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Mini review

Non-enzymatic pretreatment of nerve agent (soman) poisoning: A brief state-of-the-art review

Herman P.M. van Helden[a,*], Marloes J.A. Joosen[a], Ingrid H.C. Philippens[b]

[a] TNO Earth, Environmental and Life Sciences, CBRN Protection, P.O. Box 45, 2280 AA Rijswijk, Netherlands
[b] Biomedical Primate Research Centre, P.O. Box 3306, 2280 GH Rijswijk, Netherlands

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ABSTRACT

The rapid onset of toxic signs following nerve agent intoxication and the apprehension that current therapy (atropine, oxime, diazepam) may not prevent brain damage, requires supportive pretreatment. Since the current pretreatment drug pyridostigmine fails in protecting brain-AChE, more effective pretreatment is necessary.

A main focus of present-day pretreatment research is on bioscavengers, another is on centrally active reversible AChE-inhibitors combined with drugs showing anti-cholinergic, anti-glutamatergic, neuroprotective and non-sedating GABA-ergic activity. Strategies aimed at improving efficacy of pharmacological pretreatment will briefly be discussed. Galantamine, given as a pretreatment or stand-alone therapy, emerged as one of the best medical countermeasures against nerve agent poisoning in guinea pigs. Other preclinical studies demonstrated effective pretreatment consisting of physostigmine combined with procyclidine, scopolamine or bupropion (all single injections), against nerve agent poisoning in guinea pigs. A long sign-free pretreatment with physostigmine (Alzet pump), combined with single injection of procyclidine just before soman poisoning, enhanced the efficacy of a post-poisoning therapy consisting of 3 autoinjector equivalents of HI-6, atropine and diazepam, considerably.

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1. Introduction

The threat of nerve agent use against military personnel has prompted defence organizations to continue the search for better pretreatment and post-poisoning treatment strategies. Nerve agent intoxication is characterized by a rapid progression of toxic signs as a result of inhibition of the enzyme acetylcholinesterase (AChE), resulting in life-threatening cholinergic overstimulations and brain damage.

The current antidotal therapy for nerve agent poisoning is pretreatment before poisoning (e.g., pyridostigmine bromide), along with post-exposure treatment consisting of an anticholinergic (mostly atropine sulphate) to counteract the cholinergic overstimulation, an oxime to reactivate irreversibly inhibited AChE, and an anticonvulsant (benzodiazepine) to halt seizures in order to prevent neuronal damage.

Although the current policy is to develop a stand-alone post-poisoning treatment, pretreatment will possibly be administered, as it significantly enhances the efficacy of the current post-poisoning treatment. Another important reason for having

* Corresponding author. Tel.: +31 888661167; fax: +31 888666938.
E-mail address: herman.vanhelden@tno.nl (H.P.M. van Helden).

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Table 1
Pretreatment drugs of current interest against nerve agent poisoning.

Group	Examples	Additional properties/remarks
Centrally active reversible AChE-inhibitors, in use to treat Alzheimer's disease	Physostigmine	Non-selective ChE-inhibitor
	Galantamine	Selectively inhibits AChE; nicotinic allosteric potentiating, neuroprotective
	Donepezil	Non-selective ChE-inhibitor
	HuperzineA	Selectively inhibits AChE; affects nicotinic-R and glutamate-R
	Rivastigmine	Non-selective ChE-inhibitor
	Eptastigmine	Derivative of physostigmine, more lipophilic and less toxic than physostigmine
Central anti-cholinergics, in use to treat Parkinson's disease	Procyclidine	Anti-muscarinic, anti-nicotinic, anti-glutamatergic, anti-spasmodic
	Caramiphen	Anti-tussive, anti-muscarinic, anti-convulsant, anti-glutamatergic, anti-spasmodic
	Bupropion	Noradrenaline-dopamine reuptake inhibitor, *anti-nicotinic*, anti-depressant
	Scopolamine	Anti-muscarinic
Benzodiazepines	Bretazenil	Partial GABA-R agonist; less incapacitating than diazepam (full agonist), anxiolytic
	Imidazenil	Non-sedating anticonvulsant, more potent than diazepam against EEG-seizures and brain damage

pretreatment available is the rapid onset of toxic signs following exposure to lethal levels of a nerve agent and the notion that current treatment may not sufficiently prevent severe brain damage, supposing that victims' lives can be saved if the antidotes are administered fast enough. A chemical attack provides a very stressful situation, in which many victims should be treated. Timely administration of antidotes will then become a considerable problem. This holds in particular for soman poisoning because of its rapid entrance into the brain, and fast "aging" (within minutes) of soman-inhibited AChE, excluding further enzyme reactivation by an oxime. In addition, the action of nerve agents is target-specific, e.g., directed towards AChE, making the development target-specific drugs or biopharmaceuticals to protect this target against irreversible inhibition beforehand attractive.

