

Clinical pharmacology

Role of oximes in organophosphate poisoning – a case report

A 28-year-old man was found unconscious. Examination revealed a Glasgow Coma Scale of 4/15, constricted pupils, marked generalised muscular fasciculations, excessive sweating and salivation, pulse rate of 50 bpm and bilateral diffuse crackles on chest auscultation. The reduced pseudocholinesterase concentration of 545 U/l (normal range 3 000 – 9 300 U/l) confirmed the clinical diagnosis of organophosphate poisoning.

The patient was resuscitated; an atropine infusion was started, followed by a single dose of obidoxime 250 mg. The patient had a rapid recovery, regaining consciousness and spontaneous breathing at 2 hours. Atropine was infused for a total duration of 39 hours and the patient was discharged after 48 hours, with no sequelae. The patient gave a history of having eaten a sandwich bought from a street vendor prior to the incident.

Organophosphate poisoning

Organophosphate poisoning is a notifiable condition in South Africa. Organophosphate pesticides are widely used for agriculture, vector control and domestic purposes. Severe cholinergic toxicity may occur following accidental or intentional (usually suicidal) inhalation, ingestion or cutaneous organophosphate exposure.

Following nerve impulse transmission, acetylcholine is released from the postsynaptic membrane receptor and is broken down by acetylcholinesterase (AChE) to choline and acetic acid. Choline is recycled by an active pump at the presynaptic membrane for the formation of more acetylcholine.

Acetylcholine is released in all pre-ganglionic autonomic nerves, all postganglionic parasympathetic and some sympathetic nerves, nerves to the adrenal medulla, somatic motor nerves to skeletal muscles and some neurones in the central nervous system. The acetylcholine receptors are divided into muscarinic and nicotinic subtypes. Acetylcholine released at postganglionic parasympathetic fibres act on muscarinic receptors. These receptors occur in brain, gastric parietal cells, heart, smooth muscle

and glands. Muscarinic effects are mainly parasympathetic. The nicotinic receptors are found in all autonomic ganglia, adrenal medulla and the neuromuscular junction. The nicotinic stimulation is relatively weak and therefore the parasympathetic effects predominate.

Organophosphates are potent cholinesterase inhibitors, and slowly form an irreversible covalent bond with AChE by phosphorylation in a process called 'ageing'. This process is initially reversible and spontaneous reactivation of AChE can occur. Of note, the rate of 'ageing' is different among organophosphate compounds. The 'ageing' mean half-life for dimethylpesticides and diethylpesticides is 3.1 and 33 hours respectively. The phosphorylated AChE cannot break down ACh and accumulation of acetylcholine in the synaptic cleft causes excess stimulation at cholinergic receptors throughout the central and peripheral nervous system.

The commonest presentation is the acute cholinergic crisis, usually diarrhoea, urinary frequency, miosis, bradycardia, bronchorrhoea and bronchoconstriction, emesis, lacrimation, salivation (easily remembered by the mnemonic **DUMBELS**) and hypotension.

Nicotinic receptor stimulation leads to tachycardia, hypertension, mydriasis, fasciculations and muscle weakness, as well as respiratory failure. The central nervous system effects are altered level of consciousness, respiratory failure and seizures.

The diagnosis is confirmed by a history of exposure and characteristic signs on clinical examination. Respiratory difficulty, altered level of consciousness and muscle weakness are associated with major toxicity. A low pseudocholinesterase concentration supports the diagnosis but does not indicate the severity of clinical toxicity. An erythrocyte acetylcholinesterase concentration 20% lower than normal is indicative of severe toxicity; however, this investigation is often not available.

Airway management, along with other supportive therapy, is most important in the management of organophosphate poisoning as respiratory failure is the most common cause of death. In cutaneous exposure decontamination should be done by removing and discarding the contaminated clothing and washing the patient with copious amounts of water and

soap. It is essential to prevent contamination of the attending health personnel. Gastric lavage is only indicated if patients present within 2 hours of ingestion. Atropine, an antimuscarinic agent, given by infusion, is the cornerstone of medical therapy. Benzodiazepines are indicated for patients with fasciculations, agitation, anxiety and seizures. The role of pyridium oximes, e.g. obidoxime, in acute organophosphate poisoning, has been controversial and is discussed below.

Role of pyridium oximes

The pyridium oximes are able to reactivate the phosphorylated cholinesterases. They displace the phosphoryl moiety from AChE. Fig. 1 illustrates the reactivation of acetylcholinesterase by the introduction of the oxime. Of note, the reactivation process is not possible if the enzymes have 'aged'.

