Pharmacokinetic Models of Organophosphorus Compound Poisoning: A Literature Review

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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 [2] 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 paper [3] 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 paper [5] 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 [4], 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 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.

1 Introduction

Organophosphorus compounds (OPs) are highly toxic chemicals that have been used as nerve agents. The toxic action of OPs is believed to be caused by their inhibition of acetylcholinesterase (AChE) through phosphorylation. AChE is responsible for eliminating acetylcholine from neuromuscular junctions and thus regulates its effects. The inhibition by OPs subsequently causes an

accumulation of acetylcholine at neuromuscular junctions which overstimulates cholinergic receptors and blocks the neuromuscular transmission signal path, possibly leading to central respiratory depression. This blockage may lead to respiratory failure and death. At less than lethal concentrations, OPs may also affect vision, cause muscle fatigue and flaccid paralysis, gastrointestinal upset, convulsions, and disturbances in cardiac rhythm. Onset of symptoms of OP poisoning occurs on the order of minutes to hours depending on the route of exposure. The threat of potential exposure of civilians and soldiers to OPs by terrorist groups and nation states necessitates the development of new medical countermeasures.

Pharmacokinetic (PK) models containing parameters relevant to AChE inhibition have been used to advance understanding of OP mechanisms. PK models describe the effect of the body on the agent. For example, models that describe elimination or clearance of drugs would be considered PK models. Often such individual processes can be described mathematically in terms of a first or second order differential equation. The overall process requires the simultaneous solution of these equations to allow for a temporal description of drug concentration *in vivo*.

This paper aims to summarize several of the relevant papers on the topic as well as present ideas for future models and directions for research.

2 A One Compartment Model

Green [2] wrote one of the first papers of interest on the subject of OP poisoning, and his model considers the body as one homogeneous, well-mixed compartment. Though it treats the body in a simplistic way, this innovative model provides the foundation for many other models in the area.

Although the toxic mechanism of OPs occurs through its inhibition of AChE, OPs interact with other endogenous proteins and enzymes in the body. Green's model incorporates these interactions as well as those of OPs and drugs used as treatments. It considers four basic processes in OP poisoning and subsequent treatment:

i. Combination of the enzyme AChE (E) by the poison OP (P) resulting in inhibited enzyme (I),

ii. Non-toxic reactions of the OP with body tissues,

iii. Detoxification of the OP by a therapeutic agent (A), and

iv. Restoration of AChE by a therapeutic agent (B) by dephosphorylation of I.

These chemical interactions can be represented by

$$\begin{aligned}
\text{P} + \text{E} &\xrightarrow{k_1} \text{I} \\
\text{P} &\xrightarrow{k_2} \text{nontoxic products} \\
\text{P} + \text{A} &\xrightarrow{k_3'} \text{nontoxic products} \\
\text{I} + \text{B} &\xrightarrow{k_4'} \text{E} + \text{nontoxic products}
\end{aligned}$$

Mathematically, these reactions translate to

$$\frac{dE}{dt} = -k_1 EP + k_4' BI \tag{1}$$

$$\frac{dP}{dt} = -k_1 EP - k_2 P - k_3' AP. \tag{2}$$

If the concentrations of the agents A and B are assumed to be relatively constant, pseudo first-order rate constants can be used to yield

$$\frac{dE}{dt} = -k_1 EP + k_4 I \tag{3}$$

$$\frac{dP}{dt} = -k_1 EP - k_2 P - k_3 P. \tag{4}$$

With these two equations, the dose lethal to 50% of a given population (LD50) under specific circumstances can be determined, and these results can be used to ascertain the amount of protection offered by different therapies.

2.1 AChE is not reactivated

In this case, there is no therapeutic agent B to dephosphorylate the inhibited AChE, i.e., reaction (iv) is absent.

2.1.1 No treatment

Suppose $P(0) = P_0$, $E(0) = E_0$, and $P_0 \gg E_0$ as is generally the case experimentally. Then in the long run, when all the OP has disappeared,

$$p = \frac{k_2}{k_1} \ln\left(\frac{E_0}{E_{\min}}\right)$$

where p is the LD50 of P and $E_{\min}$ is the minimum AChE level reached after an LD50 dose of OP or, equivalently, the minimum AChE level compatible with life. This quantity p will be used as the basis of comparison for all other treatments. In other words, the focus will be on how much p can be expected to increase (how much larger a dose it will take to kill 50% of the population) given a particular treatment. The ratio of the treatment-based LD50 to the original LD50 will be called either the *protective ratio* or the *therapeutic efficiency.*

