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The value of novel oximes for treatment of poisoning by organophosphorus compounds

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ABSTRACT

Poisoning by organophosphorus compounds (OP) still is a major therapeutic problem. Intentional OP pesticide poisoning results in up to 300.000 deaths each year and highly toxic OP nerve agents pose a permanent threat for the civilian population and military forces. The therapeutic value of clinically used oximes, pralidoxime, obidoxime and TMB-4, in human OP pesticide poisoning is under debate. Moreover, these oximes lack efficacy in poisoning by various nerve agents. An innumerable number of novel oximes have been synthesized in the past five decades to provide more effective oximes and compounds with improved blood–brain-barrier penetration. Novel compounds were tested with largely different experimental protocols in vitro and in animals in vivo. The lack of comparable experimental conditions and the absence of human in vivo studies hamper a well-founded evaluation of the available data. At present, it appears that only a small number of (bispyridinium) oximes show superior potency and efficacy against individual OP. However, until now, no oxime with sufficient broad-spectrum activity against structurally different OP pesticides and nerve agents is available. An interim solution may be the combination of two oximes with overlapping reactivation spectrum. In conclusion, the unsatisfying situation calls for studies with standardized and comparable experimental conditions in order to allow a sound assessment of available and novel oximes.

Contents

1. Introduction

Poisoning by organophosphorus compounds (OP; Fig. 1) still is a major therapeutical problem. The worldwide use of OP pesticides for pest control causes a huge number of poisonings, primarily in developing countries (Jeyaratnam, 1990). Epidemiological studies estimate that intentional OP pesticide poisoning results in up to 300.000 deaths each year (Bertolote et al., 2006; Gunnell et al., 2007). In addition, highly toxic OP were developed as chemical warfare nerve agents (Marrs, 2007) and were used during military conflicts and terrorist attacks (MacIlwain, 1993; Morita et al., 1995; Nozaki et al., 1995; Okumura et al., 2007). Although being banned by the international chemical weapons convention large nerve agent stockpiles are still available and the synthesis routes of different nerve agents were published in the open literature (Holmstedt, 1951; Tammelin, 1957a, 1957b; Bryant et al., 1960; Black & Harrison, 1996).

The huge number of poisonings and the high acute toxicity of OP nerve agents and different OP pesticides require effective medical treatment (Johnson et al., 2000; Kales & Christiani, 2004; Eyer et al.,

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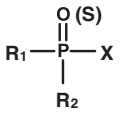

OP	R_1	R_2	X
Paraoxon-ethyl [311-45-5]	O-ethyl	O-ethyl	p-nitrophenyl
Paraoxon-methyl [950-35-6]	O-methyl	O-methyl	p-nitrophenyl
Malaoxon [1634-78-2]	O-methyl	O-methyl	S-(1,2-diethoxycarbonyl)ethyl
Omethoate [1113-02-6]	O-methyl	O-methyl	S-(2-(methylamino)-2-oxoethyl)
Tabun (GA) [77-81-6]	O-ethyl	Dimethylamido	CN
Sarin (GB) [107-44-8]	Methyl	O-isopropyl	F
Soman (GD) [96-94-0]	Methyl	O-pinacolyl	F
Cyclosarin (GF) [329-99-7]	Methyl	O-cyclohexyl	F
VX [50782-69-9]	Methyl	O-ethyl	S-[2-(diisopropylamino)ethyl]
VR [159939-87-4]	Methyl	O-isobutyl	S-[2-(diethylamino)ethyl]
CVX [468712-10-9]	Methyl	O-n-butyl	S-[2-(diethylamino)ethyl]

Fig. 1. Chemical structure of selected OP pesticides and nerve agents.

2007). Presently, standard antidote treatment of OP poisoning comprises a reversible muscarine receptor antagonist, primarily atropine, and a reactivator (oxime) of OP-inhibited acetylcholinesterase (AChE), e.g. obidoxime or pralidoxime (Fig. 2; Eyer, 2003; Eddleston et al., 2004; Eyer & Worek, 2007; Thiermann et al., 2011). However, various clinical studies doubted the therapeutic value of presently available oximes in human OP pesticide poisoning (De Silva et al., 1992; Peter et al., 2006; Eddleston et al., 2009a, 2009b). Moreover, numerous in vitro and in vivo studies demonstrated a limited efficacy of oximes against different OP nerve agents, e.g. soman, tabun and

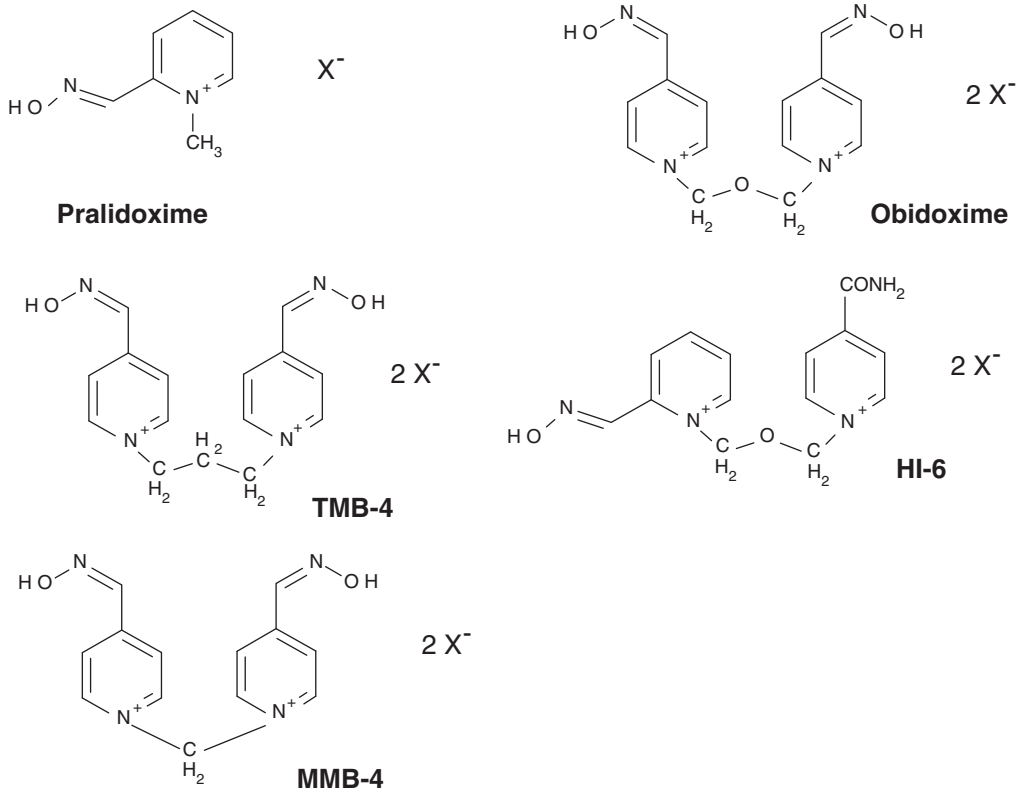

Fig. 2. Chemical structure of oximes of interest.