Organophosphorus and carbamate poisoning

Dr. R. S. Verster BVSc, BVSc (Hons), MSc e-mail ryno.vester@nwu.ac.za

1. Introduction

Insecticides are used on a massive scale worldwide and it is thus inevitable that accidental poisoning of humans and animals will occur. Organophosphors and carbamates are responsible for a substantial number of poisoning cases. Intentional poisonings are often committed by criminals, who insert aldicarb granules inside meat baits. A survey in 2003 in Gauteng confirmed that this unacceptable practice caused illness and death of many dogs. The treatment of such cases is usually based on a rudimentary understanding of the poison and the objective of this article is to broaden the scope of knowledge of the pathophysiology, diagnosis and holistic management of such cases.

2. Physiological mechanism of acetylcholine

A quick review is necessary to understand the role of this neurotransmitter. Acetylcholine acts as the neurotransmitter between nerve footplates and innervated cells of autonomic ganglia, the adrenal medulla, parasympathetic neuroeffector junctions, some sympathetic neuroeffector junctions, somatic neuromuscular junctions and certain regions of the central nervous system. Acetylcholine produces excitation in some tissues e.g. smooth muscle of the gastrointestinal tract, but causes inhibitory responses in other tissues e.g. myocardium. Depolarisation of the postsynaptic membrane is characterized by an increase in permeability of the membrane to both Na⁺ and K⁺ ions, resulting in excitatory effects. On the other hand, inhibitory effects are due to hyperpolarization of the membrane caused by a selective increase in membrane permeability to K⁺, but not Na⁺. Acetylcholine is able to combine with the esterophilic and anionic sites of both muscarinic and nicotinic receptors due to its molecular structure. The duration of action of acetylcholine is limited, due to the inactivation by acetylcholinesterases.

3. Pathophysiology of organophosphors

The organophosphor’s phosphate radical binds to the active site (the serine hydroxyl group) of acetylcholinesterase. This binding is considered irreversible as after a period of time aging (caused by dealkylation of the organophosphorus moiety on the inhibited enzyme) occurs. Phosphorylated enzymes are inactive and unable to hydrolyze acetylcholine at the synaptic - and myoneural junctions. The consequence is the accumulation of acetylcholine with prolonged effects at the receptors. Plasma cholinesterase activity takes 4 - 6 weeks to return to baseline levels and erythrocyte acetylcholinesterase activity may take up to 5 - 7 weeks.

A sub-acute syndrome, referred to as organophosphor-induced delayed neuropathy (OPIDN) may occur 7 - 14 days after exposure, but occasionally up to 21 days later. It is characterized by an asymmetrical sensory-motor axonopathy as result of the inhibition of
neuropathy target esterase (or neurotoxic esterase [NTE]), which is different from acetylcholinesterase.

Only neurotoxic organophosphors bind irreversibly, by means of phosphorylation, to NTE. This process starts with hydrolysis of an ester or amide bond, leaving an ionized acidic group on the phosphorus atom. If exposure to an appropriate neurotoxic organophosphor results in more than 70% inhibition of NTE, OPIDN usually follows. Not all organophosphors are neurotoxic, although they can also bind to NTE. As such, these non-neurotoxic organophosphors may paradoxically prevent neurotoxic effects by competing for NTE and do not undergo “aging”.

The most severe clinical sign associated with OPIDN is paralysis of the limbs, while moderate cases show high-stepping gait and ataxia with the absence of pain. Histologically, the lesion involves a process known as Wallerian degeneration of the long axons of the peripheral nerves, as well as the ascending and descending tracts of the spinal cord. There is a loss of the myelin sheath, proliferation of Schwann cells with macrophage accumulation. The thick myelinated fibres are more affected than the thin unmyelinated fibres.

4. Pathophysiology of carbamates

Carbamates react with the serine group on acetylcholinesterase to yield a carbamylation of the serine hydroxyl group. The carbamylation of acetylcholinesterase is reversible and the carbamylated complex will hydrolyze in time, usually within 48 hours. This is different from the organophosphors, which bind the esterases irreversibly and new enzyme is only resynthesized after 20–30 days.

5. Clinical signs

The accumulated acetylcholine excessively stimulates cholinergic receptors (muscarinic, nicotinic and in the central nervous system). Muscarinic effects such as salivation, lacrimation, urination, vomiting, diarrhoea, bradycardia, bronchoconstriction with excessive bronchial secretions and miosis are dominant. Nicotinic effects manifest as tremors, muscle stiffness, weakness and paralysis. Central nervous system effects include restlessness, confusion, ataxia, convulsions and cardiorespiratory depression. Mortalities are commonly attributed to respiratory failure.

