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REVIEW

Organophosphorus pesticide poisoning: cases and developments

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ABSTRACT

Self-poisoning with organophosphate pesticides is a major health problem world-wide. Through the inhibition of acetylcholinesterase, organophosphorus poisoning is characterised by the clinical picture of acute cholinergic crisis. Other manifestations are the intermediate neurotoxic syndrome and delayed polyneuropathy.

In the Western world, the occurrence of organophosphorus poisoning is less prevalent due to the declining availability of organophosphate pesticides, which could render the recognition of this particular type of intoxication and its specific treatment more difficult.

In this article we discuss some recent developments and treatment dilemmas, illustrated by cases from our clinic, followed by a review of the current recommendations in the treatment of organophosphate poisoning.

KEYWORDS

Diagnosis, intoxication, oximes, parathion, treatment

INTRODUCTION

Organophosphates (OP) are used as insecticides in agricultural and domestic settings throughout the world. As nerve agents, they have also been used in warfare[1,2] and terrorist attacks.[3] The mechanism of action is through the inhibition of the enzyme acetylcholinesterase, leading to the accumulation of acetylcholine at cholinergic synapses. The excess acetylcholine causes constant acetylcholine receptor triggering, resulting in malfunction of the autonomic, somatic and central nervous systems.

Clinical manifestations of OP poisoning lead to acute cholinergic crisis (*table 1*). Although parasympathetic overstimulation tends to predominate, the overstimulation of nicotinic receptors due to excess acetylcholine can lead to sympathetic overstimulation, as well (*table 1*).[4]

A second manifestation is the intermediate neurotoxic syndrome, characterised by cranial nerve palsies, weakness of the neck and proximal limbs, and respiratory paralysis.[5,6]

OPs are highly reactive chemicals and their toxicity is not limited to acetylcholinesterase binding. Through the binding to other enzymes delayed neurological symptoms can occur as well.[4,7]

Carbamates are cholinesterase inhibitors structurally related to OP. In comparison to organophosphates they

Table 1. *Clinical manifestations of acute organophosphate poisoning*[4,13,14,16]

Muscarinic
Diarrhoea
Urinary incontinence
Miosis
Bradycardia
Bronchorrhoea
Bronchoconstriction
Salivation
Lacrimation
Emesis
Hypotension
Cardiac arrhythmias*
Nicotinic
Fasciculations
Tremors
Muscle weakness with respiratory failure
Hypertension
Tachycardia
Sweating
Mydriasis
Central nervous system
Altered level of consciousness with respiratory failure
Seizures

*Atrial fibrillation, ventricular fibrillation and heart block have been described[4,14,37]

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cause a clinically indistinguishable pattern of symptoms which, however, tend to be milder and of shorter duration.[4]

Their common availability renders OP insecticide poisoning a worldwide health problem affecting millions of patients[8,9] with a high fatality rate.[10] The majority of these poisonings appear to be an act of self-harm.[9,11] Thousands die each year, especially in the Asian Pacific region, where pesticide poisoning is the most frequent cause of fatal self-poisoning.[10,12] Although exact figures on the contribution of insecticides to the number of poisonings in the Netherlands are not available, it is clear that this contribution, both in relative and absolute numbers, is very modest compared with that in many parts of the developing world.

Since 1994 we have admitted 512 patients with intoxication to our ICU, of whom eight had OP or carbamate intoxication. The relative unfamiliarity with pesticide poisoning in the Western part of the world might render it difficult for health care providers to correctly diagnose and treat OP poisoning.

In this article we will illustrate the clinical picture and treatment with three cases and discuss some recent developments and unresolved issues in the treatment of poisoning with OP insecticides.

