

A strategy for rational oxime use in poisoning by organophosphorus compounds.

H. Thiermann¹, P. Eyer², T. Zilker³, F. Worek¹

¹ *Bundeswehr Institute of Pharmacology and Toxicology, Neuherbergstr. 11, 80637 Munich, Germany;* ² *Walther-Straub-Institute of Pharmacology and Toxicology, Ludwig-Maximilians-University, Goethestr. 33, 80336 Munich Germany;* ³ *Toxicological Department of 2nd Medical Clinic, Technical University, Ismaningerstr. 22 81664 Munich, Germany.*

Objective: Inhibition of acetylcholinesterase (AChE) is regarded as the most important toxic mechanism of organophosphorus (OP) compounds. Antidotal therapy is directed to competitively antagonise overstimulation of muscarinic receptors with atropine and to reactivate inhibited AChE with oximes. The latter approach is crucial, especially at the neuromuscular synapse where atropine is ineffective, since peripheral neuromuscular block may eventually lead to respiratory failure. Sufficient reactivation and a corresponding improvement of neuromuscular function may be expected only when sufficient oxime doses are administered and as long as the OP-AChE complex is reactivatable. In contrast, when oxime dosing is inappropriate, the poison load extremely high or the AChE-OP conjugate completely aged no beneficial effects of oximes can be expected. Hence, clear guidance is necessary for an optimised individual treatment.

Methods, Results and Discussion: AChE is encoded by a single gene in each mammalian species and a similar structure may be assumed to occur throughout the body. Red blood cell (RBC)-AChE is expressed in RBC membranes and is therefore accessible from peripheral blood of intoxicated patients. This enzyme source may be used as surrogate for AChE present at the synaptic site, as both enzymes are expected to undergo identical chemical reaction with OP (1). Accordingly, it appeared rational to use reaction rate constants of inhibition, aging, spontaneous and oxime induced reactivation derived from RBC-AChE to predict efficient oxime concentrations (2). It turned out, that about 10 μM obidoxime are efficient in most pesticide OP poisonings while much higher pralidoxime concentrations are necessary to achieve sufficient reactivation (3). In parathion poisoned patients who were treated with obidoxime (250 mg bolus, followed by 750 mg/day), it was found that the RBC-AChE activity determined during poisoning was in good correlation with predicted values that were calculated from the patients' plasma concentrations of obidoxime and paraoxon using the respective reaction rate constants (4). It was shown that significant reactivation could be achieved with an obidoxime plasma level of about 10 μM when the poison load was not too high. Similarly, high dose pralidoxime treatment was associated with clear clinical benefit as shown in a recent study in India (5).

Together with clinical signs and symptoms a significantly reduced RBC-AChE activity clearly indicates intoxication by a cholinesterase inhibitor. With an advanced laboratory monitoring system (cholinesterase status) comprising RBC-AChE activity, reactivatability of inhibited RBC-AChE by oximes, butyrylcholinesterase activity and inhibitory activity in patients' plasma, the course of intoxication in individual patients can be followed. From these objective data, it can be

judged, whether oxime therapy is effective in reactivating AChE (3;6). Oxime therapy should be performed as long as the inhibited enzyme is reactivatable and poison is persisting in the body.

However, when RBC-AChE is aged completely, RBC-AChE can no longer be regarded as suitable parameter to indicate the end of the cholinergic crisis. Under such conditions, investigation of neuromuscular transmission could be helpful. After high frequency stimulation (about 30-50 Hz) typical response for OP- poisoning (so called decrement or decrement-increment phenomena) can be assessed to estimate the failure in neuromuscular transmission (7-9).

Conclusions: The laboratory test system of the cholinesterase status and the investigation of the neuromuscular transmission should be used for monitoring the course of OP-intoxication. Based on these data an optimised individual oxime treatment can be performed. Using this approach maximal benefit can be expected in eligible patients and insufficient use of oximes can be avoided.

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