ABSTRACT

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Nerve agents belong to the group of OFI that irreversibly binds to acetylcholinesterase (AChE). Neurotransmitter acetylcholine (ACh) cannot be degraded and its increased concentration causes excessive overstimulation of cholinergic receptors, known as acute cholinergic crisis (Patočka et al., 2004). Reactivators of acetylcholinesterase, also called oximes, are causal antidotes for the treatment of OFI poisonings and therefore nerve agents. Their mechanism of action is to break bond between inhibitor and AChE active site and prevent its subsequent covalent binding (Šepsová, 2010).

In this study pharmacokinetics of five selected reactivators of AChE (oxime HI-6, obidoxime, trimedoxime, oxime K203 and oxime K027) were monitored. Rats were used as a convenient model organism (male, tribe Wistar) for presented in vivo study.

High Performance Liquid Chromatography (HPLC) was selected as the most suitable separation method to studied pharmacokinetics of oximes. In this study it was necessary to determine convenient mobile phase (its composition, pH). As the optimal mobile phase was used mobile phase consisting of 24% acetonitrile and 76% distilled and deionized water, containing 5 mM sodium octansulfonate and 5 mM tetramethylammonium chloride. pH was adjusted to 2.3 by phosphoric acid addition.

Distribution of AChE reactivators was determined in groups (n = 7) of selected animals. The result for the individual determination of concentration in the corresponding time interval was the average value of three measurements. Due to the high rate of AChE inhibition by nerve agents it is clear that the distribution of therapeutics should be really quick. The best results were showed after obidoxime application (maximum concentration 23.60 ± 1.35 μg/ml, reached in the 10th minute), followed by trimedoxime (the maximum concentration of 16.60 ± 2.68 μg/ml in the 20th

minute), oxime HI-6 (maximum concentration of 15.30 ± 0.65 μg/ml in the 40th minute), oxime K027 (maximum concentration of 17.60 ± 0.62 μg/ml in the 40th minute) and lastly oxime K203 (maximum concentration of 16.60 ± 2.00 μg/ml in the 60th minute). Differences in pharmacokinetics profile of tested oxime should be explained by changes in their structures. These differences can help us to understand possible relationship between oxime structure and its therapeutic efficacy.