. Such patients require careful observation; most can be discharged home after 24-48hrs if they have shown no clinical signs of toxicity. Better descriptive and experimental studies of pesticide poisoning are urgently required with the ultimate aim of improving medical management.

**KEY WORDS** • Organophosphorus pesticides - Carbamates - Atropine.

The management of pesticide poisoned patients is a common but difficult clinical problem across the tropics (1, 2). Most severe cases are due to intentional self-poisoning, and occur in the Asia Pacific region rather than Africa or the Americas. However, where very toxic pesticides (WHO Class I pesticides) are still used, occupational exposure can result in severe toxicity. Current estimates suggest that 260,000-370,000 deaths occur annually from pesticide suicide (3) with perhaps another 20,000 from unintentional exposure (4).

Organophosphorus (OP) insecticides are responsible for the majority of severe and fatal cases of both intentional and occupational cases of pesticide poisoning. Carbamate and organochlorine insecticides, the herbicide paraquat, and the

fumigant aluminium phosphide cause most of the other cases of severe poisoning (1). However, for clinicians, the important classes are OP and carbamate insecticides because early careful treatment with antidotes should improve outcome. Supportive care is all that can be offered to patients with severe poisoning by these other pesticides.

### EARLY MANAGEMENT OF A PESTICIDE POISONED PATIENT

Early management is similar to that of any other ill patient, requiring assessment of Airway, Breathing, and Circulation, and resuscitation with oxygen and fluids (5). Positioning of the patient in the 'Left Lateral Position' is important because vomiting is common and aspiration of the pesticide may cause fatal aspiration pneumonitis and pneu-

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monia. This position also helps keep the airway patent. Raising the legs of the bottom of the bed (on bricks if necessary) will reduce the risk of aspiration further. Seizures can be treated using standard benzodiazepine doses, in addition to ensuring adequate oxygenation. Patients unable to protect their airway or to ventilate effectively require tracheal intubation and mechanical ventilation.

Concurrently, it is essential to determine whether the patient requires atropine, ie. whether the patient is exhibiting the cholinergic toxidrome typical of OP or carbamate poisoning (5). Textbooks list a wide range of different clinical features associated with the toxidrome but in our tropical practice we have found the majority of ill patients to have pinpoint pupils, copious sweat, and crepitations on auscultation of the lungs. They are often peripherally cold and breathe slowly and irregularly, using their diaphragm more than intercostals muscles. This picture is characteristic and warrants the administration of atropine without delay (see below).

Patients not exhibiting this toxidrome may have ingested another type of pesticide (see later), a very small amount of OP or carbamate that is insufficient to cause clinical features, or an OP that has a slow onset of action (eg. fenthion) (6). They do not need atropine yet. However, since it is usually impossible to be absolutely certain about the pesticide ingested, an asymptomatic patient must be observed carefully for at least 24 hrs and until they feel completely well again. Patients ingesting a slow onset OP that causes severe illness, such as delayed respiratory failure, will usually feel unwell and show some signs of poisoning for the hours leading up to this event. A completely well patient at 24-48 hrs rarely becomes ill after this time.

Gastric decontamination should only be considered after resuscitation and administration of atropine as necessary. Forced emesis with ipecacuanha is not recommended since patients are at risk of a sudden reduction in GCS with increased risk of aspiration (7). Gastric lavage should only be done in a patient who has taken potentially lethal dose within 1-2 hrs and who either gives clear consent for the procedure and cooperates, or is sedated and intubated (8). Lavage in an uncooperative patient can have disastrous consequences (9). Multiple doses of activated charcoal do not offer benefit (10); there is also no evidence of a clear benefit from a single dose of activated charcoal (10). However, this procedure is safe and a trial should start soon to assess the usefulness of a single dose of charcoal in patients presenting within 2 hrs.