2.1.2 Acetylcholine antagonist

An acetylcholine antagonist such as atropine binds to acetylcholine receptors and blocks acetylcholine from binding there, thereby preventing its accumulation. If such an acetylcholine antagonist is present, then the minimum essential AChE level will decrease from $E_{\min}$ to $E'_{\min}$ and the LD50 will correspondingly rise from p to p_a. The protection ratio provided by such an acetylcholine antagonist is

$$\frac{p_a}{p} = \frac{\ln\left(\frac{E_0}{E'_{\min}}\right)}{\ln\left(\frac{E_0}{E_{\min}}\right)}.$$

2.1.3 Therapeutic agent A

If a detoxicating agent A is given, the LD50 is raised to p_b, and the therapeutic efficiency is

$$\begin{aligned} \frac{p_b}{p} &= 1 + \ln\left(\frac{E_0}{E_{\min}}\right) \frac{k'_3 A}{k_1 p} \\ &= 1 + \frac{k'_3 A}{k_2}. \end{aligned}$$

2.1.4 Acetylcholine antagonist and therapeutic agent A

Combining the effects of an acetylcholine antagonist and a therapeutic agent A reduces $E_{\min}$ to $E'_{\min}$ and gives a new LD50 of

$$p_c = \ln\left(\frac{E_0}{E'_{\min}}\right)\left(\frac{k_2 + k'_3 A}{k_1}\right)$$

which means that the protective ratio afforded from both therapies is

$$\begin{aligned}\frac{p_c}{p} &= \frac{\ln\left(\frac{E_0}{E'_{\min}}\right)}{\ln\left(\frac{E_0}{E_{\min}}\right)}\left(1 + \frac{k'_3 A \ln\left(\frac{E_0}{E_{\min}}\right)}{k_1 p}\right) \\ &= \frac{\ln\left(\frac{E_0}{E'_{\min}}\right)}{\ln\left(\frac{E_0}{E_{\min}}\right)}\left(1 + \frac{k'_3 A}{k_2}\right).\end{aligned}$$

2.2 AChE is reactivated

An agent B that reactivates AChE adds some complexity to analysis. Green assumes that $k_2 + k_3 \gg k_1 E$, a condition that is likely to be met experimentally, and derives a formula from data for the therapeutic efficiency of the reactivator B.

$$\frac{p_d}{p} \approx 1 + 1.6\left(\frac{E_0 k_4}{k_1 p E_{\min}}\right)^{0.8}$$

Green cautions that since the derivation of the formula is empirical, it should be used with care for AChE levels outside the range 0.1 - 10%, for values of $k_4/k_1 p$ above 0.5, or for therapeutic efficiencies greater than 20.

3 Multiple Compartments with Scavengers

Maxwell, Vlahacos, and Lenz's 1988 paper [3] refined Green's model by including detoxification, blood flow, and agent distribution in multiple compartments. These compartments were assumed to be well-mixed and homogeneous and only interconnected through the circulatory system. The compartments in consideration are plasma (Pl), brain (Br), liver (Li), kidney (Kid), muscle (Mu),

diaphragm (Dia), heart (H), and carcass (Car). In this case, the authors specifically looked at the OP soman and included the effects of the endogenous enzymes carboxylesterase (CaE), which detoxifies an OP by irreversibly binding to it before it can react with AChE, and diisopropylfluorophosphatase (DFPase), which detoxifies an OP by hydrolyzing it before it can inhibit AChE. Agents such as CaE and DFPase that detoxify OPs are called *scavengers*.

Let S be soman concentration, E be AChE concentration, C be CaE concentration, Q be plasma flow through tissue, V be volume of tissue, R be tissue-plasma partition coefficient, k_E be the bimolecular rate constant for reaction of soman and AChE, k_C be the bimolecular rate constant for reaction of soman and CaE, k be the observed first-order rate constant for DFPase-catalyzed hydrolysis of soman, t be the time, $D/2$ be the administered dose of soman, $g(t)$ be the function describing introduction of soman into blood, and i be any tissue except blood. For blood, the interactions can then be described by

