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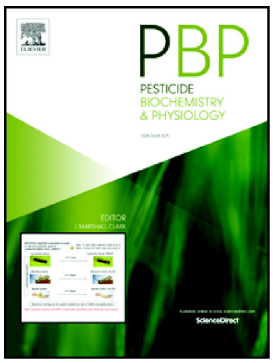

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Robert A. Moyer, Kevin G. McGarry, Michael C. Babin, Gennady E. Platoff, David A. Jett, David T. Yeung

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Kinetic Analysis of Oxime-Assisted Reactivation of Human, Guinea Pig, and Rat Acetylcholinesterase Inhibited by the Organophosphorus Pesticide Metabolite Phorate Oxon (PHO)

Moyer, Robert A.[1], McGarry, Kevin G., Jr[1], Babin, Michael C.[1], Platoff, Gennady E., Jr[2], Jett, David A.[3], Yeung, David T.[3]
[1]Battelle, Columbus, OH
[2]National Institutes of Health/National Institute of Allergy and Infectious Diseases, Rockville, MD
[3]National Institutes of Health/National Institute of Neurological Disorders and Stroke, Rockville, MD

Corresponding Author:
Robert A. Moyer
505 King Avenue, JM-7
Columbus, OH 43201
614-424-3362
moyerr@battelle.org

Abstract:
Phorate is a highly toxic agricultural pesticide currently in use throughout the world. Like many other organophosphorus (OP) pesticides, the primary mechanism of the acute toxicity of phorate is acetylcholinesterase (AChE) inhibition mediated by its bioactivated oxon metabolite. AChE reactivation is a critical aspect in the treatment of acute OP intoxication. Unfortunately, very little is currently known about the capacity of various oximes to rescue phorate oxon (PHO)-inhibited AChE. To help fill this knowledge gap, we evaluated the kinetics of inhibition, reactivation, and aging of PHO using recombinant AChE derived from three species (rat, guinea pig and human) commonly utilized to study the toxicity of OP compounds and five oximes that are currently fielded (or have been deemed extremely promising) as anti-OP therapies by various nations around the globe: 2-PAM Cl, HI-6 DMS, obidoxime Cl_2, MMB4-DMS, and HLö7 DMS. The inhibition rate constants (k_i) for PHO were calculated for AChE derived from each species and found to be low (i.e., 4.8×10^3 to 1.4×10^4 M^{-1} min^{-1}) compared to many other OPs. Obidoxime Cl_2 was the most effective reactivator tested. The aging rate of PHO-inhibited AChE was very slow (limited aging was observed out to 48 hours) for all three species. Conclusions: (1) Obidoxime Cl_2 was the most effective reactivator tested. (2) 2-PAM Cl, showed limited effectiveness in reactivating PHO-inhibited AChE, suggesting that it may have limited usefulness in the clinical management of acute PHO intoxication. (3) The therapeutic window for oxime administration following exposure to phorate (or PHO) is not limited by aging.

Keywords:
phorate; acetylcholinesterase; kinetics; oxime

Abbreviations:
AChE: acetylcholinesterase
ATC: acetylthiocholine
CAS: Chemical Abstracts Service
CWNA: chemical warfare nerve agent
DTNB: 5,5'-dithio-bis-[2-nitrobenzoic acid]
OP: organophosphorus
PHO: phorate oxon