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### ADMINISTRATION OF ATROPINE

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OP and carbamate poisoning usually causes hypotension, sometimes with bradycardia, and respiratory failure due to bronchospasm, bronchorrhoea, neuromuscular dysfunction, and loss of central respiratory drive (11). The

cardiovascular and direct pulmonary effects (bronchospasm and bronchorrhoea) can be reversed by atropine; the other respiratory complications require mechanical ventilation. Therefore, atropine dosing is aimed at improving cardiovascular status (targets: pulse > 80 bpm, systolic BP >80 mmHg) and reversing bronchospasm and bronchorrhoea (5). While sweating and pinpoint pupils are useful 'triggers' for administering atropine, they do not kill patients and are therefore not useful endpoints.

Rapid administration of atropine is important to stabilize the patient's cardiorespiratory function. We typically give 1-3mg of atropine as an initial bolus dose to a patient with significant poisoning. We then give doubling doses if the patient's cardiorespiratory function does not respond within 5-10 minutes (5). Some patients will require 50 mg of atropine or more - this regimen can provide such doses in 20 min or so (12).

An alternative strategy that is commonly used is to give large initial bolus doses, of 50 mg or so. This ensures that the patient receives enough atropine; however, it may also push the patient into atropine toxicity for many hours. This is dangerous in hot tropical wards where insufficient staff means that patients with anticholinergic delirium are tied down to control them. By giving a small initial dose, and then doubling the dose every 5-10 min, we ensure that sufficient, but not toxic, doses of atropine are given rapidly. This practice is further illustrated in ref (5).

Once the patient is 'atropinised' - ie. has adequate cardiorespiratory function with all targets (see above) attained - atropine can be continued as a constant infusion with regular checks for signs of under-atropinisation (pulse <80 bpm, systolic BP <80 mmHg, bronchospasm or bronchorrhoea, pinpoint pupils, excess sweating) or atropine toxicity (absent bowel sounds, confusion, pyrexia, tachycardia >140 bpm) (5). Signs of under-atropinisation should result in further bolus doses until the patient becomes stable again and then an increase in infusion rate. Signs of atropine toxicity should result in the infusion being stopped for 30 min or so, before being restarted at a lower rate. Patients poisoned by fat soluble OPs can develop recurrent cholinergic toxicity for many days after the original poisoning (13) - they should be carefully observed until they are completely better.

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### USE OF OXIMES

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The clinical usefulness of oximes in OP poisoning is currently unclear. Patients poisoned by some OPs, particularly those with dimethyl or S-alkyl chemical groups attached to the phosphate ion, do not seem to benefit from oximes (6, 14). Patients poisoned by diethyl OPs are more likely to benefit. However, only one RCT has thus far shown clinical benefit from oxime administration and these patients presented early, were only moderately ill, and received a very high standard of supportive care (15, 16).

The benefit of oximes in patients who present late, or to less well equipped hospitals, may not be so clear.

Despite this lack of high quality evidence, it currently seems sensible to administer either pralidoxime chloride (>30 mg/kg loading dose over 20-30 min, followed by ~10 mg/kg/hr) or obidoxime (250 mg loading dose over 20-30 min, followed by 750 mg over 24hr) to any patients presenting a cholinergic toxidrome who has not definitely ingested a carbamate insecticide (for which oximes are not generally recommended) (14). The oxime can be continued until atropine has not been required for 12-24 hrs. More evidence may become available over the next few years to qualify this recommendation. However, any recommendation not to give oximes will likely be specific to particular OPs and it is usually clinically difficult to be absolutely sure about the specific OP ingested by any particular patient.

Other therapies are currently experimental (14). Studies are ongoing to determine whether the addition of magnesium sulphate, bicarbonate, or clonidine to standard therapy produces clinical benefit (17). None can presently be recommended.

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### **OUTCOME OF OP PESTICIDE POISONING**

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The outcome of best current practice is poor. Despite good use of atropine and oximes, and provision of supportive care, many patients still die. One reason is that poisoning often develops before patients present to hospital. As a consequence, respiratory failure occurs in the absence of a health care worker able to intubate the patient and prevent the common complications of respiratory failure: anoxic brain damage and aspiration pneumonia. If these complications do occur, supportive care and antidote administration will never be effective, no matter how excellent the provision.

