

Alternative Antidotes for Organophosphate Poisoning: Atropine, Pralidoxime and Beyond.

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Despite organophosphates being a common poisoning only one antidote, atropine for OP poisoning, could be clearly regarded as effective. The efficacy of oximes remains to be defined and relies on understanding of the reasons for treatment failure. There is considerable variation in the clinical syndrome and response to oxime treatment between various organophosphates. (1) Of particular importance are the different rates of cholinesterase inhibition and aging of the organophosphate cholinesterase complex. This suggests a need for better evidence on the effects of current treatments and alternate antidotes. There has been little clinical development of a large number of low cost antidotes that have been shown to be effective in animals and which could be clinically useful. Such antidotes need to be accessible and affordable. Drugs that fulfill these criteria include: sodium bicarbonate, clonidine, magnesium and diazepam. All of these have a good biological rationale, positive evidence from animal studies (2-6) and have been used in humans for many years. Recently a number of trials have been underway to try and define the role of such potential antidotes. A major issue in the clinical trials is the selection of outcome measures that account for the variation in pesticides, patient response and treatment resources. Arguably this requires the use of validated intermediate outcomes in addition to outcomes such as death and ventilation. Putative mechanisms for such antidotes include direct alterations in pesticide kinetics such altered binding, enhanced clearance and alterations in the pharmacodynamics of the OP-cholinesterase complex. Alternate strategies include alteration in synaptic acetylcholine release. Both Magnesium and Clonidine reduces acetylcholine synaptic concentration. Diazepam appears to reduce centrally mediated respiratory failure in animals and had synergistic activity with anticholinergics. Treatment with intravenous sodium bicarbonate had been reported to be protective in some animal models and anecdotally in humans. A recent study demonstrated that sodium bicarbonate in a dose of that 5 mEq/Kg of over 60 minutes followed by 5-6 mEq/Kg over 24 hours could safely alkalinize patients and reduce bed stay.(7) Other potential OP antidotes include: organophosphate (OP) hydrolyses which break down OPs and speed up reactivation of AChE,(8) reversible anticholinesterases (e.g. pyridostigmine) which competitively bind to AChE and thereby prevent binding by OP, and glutamate antagonists and agonists for adenosine and alpha-2 receptors which may limit damage to the central nervous system by non-specific mechanisms.

The clinical role of these antidotes is still being defined but it is likely that some will find a therapeutic role.

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