6. Necropsy findings

Post-mortem findings are mostly non-specific (e.g. congestion and cyanosis) and not consistent. Lesions include rupture of large bronchi, pulmonary oedema and emphysema and petechiation of some organs. Other lesions that have been reported are pancreatitis and enteritis in dogs and myopathy of the diaphragmatic and intercostal muscles in severe cases.
8. Diagnosis of organophosphor and carbamate poisoning

The history and clinical signs are important criteria in the diagnosis of suspected poisoning. Confirmation of toxicity can be obtained by analyzing the stomach or rumen contents for the presence of the organophosphors or carbamates. Determination of blood cholinesterase activity is also a good indicator of organophosphor poisoning as it quantifies enzyme activity.

Variations in acetylcholinesterase activity between species are too great to establish a general reference range and are therefore, a critical factor that influences interpretation of laboratory results. Thus, a database with normal values is needed for each species. Erythrocyte acetylcholinesterase inhibition is a useful tool to aid in the diagnosis of organophosphor poisoning in cattle and sheep, because 90% or more of the total cholinesterase is found in the red blood cells. Dogs and cats, on the other hand, have similar pseudocholinesterase and acetylcholinesterase activities. Cholinesterases in whole blood, plasma or brain are inhibited to a similar degree in goats, therefore, any depression of cholinesterase activity is a reliable index of exposure to organophosphors.

Samples collected during the post mortem examination should therefore include stomach/rumen contents, whole blood (if possible), blood clots, brain, eyes (ocular fluid) and liver.

Reduction of cholinesterase activity to less than 25% of normal is seen in severe cases, but a 50% reduction is considered a significant inhibition. Although the determination of cholinesterase activity is the gold standard for confirmation of organophosphor poisoning it is not reliable to confirm exposure to carbamates, as the cholinesterases spontaneously re activate and give false negative results.

9. Treatment of organophosphor and carbamate toxicosis

In companion animals it would appear that mild intoxication could be successfully treated, although the more severe cases usually die, despite intensive treatment. The most important treatment is repeated parenteral administration of atropine at 0.1 - 0.2 mg/kg in dogs and cats. The dose of atropine is 0.25 - 0.5 mg/kg in cattle and up to 1 mg/kg in sheep. A total dose of 65 mg is recommended for the average horse. The total dose of atropine in humans is only 2 mg intravenously. Atropine is a competitive antagonist of acetylcholine. Atropine has no effect on nicotinic receptors and will not counteract muscle tremors, weakness or paralysis. Diphenhydramine dosed at 1 - 4 mg/kg per os every 6 - 8 hours may be useful to counteract the nicotinic effects. Even a dose of 5 mg/kg diphenhydramine is acceptable.

Enzyme reactivators are useful in the treatment of organophosphor poisoning, but not with carbamate poisoning, as the acetylcholinesterase inhibition in the latter is reversible, the enzyme will re-activate spontaneously in a short period of time irrespective of treatment. The reactivators are used in organophosphor poisoning because of stronger and longer inhibition of acetylcholinesterase. They must, however, be administered within 24 hours before “aging” occurs and, preferably, within the first 12 - 18 hours. Pralidoxime
chloride (2-PAM) is administered at 10 - 15 mg/kg 2 - 3 times a day in dogs and cats. The reactivator competes for the phosphate moiety of the organophosphor compound and releases it from the acetycholinesterase enzyme.

The clinician should also remove the poison to prevent further exposure and absobtnt. Further absorption from the stomach of dogs can be avoided by administering the emetics, apomorphine (0.04 mg/kg i/v or 0.08 mg/kg i/m or s/c or syrup of ipecac (1 - 2 ml/kg p.o. [not more than 15 ml in total]). For cats the dosage of syrup of ipecac is 3.3 ml/kg p.o. Gastric lavage in small animals or rumenotomy in large animals can also be considered.

Adsorbants e.g. activated charcoal 1 - 4 g/kg p.o. are very effective in binding ingested pesticides. A cathartic must be used at the same time, because activated charcoal becomes stationary in the gastro-intestinal tract and slowly releases the adsorbed toxin. The cathartic promotes passage of the activated charcoal and elimination of the adsorbed toxin via the faeces.

Additional supportive treatment must be given, which could include light anaesthesia or deep sedation and fluid therapy until the dog has eliminated the poison.

References


