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Lessons to be learnt from organophosphorus pesticide poisoning for the treatment of nerve agent poisoning

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Abstract

The increasing threat of nerve agent use for terrorist purposes against civilian and military population calls for effective therapeutic preparedness. At present, administration of atropine and an oxime are recommended, although effectiveness of this treatment is not proved in clinical trials. Here, monitoring of intoxications with organophosphorus (OP) pesticides may be of help, as their actions are closely related to those of nerve agents and intoxication and therapy follow the same principles. To this end, the clinical course of poisoning and the effectiveness of antidotal therapy were investigated in patients requiring artificial ventilation being treated with atropine and obidoxime. However, poisoning with OP pesticides shows extremely heterogeneous pictures of cholinergic crisis frequently associated with clinical complications. To achieve valuable information for the therapy of nerve agent poisoning, cases resembling situations in nerve agent poisoning had to be extracted: (a) intoxication with OPs forming reactivatable OP–AChE-complexes with short persistence of the OP in the body resembling inhalational sarin intoxication; (b) intoxication with OPs resulting rapidly in an aged OP–AChE-complex resembling inhalational soman intoxication; (c) intoxications with OPs forming a reactivatable AChE–OP complex with prolonged persistence of the OP in the body resembling percutaneous VX intoxication. From these cases it was concluded that sufficient reactivation of nerve agent inhibited non-aged AChE should be possible, if the poison load was not too high and the effective oximes were administered early and with an appropriate duration. When RBC–AChE activity was higher than some 30%, neuromuscular transmission was relatively normal. Relatively low atropine doses (several milligrams) should be sufficient to cope with muscarinic symptoms during oxime therapy.

Keywords: Organophosphorus compounds; Nerve agents; Oximes; Neuromuscular transmission; Therapy; Human

1. Introduction

The increasing threat of nerve agent use for terrorist purposes against both, civilian and military population calls for effective therapeutic preparedness. Since human poisoning with nerve agents rarely occurs and intentional administration of nerve agents to humans for study purposes is unethical, research is mainly reliant on *in vitro* and animal experiments. Based on the assumption that inhibition of acetylcholinesterase (AChE, EC 3.1.1.7) is the most important toxic mechanism, efforts are directed either to block or modulate receptors of neurotransmitter stimulation (atropine, benzodi-

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azepines) or to reverse AChE inhibition (oximes). The latter option was the objective of experimental research over the last years, leading to a better understanding of the individual reactions occurring during inhibition and in the post-inhibition phase (aging, spontaneous reactivation, oxime-induced reactivation, formation of phosphoryloximes and their interactions) (for review see Eyer, 2003). It was also revealed that the kinetics of these reactions show remarkable species differences (Worek et al., 2002). Accordingly, extrapolation from animal data to humans has to be judged with great reservation.

In principal, results derived from experiments with human material, e.g. red blood cell (RBC)–AChE (Worek et al., 1996, 1998a, 1998b, 1999a, 2002, 2004a, 2004b) or human muscle strips (Wolthuis et al., 1981), may be useful, although they cannot substitute clinical evidence for therapeutic effectiveness. Here, monitoring of intoxications with organophosphorus (OP) pesticides may be of help, as their actions are closely related to those of nerve agents, and intoxication and therapy follow the same principles. Moreover, data on the above mentioned reaction kinetics are available for the most important OP pesticides (Worek et al., 1996, 1997, 1999a) and can be used for calculation of effective oxime dosage (Eyer, 1996; Thiermann et al., 1997, 1999) as well as for the judgment of effective oxime-induced reactivation in OP poisoned patients (Eyer et al., 2003; Eyer, 2003). However, poisoning with OP pesticides may show extremely heterogeneous pictures of cholinergic crisis frequently associated with clinical complications. This confusing situation has lead to uncertainty in judgment of antidotal strategies (e.g. appropriateness of oximes, dose of atropine, use of benzodiazepines), so that a general treatment regimen is still a matter of debate (for review see Eddleston et al., 2004; Eyer, 2003; Marrs, 2003). However, methods are proposed, to closely analyse clinical effectiveness of antidotes in single cases (Thiermann et al., 1997, 1999; Worek et al., 1999b). Using such methods, it should be able to extract valuable information from single cases that reflect the course of nerve agent poisoning. Accordingly, it appears rational to look for: (a) intoxications with OPs with a short half life in the body, resembling inhalational sarin intoxication; (b) intoxication with OPs resulting in a completely aged OP–AChE-complex resembling inhalational soman intoxication; (c) intoxications with persisting OPs resembling percutaneous VX intoxication. From such cases, it should be possible to draw conclusions relevant for the therapy of nerve agent poisoning.

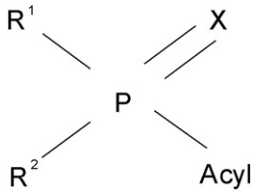

Fig. 1. Structure of phosphororganic compounds. Biologically active compounds show the following features: X = oxygen or sulfur double bonded to phosphorus; R1 and R2: alkyl, alkoxy, or amino-groups; Acyl: mercaptane, enole, phenole, fluoride, cyanide, rhodanide.

2. Similarities and differences between OP pesticides and nerve agents

2.1. General considerations

OPs are based on a common structure that was proposed by Schrader in 1937 (Schrader, 1963) (Fig. 1).

Compounds with double bonded sulphur, called phosphorothioates or phosphonothioates (Chambers et al., 2001), are generally less toxic than phosphates or phosphonates. However, thioates may be metabolized to phosphates or phosphonates, thereby resulting in highly toxic compounds (e.g. parathion–paraoxon, malathion–malaoxon) (Ballantyne and Marrs, 1992; Eyer et al., 2003). Esters of phosphoric and phosphonic acids represent the most important compounds among OP pesticides and nerve agents (Table 1), with most of the latter belonging to the phosphonates (exception: tabun). The majority of the world wide used OP pesticides belong either to the dimethylphosphoryl- or diethylphosphoryl-type OP, named according to the phosphoryl moiety at the AChE active site after inhibition. The respective diethylphosphoryl-AChE or dimethylphosphoryl-AChE differ substantially in their reaction properties, e.g. reactivation or aging. These types of OPs bear no chiral centre and form the same species of diethylphosphoryl- or dimethylphosphoryl-AChE, thus simplifying therapeutic considerations. In contrast, nerve agents (derivatives of the phosphonic acid) are chiral compounds with an optically active centre at the phosphorus (soman has an additional chiral centre at the pinacolyl moiety). A very prominent representative of this group is soman with its four isomers of which the P(−) isomers are about 4 orders of magnitude more toxic than the P(+) isomers (Benschop et al., 1995). Table 1 shows the formula, inhibition constants, half time of aging and LD_{50} (rat) of the compounds relevant in this manuscript.