Neuroscience and Biobehavioral Reviews 71 (2016) 657–670

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Pretreatment and prophylaxis against nerve agent poisoning: Are undesirable behavioral side effects unavoidable?

Trond Myhrer, Pål Aas*

Norwegian Defence Research Establishment (FFI), Protection and Societal Security Division, Kjeller, Norway

ARTICLE INFO

Article history:
Received 29 March 2016
Received in revised form
28 September 2016
Accepted 19 October 2016
Available online 20 October 2016

Keywords:
Nerve agents
Pharmacological protection
Enzymatic protection
Behavioral side effects

ABSTRACT

The threat of chemical warfare agents like nerve agents requires life saving measures of medical pretreatment combined with treatment after exposure. Pretreatment (pyridostigmine) may cause some side effects in a small number of individuals. A comprehensive research on animals has been performed to clarify effects on behavior. The results from these studies are far from unambiguous, since pyridostigmine may produce adverse effects on behavior in animals in relatively high doses, but not in a consistent way. Other animal studies have examined the potential of drugs like physostigmine, galantamine, benactyzine, trihexyphenidyl, and procyclidine, but they all produce marked behavioral impairment at doses sufficient to contribute to protection against a convulsant dose of soman. Attempts have also been made to develop a combination of drugs capable of assuring full protection (prophylaxis) against nerve agents. However, common to all combinations is that they at anticonvulsant doses cause behavioral deficits. Therefore, the use of limited pretreatment doses may be performed without marked side effects followed by post-exposure therapy with a combination of drugs.

Contents

Abbreviations: ACh, acetylcholine; AChE, acetylcholinesterase; BBB, blood-brain barrier; BuChE, butyrylcholinesterase; CNS, central nervous system; DCG IV, 2S,2'R,3'R-2-(2',3'-dicarboxycyclopropyl)glycine; FDA, Food & Drug Administration (USA); GABA, γ-amino butyric acid; GMP, good manufacturing practice; HA-966, 3-amino-1-hydroxy-2-pyrrolidinone; HI-6, 1-[([4-aminocarbonyl)pyridino](methoxy)methyl]-2-[(hydroxyimino)methyl]pyridinium; HuBuChE, Human butyrylcholinesterase; HuPON1, human paraoxonase1; llG1, chimeric PON1 mutant; MPEP, 2-methyl-6-(phenylethynyl)pyridine; NMDA, *N*-methyl-D-aspartic acid; 6-OxP-CD, β-cyclodextrin with an oxime derived substituent in position 6; PANPAL, prophylactic antidote against nerve paralytic agent; 2-PAM, pralidoxime-2-chloride; PON1, paraoxonase1; P2S, pralidoxime mesylas; rePON1, recombinant PON1 mutant; SD, Sprague Dawley; TRANSANT, transdermal prophylactic antidote against nerve agents; WKY, Wistar-Kyoto; VX, S-2-(diisopropylamino)ethyl *O*-etyl metylphosphonothioate.

* Corresponding author at: Norwegian Defence Research Establishment (FFI), Protection and Societal Security Division, P O Box 25, NO-2027 Kjeller, Norway.
E-mail address: pal.aas@ffi.no (P. Aas).

http://dx.doi.org/10.1016/j.neubiorev.2016.10.017
0149-7634/

1. Introduction

Organophosphates called nerve agents are considered to be the most toxic among all chemical weapons. Nerve agents can create a substantial threat on the battlefield, and in the hands of terrorist groups they will represent a threat to civilians. The nerve agents were originally synthesized during the 1930s in Germany in order to obtain more effective pesticides based on organophosphorus compounds. Some of these agents, however, turned out to be too toxic for their original purpose. The organophosphorus nerve agents are highly potent inhibitors of the enzyme acetylcholinesterase (AChE) that hydrolyzes acetylcholine (ACh). Accumulation of ACh in the synaptic cleft results in over-stimulation of muscarinic and nicotinic receptors. This increased cholinergic activity can affect all organ systems. The toxic signs include miosis, hypersalivation, respiratory distress, tremor, seizures/convulsions, coma, and death (Taylor, 2001).

Acute exposure to nerve agent, particularly by inhalation, requires immediate medical treatment. Compared with other agents, the time window of opportunity for therapeutic intervention is very limited following nerve agent intoxication, in particular after exposure to soman vapor. In the case of military deployment, medical pretreatment represents an option to be considered, but might be of minor relevance for civilian populations. Pretreatment drugs are administered prior to nerve agent and are part of a continuum requiring post-exposure treatment (partial protection). The term prophylaxis denotes drugs applied before exposure to intoxication, but are not supposed to be followed by adjuvant therapy (full protection). The purpose of a pretreatment is to provide a more efficacious impact of post-poisoning therapy. Prophylactic treatment is intended to ensure anticonvulsant and life preserving effects when/if no post-exposure therapy is available. It may, however, occur unsafe to give medical pretreatment to healthy persons. It is therefore crucial that the countermeasures administered do not by themselves impair normal functions.

