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Original Research Article

Neuroprotective efficacy of newly developed oximes in comparison with currently available oximes in tabun-poisoned rats

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Abbreviations:
A, atropine
AChE, acetylcholinesterase
BBB, blood–brain barrier
b.w., body weight
CNS, central nervous system
FOB, functional observational battery
HPLC, high pressure liquid chromatography
i.m., intramuscularly
n, number of surviving animals
PC, personal computer
RRF, air righting reflex
RRV, air righting reflex from vertical position
x/M, average or modus value
± s, standard deviation

ABSTRACT

The ability of two newly developed oximes (K361, K378) to reduce tabun-induced acute neurotoxic signs and symptoms was compared with the oxime K203 and trimedoxime using a functional observational battery. The neuroprotective effects of the oximes studied combined with atropine on rats poisoned with tabun at a sublethal dose (310 μg/kg i.m.; 90% of LD_{50} value) were evaluated. Tabun-induced neurotoxicity was monitored by functional observational battery at 2 h following tabun challenge. The results indicate that all tested oximes combined with atropine enable tabun-poisoned rats to survive till the end of experiment. Both newly developed oximes (K361, K378) combined with atropine were able to decrease tabun-induced neurotoxicity in the case of sublethal poisonings although they did not eliminate all tabun-induced acute neurotoxic signs and symptoms. Their ability to decrease tabun-induced acute neurotoxicity was slightly lower than that of trimedoxime and the oxime K203. Therefore, the newly developed oximes are not suitable for the replacement of commonly used oximes (especially trimedoxime and obidoxime) in the treatment of acute tabun poisonings.

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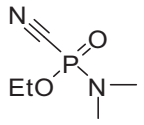
Introduction

Organophosphorus nerve agents are considered to be the most dangerous chemical warfare agents because of high toxicity, rapid onset of clinical signs and symptoms and rapid progression of acute poisoning to the death. Their acute toxic effects are based on the phosphonylation of acetylcholinesterase (AChE; EC 3.1.1.7), leading to the overstimulation of postsynaptic cholinergic receptors due to the accumulation of the neurotransmitter acetylcholine in the synapses of the central and peripheral nervous systems (Bajgar, 2004). A current standard treatment of poisoning with nerve agents usually consists of a combined administration of an anticholinergic drug (preferably atropine) and an oxime (preferably pralidoxime or obidoxime). Generally, anticholinergics are used for relieving muscarinic signs and symptoms whereas oximes are used for reactivation of nerve agent-inhibited AChE (Bajgar, 2004; Colovic et al., 2013).

One of the most resistant nerve agents is tabun (*O*-ethyl-*N*, *N*-dimethyl phosphoramido-cyanidate) (Fig. 1). It differs from other highly toxic organophosphates in its chemical structure and by the fact that commonly used antidotes are not able to sufficiently prevent tabun-induced acute toxic effects. Deleterious effects of tabun are extraordinarily difficult to antagonize due to the changes in hydrogen bonding and conformational changes of AChE-tabun complex in the AChE active site that make the nucleophilic attack of oximes very difficult (Cabal and Bajgar, 1999; Ekström et al., 2006).

In the case of severe intoxication, some nerve agents including tabun can cause centrally mediated seizure activity that can rapidly progress to status epilepticus and contribute to profound brain damage that is associated with long-lasting neurological and psychological injuries (Hoffman et al., 2007; Yamasue et al., 2007). Therefore, the ability of antidotes to counteract acute neurotoxic effects of nerve agents and prevent nerve agent-poisoned organisms from irreversible lesions in the central nervous system (CNS) is very important for the successful antidotal treatment of acute nerve agent poisonings. Generally, the oximes exert more potent effects in the peripheral nervous system compared to CNS due to their low penetration across the blood–brain barrier (BBB). However, the penetration of oximes into CNS and subsequent reactivation of



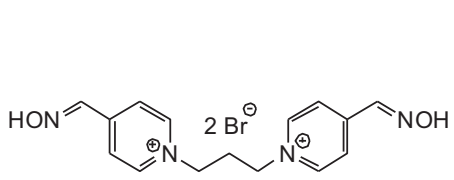
tabun

Fig. 1 – Chemical structure of tabun.

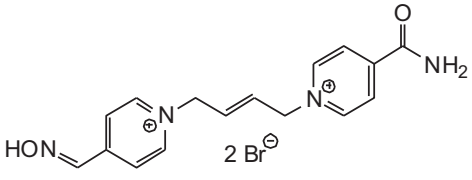
nerve agent-inhibited AChE in the brain was demonstrated in the literature (Lorke et al., 2008). Although the percentage of reactivation of nerve agent-inhibited AChE in the brain is lower compared to the peripheral system, the role of reactivation of nerve agent-inhibited AChE in the brain is important for survival from nerve agent exposure (Bajgar, 2004).

Unfortunately, currently available antidotal treatment consisting of atropine and commonly used reactivator of inhibited AChE (pralidoxime, obidoxime, trimedoxime, HI-6) is not able to sufficiently counteract acute toxic effects of tabun because of very low ability of oximes to reactivate tabun-inhibited AChE (Jokanovic, 2012). Therefore, the replacement of commonly used oximes (pralidoxime, obidoxime, HI-6) with a more effective oxime has been a long-standing goal for the treatment of tabun poisoning. The oxime K203, developed at our Department of Toxicology and Military Pharmacy several years ago, was considered to be promising reactivator of tabun-inhibited AChE. However, the differences between the reactivating and therapeutic efficacy of the oxime K203 and commonly used bispyridinium oximes (obidoxime, trimedoxime) are relatively small (Kassa et al., 2008). Therefore, we are still searching for a more efficacious oxime able to sufficiently reactivate tabun-inhibited AChE. For this purpose, two novel oximes, K361 [4-(1-amino-1-hydroxyiminomethyl)-4′-hydroxyiminomethyl-1,1′-(but-1,4-diyl)-bispyridinium dibromide] and K378 [1-(3-phenylpropyl-4-hydroxyiminomethyl)-pyridinium bromide] (Fig. 2) were synthesized at our Department of Toxicology and Military Pharmacy (Musilek et al., 2008) to improve the efficacy of antidotal treatment of tabun poisonings.

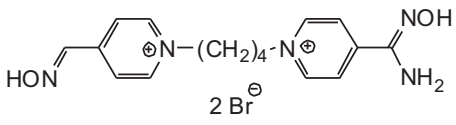
The aim of this study was to evaluate the potential neuroprotective effects of two newly developed oximes (K361, K378) with the oxime K203 and trimedoxime in



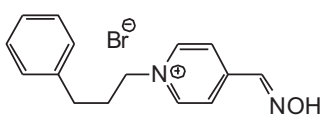
trimedoxime



K203



K361



K378

Fig. 2 – Chemical structure of oximes studied.