In clinical practice, pralidoxime and obidoxime are the most widely used. In South Africa, obidoxime is the only agent available. The data for efficacy and safety of the oximes are controversial. Experimental *in vitro* studies suggest complete reactivation of AChE within an hour. Few randomised controlled clinical trials (RCTs) are available. A Cochrane systematic review identified one RCT in 110 patients, where 12 g of pralidoxime over 3 days was compared with standard care. The authors concluded that there was insufficient evidence to indicate whether the oximes were beneficial or harmful and they suggested that better RCTs were required.

The most recent meta-analysis included retrospective and prospective trials with 188 patients on variable doses of oximes. The retrospective trials showed no mortality benefit with risk difference of 0 (95% CI -0.10 - 0.10) and prospective trials showed some evidence of harm with the risk difference of 0.18 (95% CI 0.06 - 0.30). The overall effect showed a trend towards harm. Most of the individual trials were criticised for poor methodology and were underpowered to detect a mortality benefit.

A recently published study randomised patients with moderately severe organophosphate poisoning to receive standard or high-dose pralidoxime regimens, after resuscitation and initiating an atropine infusion. The patients who received a high-dose infusion had

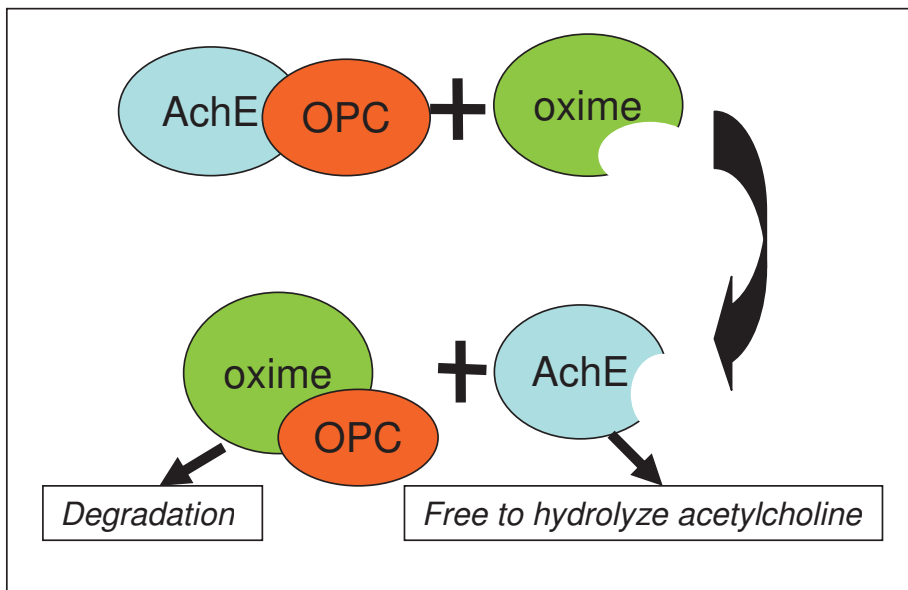


Fig. 1. Schematic representation of a reaction between an acetylcholinesterase (AChE) organophosphate compound (OPC) complex and a cholinesterase reactivator (oxime) before the 'ageing' process.

lower mortality (1% v. 8%), less need of intubation and artificial ventilation. They also required less atropine on the first day and fewer developed pneumonia. This is the first published RCT that suggests high-dose pralidoxime is superior to the standard regimen. The recommended dose of obidoxime (the only preparation available in South Africa) is 250 mg immediately, repeated at 2 hours if there is improvement.

Can we extrapolate from the pralidoxime RCT that giving higher doses will be

beneficial? As organophosphate poisoning in South Africa is common, and it would be ethically difficult to repeat the study, it seems prudent that the use of the oximes should be advised in patients with a significant poisoning history.

WHO guidelines recommend an initial intravenous bolus dose of 250 mg of obidoxime followed by an infusion of 750 mg over 24 hours. Atropine must be administered to all patients, with the following clinical end-points confirming adequate atropinisation: no bronchial

secretions, dry mucous membranes, no axillary sweating and heart rate of 100 bpm.

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Further reading

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In a nutshell

- Supportive therapy, including assisted ventilation, is the mainstay of managing organophosphate pesticide poisoning.
- Atropine is the cornerstone of medical therapy.
- The role of oximes has been controversial for many years with insufficient evidence for benefit or harm. However, a recent RCT showed that higher doses of pralidoxime resulted in better outcomes than standard doses. Early administration of the oximes (within 2 hours) is therefore recommended in patients with major toxicity.
- In South Africa, an IV bolus of 250 mg obidoxime, followed by an infusion of 750 mg over 24 hours is now recommended. Although this is off-label, i.e. different dosing instruction from the package insert, this recommendation is consistent with WHO guidelines and the recent RCT showing a favourable response to high-dose early therapy.