During the cold war and prior to entry into force of The Chemical Weapons Convention in 1997, use of large quantities of chemical warfare agents, in particular soman with its brief onset to the aging process, was a real threat (Aas, 2003). Pretreatment against nerve agents was introduced in most armies to be combined with a post-poisoning treatment to increase survival. Since the threat of large scale use of chemical warfare weapons has decreased, but potential for use against civilians has increased, the prevalent opinion has been to reduce reliance on pretreatment against nerve agent. Pretreatment against nerve agents can be obtained by the use of a reversible AChE inhibitor (pyridostigmine) shielding a portion of AChE from irreversible inhibition by nerve agents prior to nerve agent exposure. Furthermore, reactivation of any unaged AChE by an oxime is regarded as important immediate treatment after nerve agent exposure. A number of armed forces have based their therapy against nerve agent intoxication on an oxime (obidoxime, pralidoxime-2-chloride (2-PAM), 1-[([4-aminocarbonyl)pyridino]methoxy)methyl]-2-[((hydroxyimino)methyl]pyridinium (HI-6)), an anticholinergic (atropine), and a benzodiazepine (diazepam, avizafone, midazolam) combined with carbamate (pyridostigmine) pretreatment (Aas, 2003). Atropine is, however, considered as the most important component of the therapy (Newmark, 2004). Such treatment regimens can reduce immediate lethality, but they do not attenuate the occurrence of nerve agent-induced seizure activity and concomitant convulsions if treatment is delayed (McDonough and Shih, 1997). Such seizures rapidly progress to status epilepticus, a condition that is strongly associated with brain damage and mortality in experimental animals (Shih et al., 2003).

Pretreatment with pyridostigmine was used on a large scale during the “Operation Desert Storm” in Kuwait in 1991. Neurocognitive deficits, neuroendocrine alterations as well as anxiety and mood alterations in Gulf War veterans have been attributed to the use of pyridostigmine and pesticides during deployment (Research Advisory Committee on Gulf War Veterans’ Illnesses, 2008). However, Institute of Medicine of the National Academies, 2010 is of a different opinion. In its report of 2010 (Gulf War and Health), the Institute disagrees with the Research Advisory Committee’s conclusion and maintains that current available evidence is not sufficient to establish a causative relationship between chronic multi symptom illness and any specific drug, toxin, plume, or other agent, either alone or in combination. The US Food and Drug Administration (FDA) has summarized the existing knowledge and concluded that despite a long history of pyridostigmine being used in the treatment of myasthenia gravis in humans, no evidence of long-term health effects has emerged to date (FDA, 2009).

The purpose of the present review was to examine whether pretreatment or prophylaxis against nerve agent intoxication can be administered without causing adverse effects on the recipients. This process was performed by reviewing animal studies of pretreatments and prophylaxes against nerve agent and their potential effects on cognitive behavior. A critical evaluation was made of the ability of various behavioral tests to reveal subtle cognitive deficits. The results from relevant studies presented in Sections 2–6 are discussed in view of additional information in Section 7. Comparisons of drug doses for animals and humans are made in the discussion Section 7.

2. Pyridostigmine

Pretreatment with the carbamate pyridostigmine is a well-established method to enhance the efficacy of post-exposure therapy against nerve agent intoxication in the armed forces in a number of nations. A tablet (30 mg) of pyridostigmine bromide is supposed to be taken every 8 h by the service personnel. The rationale behind this use is that carbamate occupies a portion of the available AChE (15–40% of the erythrocyte AChE) and renders it inaccessible to nerve agents in the blood, since nerve agents only bind to unprotected enzyme (Dirnhuber et al., 1979; Leadbeater et al., 1985). The AChE that has been reversibly inhibited by pyridostigmine spontaneously decarbamoylates, and the enzyme is again able to hydrolyze ACh. The quaternary carbamate pyridostigmine does not readily cross the blood-brain barrier (BBB), even at a dose that inhibits blood AChE, pyridostigmine does not substantially change brain AChE activity in rats (Amourette et al., 2009), guinea pigs (Lallement et al., 1998), or mice (Grauer et al., 2000). Hence, pyridostigmine only protects the peripheral nervous system, and alone it does not protect against nerve agent poisoning.

In a number of studies, pyridostigmine has been reported to have no detrimental physiological or psychological effects on military personnel or healthy volunteers when given 30 mg/8-h. Effects of pyridostigmine on aircrew performance has been examined in several studies. Twenty-one C-130 pilots flew 2 familiarization and 4 data flights in simulator. The results show that the aircrews successfully completed their assigned mission without being affected by pyridostigmine (Gawron et al., 1990). In a similar study, 10 pilots performed normally in flight simulator when the whole blood AChE level was reduced by 29% of control (Israeli et al., 1990). Selected visual functions were measured in 4 aviator candidates. Under the influence of pyridostigmine, the subjects‘ visual abilities were not compromised. Only refractive error and pupil diameter were significantly different (Wiley et al., 1992).

Increased arousal and attention have been demonstrated following administration of pyridostigmine in healthy volunteers. Results from recordings of psychomotor performance and visual function show that visual-motor coordination was not impaired for