$$\begin{aligned}
\frac{dS_{\mathrm{Pl}}}{dt} &= \frac{\left(\frac{Q_{\mathrm{Br}}S_{\mathrm{Br}}}{R_{\mathrm{Br}}} + \frac{Q_{\mathrm{Li}}S_{\mathrm{Li}}}{R_{\mathrm{Li}}} + \frac{Q_{\mathrm{Kid}}S_{\mathrm{Kid}}}{R_{\mathrm{Kid}}} + \frac{Q_{\mathrm{Mu}}S_{\mathrm{Mu}}}{R_{\mathrm{Mu}}} + \frac{Q_{\mathrm{Dia}}S_{\mathrm{Dia}}}{R_{\mathrm{Dia}}} + \frac{Q_{\mathrm{H}}S_{\mathrm{H}}}{R_{\mathrm{H}}} + \frac{Q_{\mathrm{Car}}S_{\mathrm{Car}}}{R_{\mathrm{Car}}}\right)}{V_{\mathrm{Pl}}} \\
&\quad - S_{\mathrm{Pl}}(k_E E_{\mathrm{Pl}} + k_C C_{\mathrm{Pl}} + k_{\mathrm{Pl}}) - \frac{Q_{\mathrm{Pl}}S_{\mathrm{Pl}}}{V_{\mathrm{Pl}}} + \left(\frac{D}{2}\right) g(t) && (5) \\
\frac{dE_{\mathrm{Pl}}}{dt} &= -k_E E_{\mathrm{Pl}} S_{\mathrm{Pl}} && (6) \\
\frac{dC_{\mathrm{Pl}}}{dt} &= -k_C C_{\mathrm{Pl}} S_{\mathrm{Pl}} && (7)
\end{aligned}$$

while in other tissues,

$$\begin{aligned}
\frac{dS_i}{dt} &= Q_i \left(\frac{S_{\mathrm{Pl}} - \frac{S_i}{R_i}}{V_i}\right) - S_i(k_E E_i + k_C C_i + k_i) && (8) \\
\frac{dE_i}{dt} &= -k_E E_i S_i && (9) \\
\frac{dC_i}{dt} &= -k_C C_i S_i. && (10)
\end{aligned}$$

Maxwell, Vlahacos, and Lenz validated the model by comparing model predictions and experimental data for several tissues. Prediction was considered to agree with experimental results if

it was within one standard deviation of the mean of the experimental measurements. The model was also used to determine the relative importance of various parameters, and these results agreed with those resulting from other research methods. Its importance lies in both the use of multiple compartments and the inclusion of CaE and DFPase as soman scavengers.

4 Single Compartment Model for Toxicity Levels

Sweeney and Maxwell's 1999 model [5] returns to consideration of the body as a single compartment of constant volume [2], but they draw some important conclusions about prediction of the protective effects of catalytic and stoichiometric scavengers. The authors allow endogenous CaE levels to change and neglect reactivation of inhibited AChE and the actions of AChE agonists or antagonists, and thus

$$\begin{aligned} \text{AChE} + \text{OP} &\xrightarrow{k_2} \text{OP inhibited AChE} \\ \text{CaE} + \text{OP} &\xrightarrow{k_3} \text{OP inhibited CaE} \\ \text{OP} &\xrightarrow{k_1} \text{OP metabolites.} \end{aligned}$$

Then if E is the molar concentration of AChE, I is the molar concentration of the OP compound, and C is the molar concentration of CaE,

$$\frac{dE}{dt} = -k_2 EI \tag{11}$$

$$\frac{dI}{dt} = -k_1 I - k_2 EI - k_3 CI \tag{12}$$

$$\frac{dC}{dt} = -k_3 CI \tag{13}$$

After uncoupling of the equation on E, the authors find

$$\frac{dE}{dt} = -k_2 E \left(I_0 - C_0 \left(1 - \left(\frac{E}{E_0} \right)^{(k_3/k_2)} \right) - (E_0 - E) + \left(\frac{k_1}{k_2} \right) \ln \left(\frac{E}{E_0} \right) \right)$$

which enables them to find the initial amounts of OP required to cause AChE to fall to and remain at a non-zero steady state value given initial concentrations of AChE and CaE and particular values

for rate constants. They use this information to generate a "toxicity surface" as shown in figure 1. This surface shows several relevant features of OP poisoning. First, it shows a "hydrolysis plane,"

