MMSL
Military Medical
Science Letters
Since 1925

Mil. Med. Sci. Lett. (Voj. Zdrav. Listy) 2018, 87(supplementum 1)
ISSN 2571-113X (Online)

MEETING ABSTRACTS

IONIZABLE, ZWITTERIONIC OXIMES AS COUNTERMEASURES TO VOLATILE ORGANOPHOSPHATE (OP) EXPOSURE

Palmer Taylor [1], William C. Hou [1], Jeremiah Momper [1], Yan-Jye Shyong [1], Zoran Radic [1], John McDonough [2], Zrinka Kovarik [3], Yvonne Rosenberg [4], K. Barry Sharpless [5]

[1] University of California, San Diego; La Jolla, CA 92093
[2] US Army Med. Research, Inst. Chem. Def., Edgewood, MD
[3] Institute for Medical Research & Occupational Health, Zagreb, Croatia
[4] PlantVax, Inc. Rockville, MD
[5] The Scripps Research Institute, San Diego, CA

Small ionizable, zwitterionic oximes of limited toxicity show successful outcomes in non-human primates upon intramuscular post-treatment of exposures to OP's, that enter via the respiratory tract. Along with their inherent limitations, we consider the bases for success in post-exposure treatment of OP toxicity and reversal of OP-induced sequelae of symptoms[1]. (1) High vapor pressure OPs carry the largest acute exposure risk in mass terrorism. Toxic OPs released from explosive devices or into controlled ventilation environments are governed by partial pressure and Fick's Second Law of Diffusion (inverse square of the distance); (2) Low molecular weight, zwitterionic oximes confer optimal nucleophile orientation and activity within the confines of the OP-impacted, active center gorge of human acetylcholinesterase (AChE). (3) We emphasize features of ionizable neutral oximes of low toxicity that allow facile passage of membranes to peripheral and central AChE targets and optimal attack angles in the AChE active center. Hence, for volatile OP's, antidotes must rapidly enter the circulation, post-exposure, to chase the offending OP. Following entry, antidotes should then hastily equilibrate between tissue compartments and cross the blood-brain barrier. Accordingly, we examine the ionization states of zwitterionic oximes and other cationic and anionic (F-) nucleophiles in relation to their kinetic parameters of reactivation[2]. Toxicities, both realized and potential, of nucleophilic antidotes in different ionization states, and pharmacokinetics in mice and macaques, under control and exposure conditions, emerge as critical factors for determining in vivo antidote efficacy. Data will be presented on multiple OP's and their enzyme conjugates[1-3], comparator oximes and in three animal species/strains.

Keywords: zwitterionic oximes; reactivation; organophosphate conjugates; CNS permeability; antidotes

Acknowledgement

Collaborators at TSRI, USAMR-ICD, IMROH, & PlantVax are gratefully acknowledged.

References

1. Rosenberg *et al, Chem-biol. Interact*. (2017), 274, 50-57
2. Hou *et al*., in preparation
3. 3Sit, R. *et al*., submitted (2018); Kalisiak, J. *et al*, submitted (2018).