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Mini review

Developments in alternative treatments for organophosphate poisoning

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HIGHLIGHTS

- Organophosphorus poisoning remains a worldwide health concern.
- Current treatment does not proactively prevent neurotoxicity in patients.
- Novel support drugs and enzymatic bioscavengers are being investigated.
- Broad-spectrum prophylaxis remains the top priority for researchers.

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ABSTRACT

Organophosphosphates (OPs) are highly effective acetylcholinesterase (AChE) inhibitors that are used worldwide as cheap, multi-purpose insecticides. OPs are also used as chemical weapons forming the active core of G-series and V-series chemical agents including tabun, sarin, soman, cyclosarin, VX, and their chemical analogs. Human exposure to any of these compounds leads to neurotoxic accumulation of the neurotransmitter acetylcholine, resulting in abnormal nerve function and multiple secondary health complications. Suicide from deliberate exposure to OPs is particularly prevalent in developing countries across the world and constitutes a major global health crisis. The prevalence and accessible nature of OP compounds within modern agricultural spheres and concern over their potential use in biochemical weapon attacks have incentivized both government agencies and medical researchers to enact stricter regulatory policies over their usage and to begin developing more proactive medical treatments in cases of OP poisoning. This review will discuss the research undertaken in recent years that has investigated new supplementary drug options for OP treatment and support therapy, including progress in the development of enzymatic prophylaxis.

Contents

Abbreviations: AChE, acetylcholinesterase; BBB, blood–brain barrier; HuBChE, human butyrylcholinesterase; OP, organophosphate; PON1, serum paraoxanase-1; PTE, phosphotriesterase; SE, status epilepticus.

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1. Introduction

Organophosphorus (OP) insecticides and nerve agents are designed to function as acetylcholinesterase (AChE) inhibitors. OP compounds are highly lipophilic and quickly migrate to the nervous system where OP intoxication is initiated through the binding and subsequent inactivation of AChE. While many phosphorothioate (P=S bond) OP insecticides, such as malathion, parathion, chlorpyrifos, and diazinon happen to be poor direct inhibitors of AChE, once in the body they will readily interact with cytochrome P450 monooxygenease isoforms to produce oxon metabolites (Fig. 1) (Hodgson and Rose, 2007). These metabolic oxons as well as natural OP phosphotriesters will strongly associate with cholinesterase enzymes inhibiting their function. As active AChE levels fall, the neurotransmitter acetylcholine pools at muscarinic receptors in the central nervous system and at critical nicotinic receptors in the central nervous system, autonomic ganglia, and neuromuscular junctions that regulate proper muscle contraction. Unregulated stimulation of these receptors then results in a state known as cholinergic syndrome. Cholinergic syndrome is characterized by muscarinic symptoms medical professionals refer to as SLUDGEM, which stands for stimulation of salivation, lacrimation, urination, defecation, gastrointestinal distress, emesis (vomiting), and miosis, which is defined as the constriction of the pupil of the eye. In acute cases, AChE depletion at nicotinic receptors causes extended periods of neuromuscular depolarization characterized by uncontrollable muscle twitches or spasms that can lead to tachycardia, muscle weakness, or even respiratory muscle dysfunction or paralysis resulting in the death of the victim (Jokanović and Kosanović, 2010). Exposure to these neurotoxic organophosphorus (OP) insecticides is estimated to poison millions of people annually with potentially hundreds of thousands of those cases resulting in fatalities (Aardema et al., 2008; Gunnell et al., 2007a). Furthermore, purposeful exposure to these compounds has been estimated to account for approximately 30% of all suicides worldwide based on data collected in 2007 (Gunnell et al., 2007a).

Governmental strategies to combat the prevalence of OP poisoning has centered on “means restriction”, the act of governmental regulations placed on the acquisition and allowed uses of certain OP insecticides, as well as the proscribed substitution of the most harmful compounds with less toxic alternatives. In the United States OP compounds have been principally confined to agricultural sectors. Chlorpyrifos remains an extensive OP insecticide, but has been reduced in overall usage by approximately 50% since 2000 with little evidence suggesting the presence of further environmental contamination (Giesy and Solomon, 2014). Across the world stricter regulations have also significantly reduced both the number and percentage of OP compounds in use overall limiting unintentional contamination and reducing suicide rates. However, in Asiatic and Western Pacific countries, exposure and suicidal ingestion remain a persistent problem in countries that are heavily reliant on agriculture and therefore provide greater access to pesticides including OPs. In

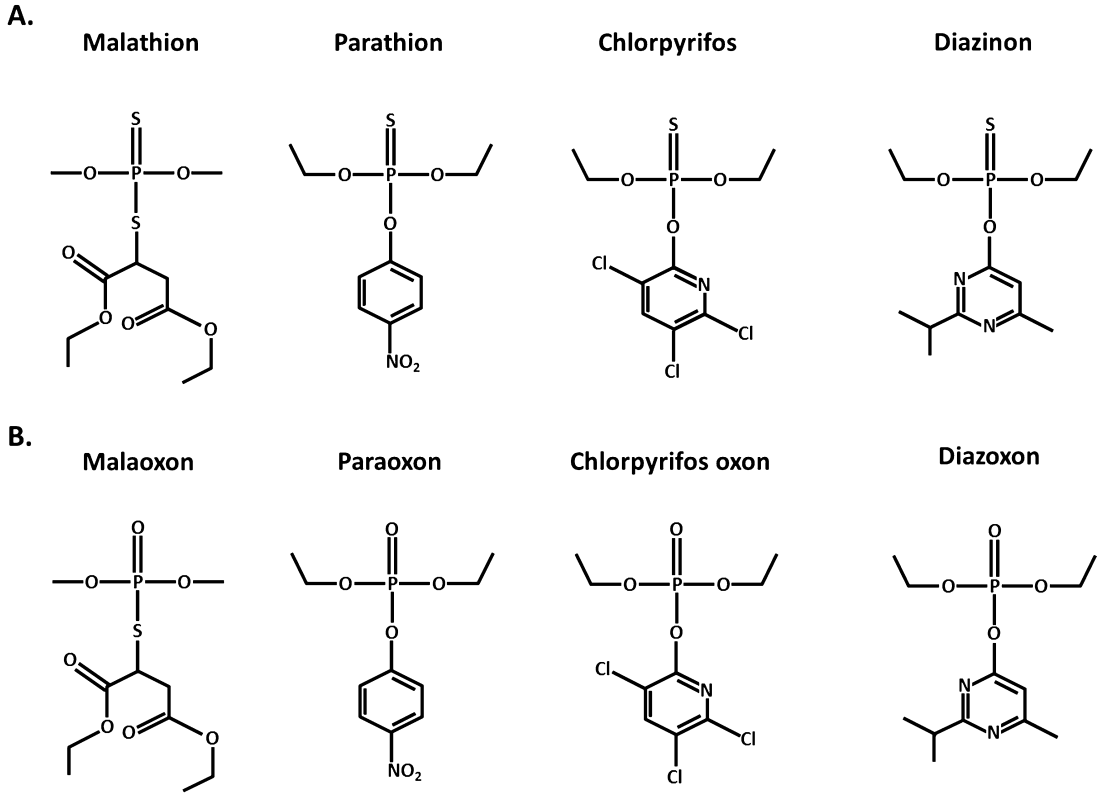

Fig. 1. Structures of the OP insecticides and their metabolic oxons discussed in this review.
(A) Malathion, parathion, chlorpyrifos and diazinon. (B) Malaoxon, paraoxon, chlorpyrifos oxon and diazoxon.