Pharmacokinetic Models of Organophosphorus Compound Poisoning: A Literature Review

Dr. Amy H. Lin Erickson
Department of Mathematical Sciences
United States Military Academy
West Point, New York 10996

Sponsors:
Dr. Raju Namburu
Computational and Information Sciences Directorate
U.S. Army Research Laboratory
Aberdeen Proving Ground, Maryland 21005

Dr. David Lenz
U.S. Army Medical Research Institute of Chemical Defense
U.S. Army Medical Research and Materiel Command
Aberdeen Proving Ground, Maryland 21010

Abstract:

Chemical warfare nerve agents include highly toxic organophosphorus compounds (OPs) that inhibit acetylcholinesterase (AChE). This inhibition induces central respiratory depression and may lead to respiratory failure and death. To better understand the toxicokinetics of poisoning and to determine the efficacy of drugs to either prevent or treat OP attack, several mathematical models have been created. We offer a summary of these differential equation models and their results. Green's 1958 paper [1] assumes that the body acts as one homogeneous, well-mixed compartment. His model accounts for the interaction of OPs with both AChE and a therapeutic agent, and the model also shows what happens if an organism is then treated with a substance that mediates toxicity by reactivating inhibited AChE. Maxwell, Vlahacos, and Lenz's 1988 [2] paper takes a different approach by considering the body as multiple compartments without the effect of treatment. In particular, these authors consider the body to be split into plasma, brain, liver, kidney, muscle, diaphragm, heart, and carcass compartments. Sweeney and Maxwell's 1999 [4] paper returned to the one-compartment model presented by Green. The authors ignore exogenous treatment effects but specifically include hydrolysis of OPs and inhibition of OPs by carboxylesterase, and their results show the amount of toxins needed to protect against a toxic threat given the innate protection afforded by a body's natural carboxylesterase and OP hydrolase stores. Sweeney and Maxwell follow this paper with another in 2003 [3], in which the one-compartment model incorporates the protective action of both stoichiometric and catalytic scavengers. We end this paper with future directions for research, in particular the idea of expanding the multi-compartment model to include protection by scavengers. This model can then be used to design experiments and run simulations with high-performance computing.

KEY WORDS: toxicokinetics, organophosphates, scavengers, differential equations, multi-compartment modeling

CONTACT: Dr. Amy H. Erickson, Department of Mathematical Sciences, USMA, West Point, NY 10996
Tel: (845) 938-6419 email: Amy.H.Erickson@usma.edu

Dr. Raju Namburu, ARL, APG, MD 21005
Tel: (410) 278-0274 email: Raju@arl.army.mil

Dr. David Lenz, USAMRICD, APG, MD 21010
Tel: (410) 436-3525 email: David.Lenz@us.army.mil

References

[1] Green, A.L., 1958. The Kinetic Basis of Organophosphate Poisoning and its Treatment. Biochem Pharmacol 1, 115-128.

[2] Maxwell, D.M., Vlahacos, C.P., Lenz, D.E., 1988. A Pharmacodynamic Model for Soman in the Rat. Toxicol Letters 43, 175-188.

[3] Sweeney, R.E., Maxwell, D.M., 2003. A Theoretical Expression for the Protection Associated with Stoichiometric and Catalytic Scavengers in a Single Compartment Model of Organophosphorus Poisoning. Math Biosci 181, 133-143.

[4] Sweeney, R.E., Maxwell, D.M., 1999. A Theoretical Model of the Competition Between Hydrolase and Carboxylesterase in Protection Against Organophosphorus Poisoning. Math Biosci 160, 175-190.