The onset of clinical features is determined by how rapidly the OP or carbamate inhibits acetylcholinesterase, the enzyme that breaks down acetylcholine and therefore terminates cholinergic transmission. Many OPs are «pro-poisons», «thions» that need to be converted by cytochrome P450s in the gut wall and liver into active «oxons». The speed of this conversion is highly variable - the conversion of dimethoate to omethoate for example is very slow (18) whilst the conversion of parathion to paraoxon is very fast (19). Some OPs are already active oxons, eg. monocrotophos and dichlorvos, and therefore act as soon as they are absorbed. In addition, once an oxon is formed, there is variability in the speed of action - omethoate is a slow inhibitor of acetylcholinesterase while parathion is fast (20).

As a consequence, people ingesting an OP pesticide that is already an oxon, or a thion that is very rapidly conver-

ted to an oxon, can start showing clinical features within minutes of ingestion and be unconscious within 30 min. Such rapid onset of poisoning, especially in countries where there is no rapid paramedic response, makes it highly likely that patients will develop complications of poisoning that will not respond to antidotes, if they survive to reach hospital at all. In such a situation, oximes will not be expected to produce clinical benefit.

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### **OTHER TOXIC PESTICIDES**

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Organochlorine poisoning is becoming less common now as this pesticide class is being progressively banned globally due to the Stockholm Convention. Severe poisoning typically presents with status epilepticus that is often resistant to first and second line therapy, requiring general anaesthesia to control the seizures (21). Since benzodiazepines and phenobarbital complement each other at the GABA-A receptor, phenobarbital rather than phenytoin is the preferred second line treatment for organochlorine induced seizures and may be effective in some patients.

High dose paraquat ingestion causes multiorgan failure that is resistant to all current therapies. Death usually occurs from 6-48 hrs (22). A few patients die after several days or weeks due to lung fibrosis. This occurs because moderate quantities of paraquat that are insufficient to cause multiorgan failure are taken up specifically by the lung and initiate an inflammatory process (23). Overall mortality is at least 60% (22). Several studies have suggested that early administration of pulse methylprednisolone and cyclophosphamide may control the inflammatory reaction and prevent late fibrosis, but the evidence is currently unclear (24). A trial is ongoing.

Aluminium phosphide is a major problem in north India and an uncommon problem elsewhere (25). Ingestion results in production of phosphine gas in the stomach and development of multiorgan failure. Treatment is supportive only. Mortality is usually greater than 60%.

Other pesticides may be local problems. In Sri Lanka, we see methaemaglobinaemia from propanil herbicide poisoning (26) and oxidative uncoupling in chlorphenoxy acetate herbicide poisoning (27). A good knowledge of pesticides used in local agriculture and in local households can be useful in identifying uncommon clinical syndromes.

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### **LOW TOXICITY PESTICIDES**

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Poisoning can also occur with hundreds of other agriculture pesticides that are less toxic to humans. Pesticide ingestion or occupational exposure does not always result in significant poisoning. Asymptomatic patients with a history of pesticide exposure should be carefully observed for signs of the cholinergic toxidrome or other toxic syndromes. Where the history is clearly of exposure to a low toxicity pesticide,

the adverse effects of gastric decontamination are likely to outweigh any possible benefits.

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### CONCLUSION

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Pesticide poisoning can be a complicated clinical problem in the tropics. Some patients ingest pesticides that will never cause problems and that need only careful observation. Others ingest pesticides such as paraquat and aluminium phosphide for which there is no effective therapy and supportive care is all that can be offered. The most difficult cases are OP and carbamate poisoning in which good supportive care and administration of antidotes will likely improve the outcome for some patients. However, this treatment must be started early, before onset of any complications of poisoning; current outcome of therapy is often poor. More research on the pathophysiology and treatment of pesticide poisoning is urgently required to complement global regulatory efforts to reduce the human toxicity of pesticides used in agriculture.

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