# RELATIONSHIP BETWEEN TOXICITY AND IN VIVO ANTICHOLINESTERASEPOTENCY IN NERVE AGENTS POISONING

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***Summary***

*Using originally developed method for monitoring of rat blood acetylcholinesterase activity, the toxicity and half-times of enzyme inhibition in vivo were compared following intoxication with highly toxic organophosphates of O-alkyl S-2-dialkylaminoethyl methyl phosphonothiolate type. A linear relationship between these two parameters was demonstrated. On the other hand, similar correlation for sarin and soman was not found. It suggests that mechanism of the toxic effect of phosphonofluoridates covers more reactions in comparison with phosphonothiolates.*

**Key words:** Anticholinesterase potency; Toxicity; Nerve agents; Blood; Rat.

## Introduction

Cholinesterase inhibitors are frequently used as insecticides, drugs, industrial and agricultural chemicals and some of these having extremely high toxicity can be misused as chemical weapons. Basic mechanism of their action is explained by acetylcholinesterase (AChE, EC 3.1.1.7) inhibition at cholinergic synapses and consequent accumulation of neuromediator acetylcholine followed by changes in other parameters (1). However, before this action it is necessary to transport the toxic compound to target sites. It is realized by blood stream where cholinesterases are inhibited. Therefore cholinesterase inhibition in the blood is basic information on the penetration of inhibitor into the organism. There are two types of cholinesterases, AChE in the erythrocytes and butyrylcholinesterase (BuChE, EC 3.1.1.8) in plasma. Using an originally developed method of continual monitoring of rat blood cholinesterase activity (determining 70 % of AChE and 30 % of BuChE) (2), we compared toxicity and anticholinesterase efficacy *in vivo* for highly toxic nerve agents of V-type. This class of compounds was chosen because they are not detoxified in the organism. Sarin and soman (compounds detoxified in the organism) (3) were also studied.

## Material and methods

Toxicities were expressed as $LD_{50}$ for female WISTAR rats (i.m.), calculated according to probit-logarithmic method. They were obtained from literature data (4). Half-times of blood AChE inhibition were monitored using flow Technicon system (2) following i.m. administration of $1xLD_{50}$ dose. These data were obtained also from literature (3, 5, 6).

Chemical formulas of phosphonothiolates used are summarized in Table 1. For better orientation, they were designated using two symbols - the first part of designation is abbreviation of alkyl group bound to oxygen on the phosphorus atom and the second one is dialkyl group bound to nitrogen.

Table 1

**Chemical structures and abbreviations of compounds used**

| designation | $R^1$ | $R^2$ | note |
|---|---|---|---|
| Et-Me | ethyl | dimethyl | EDMM,33SN |
| iPr-Me | i-propyl | dimethyl | 37SN |
| Et-Et | ethyl | diethyl | edemo |
| Et-Pr | ethyl | dipropyl | |
| Et-iPr | ethyl | diisopropyl | VX |
| Et-nBu | ethyl | dibutyl | |
| iPr-Et | i-propyl | diethyl | |
| iPr-iPr | i-propyl | diisopropyl | |

Statistical evaluation was made using regression analysis.

## Results

Toxicities of different V- compounds varied from 13.6 μg/kg (Et-iPr) to 96 μg/kg (iPr-Me). The half-times of blood AChE inhibition was in the range