CASE REPORTS

Patient A

A 37-year-old farmer was transferred from a community hospital to our institution on the ninth day after auto-intoxication with parathion. His medical history was nonsignificant. He had ingested an unknown quantity of parathion with suicidal intent. He had been intubated on admission. Treatment with atropine up to 4 mg/h intravenously and obidoxime 50 mg/h, after two boluses of 250 mg intravenously, was started. On the second day he was extubated. On that same day, progressive respiratory insufficiency developed, necessitating re-intubation. Antibiotics were started to treat possible aspiration. On the eighth day, while still being ventilated, his pulmonary condition worsened. He was referred to our hospital under the diagnosis of ongoing OP toxicity. On admission, he was sedated, and while being treated with dopamine 1.5 µg/kg/min and atropine 4 mg/h, he was normotensive with a heart rate of 90 beats/min and adequate diuresis. He was febrile with a temperature of 38.5°C. He was mechanically ventilated. Further medication included obidoxime 50 mg/h, potassium chloride, sufentanil, ipratropium, salbutamol, enoxaparin, cefuroxime, tobramycin, and trimethoprim-sulphamethoxazole. The chest X-ray showed bilateral infiltrates. His laboratory results showed hyperklaemia (6.7 mmol/l; range 3.6-4.8mmol/l), renal failure with a creatinine of 222 µmol/l (range 62-110), urea of 15.1 mmol/l (range 3.2-6.8) and a cholinesterase level of 140 U/l (range 3700-11,000). Arterial blood gas analysis showed a pH 7.30 (range 7.35-7.45), pCO_2 25.7 kPa (range 9.2-13.9), bicarbonate 22 mmol/l (range 21-25) and oxygen saturation 99% (range 96-100). Other laboratory results were within the normal limits. No conduction abnormalities were seen on an electrocardiogram. Trimethoprim could have played a role in both the patient's renal failure and hyperkalaemia. Other contributing factors to the latter were mild acidosis, likely linked to renal failure, and inappropriate supplementation of potassium.

Potassium suppletion and nephrotoxic drugs were stopped. Atropine infusion was decreased, and sufentanil was replaced by midazolam and morphine. Amoxicillin with clavulanic acid was started to treat suspected ventilator associated pneumonia although sputum culture did not reveal any pathogens. Obidoxime was discontinued. Optimisation of ICU care resulted in tapering of ventilatory support, improved renal function and extubation on the 12th day after initial admission. Atropine was stopped on the 13th day. On the 14th day, the patient was discharged to the medical ward with psychiatric follow-up. The prolonged course was probably due to secondary complications of ICU care such as possible ventilator-associated pneumonia and renal failure. Over-atropinisation resulting in hyperthermia can not be ruled out in retrospect; however, other signs of over-atropinisation including tachycardia and ileus were not present.

Patient B

A 61-year-old man with a history of depression, alcohol abuse and suicidal attempts was admitted to our intensive care. Shortly before admission, he had ingested an unknown quantity of parathion, whereupon he had lost consciousness. Paramedics noted asystole, and cardiopulmonary resuscitation was started. Spontaneous circulation was achieved after ten minutes. He had probably aspirated gastric contents. He was transferred to our hospital. On admission he was comatose (Glasgow-coma scale 1-1-Tube) and mechanically ventilated. He was normotensive with a heart rate of 105 beats/min. His pupils were pin-point and not responding to light. He had bronchorrhoea and diarrhoea. Fasciculations were noted. Further physical examination revealed no abnormalities. Laboratory results showed a leucocytosis of 18.6 x 10^9/l (range 4 to 10 x 10^3/mm^3), and an elevated lactate of 12.5 mmol/l (range 0.5 to 2.2 mmol/l). Further testing revealed slight liver function abnormalities: lactate dehydrogenase 610 U/l (range 114 to 235 U/l), aspartate aminotransferase 87 U/l (range 0 to 40), alanine aminotransferase 51 U/l (range 0 to 30), and γ-glutamyltransferase 64 U/l (range 0 to 65). Arterial

blood gas analysis showed profound, metabolic acidosis with pH 7.1, pCO_2 5.5 kPa, pO_2 24.1 kPa, bicarbonate of 12 mmol/l, and oxygen saturation 98%. A blood cholinesterase level was undetectable. The chest X-ray showed no abnormalities. Electrocardiogram showed no conduction abnormalities. He was treated with atropine 1 mg/h intravenously after boluses of 2 mg and 0.5 mg. Additionally, he was treated with active charcoal and diazepam 10 mg. On the second day, obidoxime was started in boluses of 250 mg. Furthermore, he received rocuronium in boluses to treat fasciculations. His course was complicated by a septic episode and persistent coma. Electroencephalography performed on day 17 showed very little activity; a somatosensory evoked potentials test performed on that same day showed no cortical activity. Based on these results treatment was stopped and the patient died on day 18.
The death of the patient was attributed to prolonged anoxia in the initial phase of intoxication. After circulation was restored, the symptoms of toxicity had been manageable.