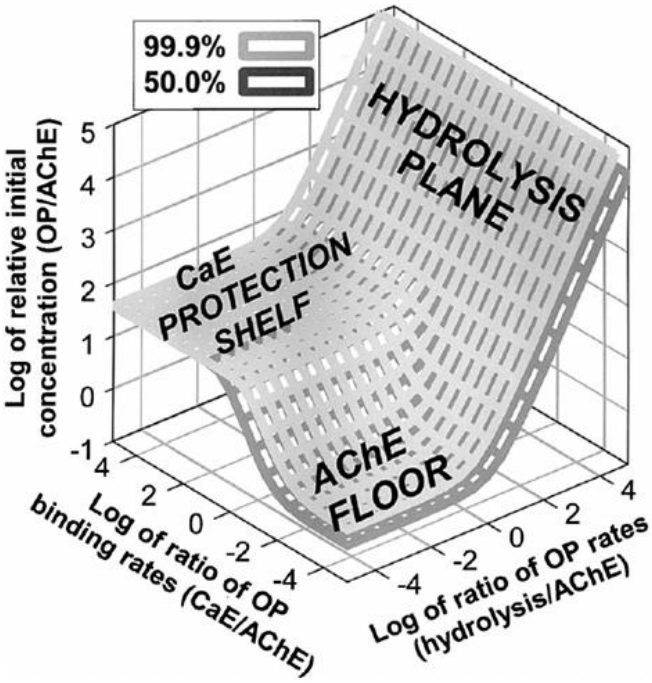

Figure 1: Sweeney and Maxwell's toxicity surface

which indicates the protection provided by the hydrolysis process. It also shows a CaE protection shelf that represents the protection afforded by the irreversible, stoichiometric binding of OP with CaE. The toxicity surface also includes an "AChE floor" region where virtually all OP combines with AChE during an OP challenge. Their surface shows what levels of OPs are needed to cause certain levels of AChE inhibition given differing levels of CaE binding rates and hydrolysis rates. Thus it provides a theoretical representation between the two differing scavenger mechanisms, and it can be used to determine the best approach for enhancing protection against specific OPs.

5 Single Compartment with Scavengers

As a continuation of their 1999 paper, Sweeney and Maxwell in 2003 [4] add exogenous stoichiometric and catalytic scavengers into their model.

$$\text{AChE} + \text{OP} \xrightarrow{k_2} \text{OP inhibited AChE}$$

$$\text{CaE} + \text{OP} \xrightarrow{k_3} \text{OP inhibited CaE}$$

$$\text{stoichiometric scavenger} + \text{OP} \xrightarrow{k_4} \text{OP inhibited stoichiometric scavenger}$$

$$\text{OP} \xrightarrow{k_1} \text{endogenous OP hydrolysis products}$$

$$\text{OP} \xrightarrow{k_5} \text{catalytic scavenger OP hydrolysis products}$$

Suppose V is the volume of the compartment, E is the molar concentration of AChE, A is the molar concentration of an AChE inhibitor (an OP compound), C is the molar concentration of CaE, S is the molar concentration of the stoichiometric scavenger, k_1 is the sum of all first-order OP elimination rate constants (including endogenous OP hydrolase activity), k_2 is the bimolecular rate constant for OP combination with AChE, k_3 is the bimolecular rate constant for OP combination with CaE, k_4 is the bimolecular rate constant for OP combination with the stoichiometric scavenger, and k_5 is a first-order rate constant for elimination of the OP by a catalytic scavenger enzyme. It is further assumed that scavenger is only lost due to irreversible binding with the OP and that loss is the means by which the scavenger provides protection. $M(t)$ is a dosing function used to model the OP challenge event, so if M_T is the total dose, then $\frac{dM}{dt}$ is zero before t_0 and after M_T is delivered. Additionally, since k_5 is a first-order constant, the concentration of the OP must be small compared to the affinity, K_m, of the scavenger for the OP. The system of equations used to model these interactions is

$$\frac{dE}{dt} = -k_2 EA \tag{14}$$

$$\frac{dA}{dt} = \frac{\frac{dM}{dt}}{V} - k_3 CA - k_4 SA - k_2 EA - (k_1 + k_5)A \tag{15}$$

$$\frac{dC}{dt} = -k_3 CA \tag{16}$$

$$\frac{dS}{dt} = -k_4 SA. \tag{17}$$

After uncoupling of the equation on E, the resulting differential equation is

$$\frac{dE}{dt} = -k_2 E \left(\frac{M(t)}{V} - C_0 \left(1 - \left(\frac{E}{E_0} \right)^{k_3/k_2} \right) - S_0 \left(1 - \left(\frac{E}{E_0} \right)^{k_4/k_2} \right) \right.$$
$$\left. - E_0 \left(1 - \frac{E}{E_0} \right) + \left(\frac{k_1 + k_5}{k_2} \right) \ln \left(\frac{E}{E_0} \right) \right). \tag{18}$$

From this work, Sweeney and Maxwell determine that the protection ratios were most sensitive to the initial levels of the stoichiometric scavenger.