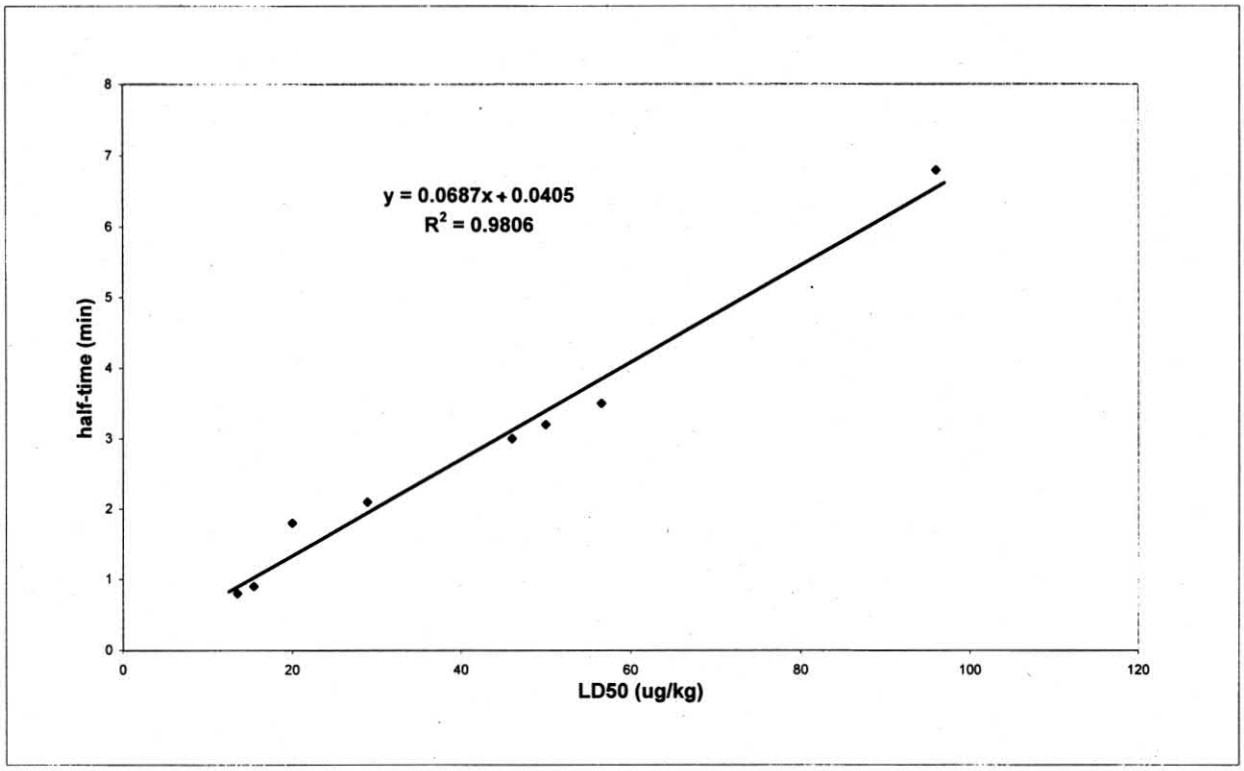
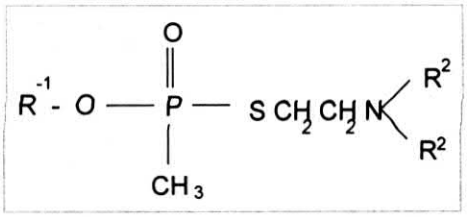



*Fig. 1.: Dependence of anticholinesterase potency (half-time in the blood) and toxicity ($LD_{50}$) for O-alkyl S-2-dialkylaminoethyl methyl phosphonothiolates.*

of 0.8 min (Et-iPr) to 6.8 min (iPr-Me). The linear relationship between toxicities and half-times of AChE inhibition for V-compounds are shown in Fig. 1. High correlation coefficient was observed. However, for sarin and soman having toxicity 108 μg/kg and -62 μg/kg (1), the half-times were very short (1.1 min for sarin and 0.7 min for soman) and relationship was not in the range as that observed for V-compounds.

## Discussion

It is known that toxicity of organophosphates can be assessed roughly from anticholinesterase potency of such compound *in vitro* (7). However, there are some disadvantages of this approach because of different penetration of various organophosphates into the target sites, different detoxification etc. For the group of compounds studied (V-agents), it was not demonstrated detoxification in the blood. On the other hand, G-agents (sarin, soman) are detoxified in the blood (3). The difference between good correlation of anticholinesterase potency *in vivo* and toxicity of V-agents (and not for G-agents) can be caused by this fact. It is of interest that hypothetic curve of dependence half--time vs. toxicity for soman and sarin has different slope but it is beginning also very near to zero. It is not excluded that this correlation (i.e. toxicity vs. AChE inhibition) does exist for G-compounds, too.

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