Patient C
A 63-year-old farmer with a history of depression was admitted to our hospital after ingestion of approximately 200 ml of parathion several hours earlier. His family alerted medical services when he was found unconscious. On arrival, paramedics saw a comatose man with bradycardia (32 beats/min), bronchorrhoea and dilated pupils. He was intubated instantaneously and started on atropine and obidoxime. On arrival in our hospital, a sedated, intubated man was seen with a blood pressure of 155/85 mmHg, and a pulse of 110 beats/min. He was mechanically ventilated. Blood gas analysis showed pH 7.11, pCO_2 8.5 kPa, pO_2 57.2 kPa, bicarbonate 20 mmol/l and O_2 saturation of 99%. Physical examination showed no abnormalities. His serum parathion level was 800 µg/l (toxic above 10 µg/l) serum cholinesterase was undetectable (range 5400 to 13,200 U/l), indicating severe intoxication. He was given activated charcoal and admitted to our intensive care. Sedation with propofol was continued. Obidoxime 40 mg/h was given intravenously but stopped shortly thereafter. As bronchorrhoea worsened, atropine was started in boluses of 3 mg. On the second day, profound diarrhoea and perspiration was noted. Atropine was titrated to effect on bronchorrhoea and diarrhoea; there was no bradycardia. Boluses of 3 mg intravenously were needed about twice a day. On the seventh day a continuous infusion of atropine 3 to 6 mg/day was started. His course was complicated by pneumonia, probably due to aspiration, and bacteraemia with *Klebsiella* species. He was successfully extubated on the eighth day. Atropine was stopped on the ninth day, to be restarted on the same day due to reappearance of bronchorrhoea and diarrhoea. On the 11th day, atropine was stopped without further complications. On the 12 day, he was discharged to the medical ward. His cholinesterase level was 2000 U/l. On the 20th day, he was discharged to the psychiatric ward.

DISCUSSION

Severely intoxicated patients should receive immediate resuscitation, including circulatory support and mechanical ventilation when indicated. In all three patients immediate adequate resuscitation was indeed started. In our patients the diagnosis of OP intoxication was based on history and confirmed by the clinical picture and decreased serum cholinesterase. All three patients showed signs of acute cholinergic crisis (*table 1*).[4,13,14] However, not all signs and symptoms were present in every patient. Usually the clinical picture and history is sufficient for the diagnosis. When the diagnosis is uncertain, measurement of plasma butyrylcholinesterase (also called plasmacholinesterase or pseudocholinesterase) or erythrocyte acetylcholinesterase can be useful.[4,15] The former is an indirect biomarker of inhibition of acetylcholinesterase and has thus no direct relation to the extent of acetylcholinesterase inhibition in synapses. It can be used, however, to detect exposure to organophosphates.[15,16] Measurement of erythrocyte acetylcholinesterase does reflect acetylcholinesterase inhibition in the nervous system; although a complex interrelationship between erythrocyte and nervous system acetylcholinesterase inhibition exists,[15] levels of erythrocyte acetylcholinesterase are a good marker of severity of OP poisoning.[15,16] For more information on the difficult interpretation of cholinesterase assays, we refer to a recent review.[16]
There is much debate about the treatment of OP toxicity. This is reflected by the treatment of our patients. Important differences in treatment occurred. Most of these differences were based on interpretation of the literature available at that time.
Atropine is undisputedly the cornerstone of the treatment of acute cholinergic syndrome. It competes with acetylcholine on muscarinic acetylcholine receptors.[17] It works within minutes[18] and has a half-life of two to five hours. Uncertainty exists about the starting dose, dose escalation and duration of therapy. Some protocols use fixed boluses for every fixed time period. A protocol with a doubling of the atropine every few minutes reaches the sometimes extreme doses of hundreds of milligrammes earlier and might be more appropriate.[4,19]
Possible parameters for drug titration are miosis, excessive perspiration, hypotension, bradycardia, bronchorrhoea and bronchospasm.[18] However, later on secondary complications due to e.g. hypoxia or pneumonia or atropine overdose, which is characterised by confusion, hyperthermia, and

ileus, can complicate the interpretation of these clinical signs.[4,18] Being a selective muscarinic antagonist, atropine has no effect on the neuromuscular junction and muscle weakness.[4]

In patient C bronchorrhoea was used as a parameter for atropinisation and re-intubation. In this patient, to control diarrhoea and bronchorrhoea, a regimen of atropine 3 mg twice daily was instituted, initially resulting in sufficient control; a switch to continuous infusion was later needed to adequately control patient's symptoms. On reflection, given the half-life of atropine (two to five hours), a twice daily regimen seems illogical. The dilated pupils seen in patient C could have been caused by initial sympathetic overstimulation.[16] However, his overall clinical picture was that of parasympathetic overstimulation, including bradycardia and bronchorrhoea. It is possible that the recording of dilated pupils was made after the administration of atropine.