As long as an adequate stand-alone post-poisoning treatment is not available, it is reassuring and necessary to have an adequate pretreatment in place. Requirements for an adequate pretreatment might be formulated as follows: (1) besides easy administration it should be efficient against a wide range of nerve agents, (2) it should be safe, i.e., having minimal adverse effects, neither at short-term nor at long-term, because any resulting physical or mental performance decrements on the battlefield are unacceptable, (3) its treatment protocol should be convenient, i.e., showing a pharmacokinetic profile that provides sufficient protective blood levels of the drug for a sufficient long period of time, and (4) it should support post-poisoning treatment efficacy.

In this overview current and new strategies aimed at improving efficacy of pharmacological pretreatment, consisting of protecting synaptic AChE from inhibition by nerve agent, and its enhancing effect on post-poisoning treatment efficacy will be discussed. Excluded from discussion is the development of stoichiometric or catalytic bioscavengers, which will be discussed elsewhere.

2. Current state

The current pretreatment regimen consists of pyridostigmine bromide (PB), a quaternary amine carbamate, which preserves a residual pool of AChE in blood and organs, but is expected not to protect the brains. However, in preclinical studies (mice), Friedman et al. (1996) showed that PB administered under stress may reach the brain and affect centrally controlled functions. In contrast, in a clinical study, Roy et al. (2006) showed that combined use of PB, diethyltoluamide, and permethrin, at rest or under stress, was well tolerated and without evidence of short-term physical or neurocognitive impairment. Since the outcome of clinical studies is considered more eloquent than that of preclinical ones, the above statement that PB does in general not penetrate the brains, should be considered correct. Besides, PB has shown to have several adverse effects. Clinical studies consistently indicate two wartime exposures as significant risk factors for Gulf War Illness: use of PB, and extensive exposure to pesticides during deployment (2008 report of the Research Advisory Committee on Gulf War Veterans' Illnesses: www.va.gov/RAC-GWVI). Dose–response effects have been identified indicating that veterans who took PB for longer periods of time have higher illness rates than veterans who took less PB (Golomb, 2008). One of the main conclusions of the Committee was that battlefield stress did not contribute to the cause of the Gulf War Illnesses.

Pyridostigmine in combination with anticholinergics (PANPAL) was introduced in the Czech Army (Bajgar, 2004). The presence of two central anticholinergics (benactyzine and trihexyphenidyl) suppressed some of the pyridostigmine-induced side effects and therefore allowed an increase in the pyridostigmine dose, leading to an increased prophylactic activity. No adverse effects were observed in volunteers following usage of PANPAL (Bajgar, 2004). However, there is fear that administration of two muscarinic blockers to healthy subjects, especially when wearing protective clothes against chemical agents, may lead to elevated heat stress due to inhibition of sweating (Kassa and Vachek, 2002), and cognitive side effects (Myhrer et al., 2008). Moreover, when it comes to nerve agent poisoning, pyridostigmine is unable to protect central AChE and to prevent brain injury and post-poisoning incapacitation. Hence, improvement of pretreatment is highly required.

3. Drugs of current interest for pretreatment against nerve agent poisoning

A number of centrally active AChE-inhibitors, mainly in use to treat *Alzheimer*'s disease, as well as a number of drugs to treat *Parkinson*'s disease and showing multiple pharmacological properties, are of interest to pretreat nerve agent intoxication (Table 1). Besides, some benzodiazepine derivatives showing a more favorably pharmacological profile than diazepam, will be discussed.

3.1. Centrally active reversible AChE inhibitors

Galantamine, a centrally acting reversible AChE inhibitor approved for treatment of mild-to-moderate Alzheimer's disease (Corey-Bloom, 2003), has been shown to counteract the acute toxicity and lethality of soman and sarin in guinea pigs with no apparent central or peripheral toxicity, provided that the animals were treated with atropine sulphate immediately after poisoning (Albuquerque et al., 2006). A number of unique actions of galantamine are attributed for contribution to its effectiveness and safety as a medical countermeasure against organophosphate (OP) poisoning. First, its selective inhibition of AChE (Thomsen and Kewitz, 1990), in contrast to pyridostigmine and physostigmine that also inhibit BuChE, should help to preserve the scavenger