6 Future Work

To date community research efforts on evaluation of efficacy of new antidotes against OP poisoning have concentrated on the use of animal models. The new animal rule issued by the FDA for drug approval when human efficacy data cannot be obtained requires efficacy data in two appropriate animal models, one rodent and one non-rodent. Non-human primate models are prohibitively expensive, leading to studies with very small sample sizes. Murine models are considerably cheaper, but results do not transfer to humans well because of differences in OP susceptibility between mice and primates. [1] The end goal of this research is to address these problems by creating models that incorporate the action and interaction of OPs and their antidotes and then scaling these models to predict responses in humans.

While this approach has been applied with success to describe the fate of a chemical warfare agent in several species [1], little work has been done to modify the equations to allow for a similar evaluation of the effect of such a poison in the presence of a therapeutic compound. Computational algorithms and appropriate solvers will be developed to take advantage of high performance computers to solve these equations. The ensuing complexity of evaluating the interaction of the two compounds simultaneously is far more complicated than the models reviewed here, and that effort will be part of the long-term research goals.

In the short term, the goal is to create a multi-compartment model that incorporates the

[1] This disparity may arise from the mouse's relatively high serum concentration of the carboxylesterase enzyme Esterase 1, which may act as a detoxifying agent.

protective effect of scavengers. Figure 2 was generated as a precursor to this model. Once the

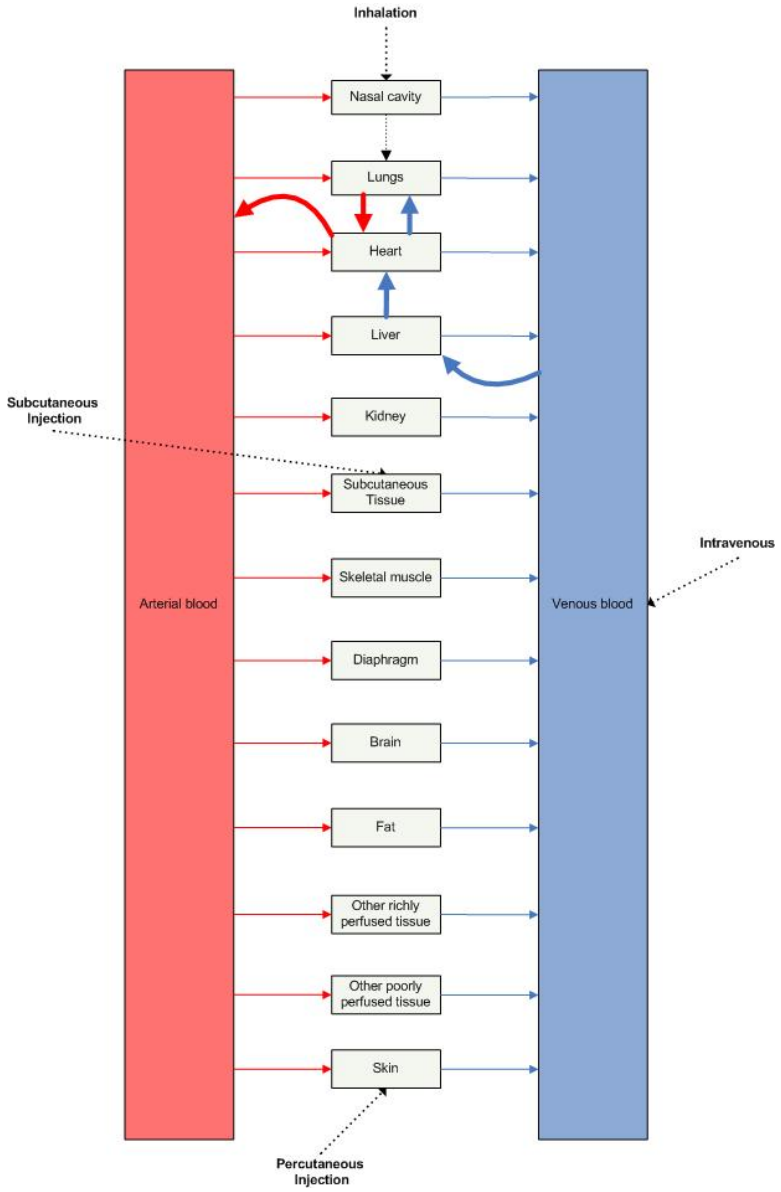

Figure 2: Blood and toxin flow through the body.

differential equations have been set up, parameters from the literature will be used, and the model will be validated with available experimental data. Then a sensitivity analysis will be performed to determine which of these parameters have significant impact on the model.

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