In patient A atropine was discontinued too early and then probably continued too long because some clinical signs were ascribed to OP instead of atropine or complications due to ICU treatment. As shown in patient C, atropine can be needed for weeks. The duration of this requirement depends on the type of OP, amount of ingested toxin and patient-related pharmacokinetic parameters. There are no clear atropine maintenance and withdrawal schedules. Daily reduction of continuous atropine dosing until clinical signs develop is one option, intermittent dosing of boluses given on indication is another. The continuous infusion of atropine as in these patients is not based on literature. Glycopyrrolate is an alternative to atropine as anticholinergic agent, although it may be less effective in counteracting central nervous system dysfunction due to organophosphorus poisoning. Its place in the therapy needs further study.[17]

Agitation and seizures are treated with benzodiazepines.[4]

The use of oximes in the treatment of OP poisoning is much debated, resulting in different and illogical oxime use in our patients. OP insecticides inhibit acetylcholinesterase by phosphorylating the serine hydroxyl group at the enzyme's active site; acetylcholinesterase is reactivated by the attack of the phosphorylated serine residue by a hydroxyl ion, thus removing the phosphate moiety from the enzyme. Before reactivation, however, the enzyme is prone to a process called ageing, whereby one alkyl side of the phosphoryl moiety is replaced by a hydroxyl group, rendering the acetylcholinesterase molecule negatively charged and therefore inaccessible for reaction with an hydroxyl ion, thus leaving the enzyme unable to be reactivated.[15,20,21] The rationale for oximes, such as obidoxime or pralidoxime, lies in their ability to catalyse the regeneration of active acetylcholinesterase by removing the phosphoryl group from inactivated acetylcholinesterase. The time frame for oximes to be effective is thus restricted to the window before ageing has occurred.[20-22] Every OP has a typical ageing time. Various systematic reviews and meta-analyses failed to find sufficient evidence for benefit from oximes or even suggested harm.[17,20,23,24] Important methodological weaknesses, including underdosing of oximes in most trials,[17,20] are major drawbacks of the trials included in these reviews. A recent randomised controlled trial including 200 patients with moderately severe OP poisoning showed reduced morbidity and mortality in patients treated with high-dose continuous pralidoxime (1 g/h for 48 h after a 2 g loading dose) compared with low-dose bolus (mortality 1% in study group *vs* 8% in control group).[25] It is the first known trial dosing oximes as recommended by the World Health Organisation (WHO) in a dose of 8 to 10 mg of pralidoxime per kg body weight per hour after a loading dose of 2 g.[26] This study, however, received criticism on methodology and ethical issues.[27-31] Some of the criticism comprised the observation that the study was biased in that only moderately severely intoxicated patients who presented very early (longest interval between presentation and randomisation 7.5 h) were included, which was acknowledged by the author.[32] Thus far, the WHO has recommended treatment with high doses of pralidoxime as mentioned above. [26]

However, in terms of evidence-based medicine the classification is level B at best. Alternatives for oximes, such as α2-adrenergic receptor antagonists or OP hydrolases, are theoretically conceivable but have either not been tested adequately or not been tested at all as yet.[8,17]

Gastric lavage and the administration of activated charcoal have no proven beneficial effect but are still frequently used.[17,18] Skin decontamination with water and soap and removal of exposed garments is advised in order to minimise the extent of intoxication.[18] Exposure of health care workers should be prevented although severe secondary intoxications have not been described. Exposure can be limited by reducing the number of caregivers involved, limiting exposure time, the usual protective clothing (eye protection, gloves and gown) and good ventilation of the room.

There are several reports of occupational exposure followed by symptoms,[33,34] although an actual secondary intoxication has thus far never been proved.[35,36] In affected health care workers, acetylcholinesterase levels were never measured;[33,34,36] most organophosphate compounds are dissolved in highly volatile foul smelling solvents which are more likely to cause complaints than the non-volatile organophosphate compounds themselves.[35] In conclusion, although a widespread problem world-wide, poisoning with insecticides is relatively rare in Western Europe. Recognition is important, as pesticide poisoning is associated with a high fatality rate. Patients are treated using standard resuscitation care with atropine to counteract muscarinic effects. Although the use of oximes is not evidence-based,

thus far it has been recommended by the WHO pending further clinical trials. Hopefully, more insight into the optimal treatment of pesticide poisoning and the regulation of availability of these highly toxic compounds will enable prevention of many deaths in the near future.

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