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Antidotes: atropine and beyond

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The clinical features of organophosphate (OP) poisoning are due to its action on the cholinergic synapses in the peripheral and central nervous system (CNS). The effect on neuromuscular nicotinic receptors (N1/Nm) results in muscle weakness while the action on sympathetic and parasympathetic ganglia and adrenal medulla (N2/Nn receptors) result in hypotension and bradycardia. CNS manifestations (anxiety, convulsions, coma) are mediated by muscarinic receptor subunits (M1 to M5) in the brain. M2 and M3 receptors present in pupils, exocrine glands and smooth muscles primarily mediate the SLUDGE (Salivation, Lacrimation, Urination, Defecation, Gastrointestinal dysfunction, Emesis) symptoms.

Anticholinergic drugs with antimuscarinic action (atropine, glycopyrrolate, scopolamine) are used in OP poisoning. Atropine, the mainstay of antidotal therapy, acts through competitive inhibition of postganglionic acetylcholine receptors and direct vagolytic action. This leads to parasympathetic inhibition of acetylcholine receptors in the smooth muscle, reduction of salivation and lacrimation through antimuscarinic effects on exocrine glands and allows for preexisting sympathetic stimulation to predominate, increasing cardiac output.

In the acute setting, rapid atropinisation is achieved with an initial bolus of 2-mg followed by doubling of dose every 2-5 minutes till atropinisation. Mandatory atropine targets (“atropinisation”) are heart rate >100/min, systolic blood pressure >90 mm Hg and clear lung fields. Once atropinisation is achieved, target heart rate and blood pressure may be maintained with atropine infusion. There is some evidence that atropine infusion may be preferred over boluses. In patients allergic to atropine or manifesting atropine toxicity, glycopyrrolate may be used. Glycopyrrolate does not cross the blood brain barrier and hence does not mitigate the CNS manifestations of OP poisoning, which atropine impacts. In one study, clinical outcomes were similar with atropine with glycopyrrolate. In another report, intravenous scopolamine was associated with rapid reversal of severe extrapyramidal signs in chlorpyrifos poisoning. However it has selective action (M1, M2) and is neurodepressive.

Atropine refractoriness is infrequently seen in mega-dose intoxications and is probably due to blockade of pre-ganglionic sympathetic neurons with reduced sympathetic outflow. Administration of small dose adrenaline (1-2 mcg/min infusion) improves hemodynamics and reduces atropine requirement.

The development of newer receptor specific anticholinergic drugs may help in the management of OP poisoning.

Learning objectives

1. Understand receptor based effects of organophosphate compounds
2. Elucidate the role of atropine in organophosphate poisoning
3. When should other anticholinergic agents be used?
4. What is atropine refractoriness and how is it managed?