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Editorial

# Oxime treatment for organophosphorus compound exposure: Getting it (into the brain) might not be that good for you, after all

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Organo-phosphorous compounds (OPC) are amongst the most frequent causes of intoxications. Each year, there are millions of cases of acute pesticide poisoning, causing the death of up to half a million people. The imminent threat of OPC poisoning is also evidenced by the chemical terrorism incidents that occurred in Japan, during which civilians were deliberately exposed to the nerve agent sarin. Subsequently, several thousands were seeking medical attention, and over a dozen people died. During the Iraq–Iran war, OPCs were employed against Iranian troops and civilians, and as a result many of them lost their lives soon after exposure. The dangers of malicious OPC poisonings were highlighted by recent news of the alleged use of chemical warfare agents in the Syria conflict.

The acute toxicity of OPCs (organophosphates and organophosphonates) is due to inhibition of the enzyme acetylcholinesterase (AChE), which metabolizes the neurotransmitter acetylcholine (ACh). The inhibition of esterases results from phosphylation (i.e. either phosphorylation or phosphonylation) of the hydroxyl group of serine in the active centre of the enzyme and translates into an ''endogenous acetylcholine poisoning''.

The accumulation of acetylcholine drives an initial sympathomimetic response due to stimulation of nicotinic receptors in the adrenal medulla followed by a longer-lasting parasympathomimetic response due to stimulation of muscarinic receptors. Both responses can and must be controlled by appropriate medications. In addition, organophosphates and organophosphonates cause an acetylcholine overflow at neuromuscular synapses with ensuing depolarizing block, requiring artificial ventilation. Furthermore activation of central cholinergic receptors results clinically in seizure activity (Petroianu et al., 1998).

The therapy of organophosphorus inhibitors of cholinesterase poisoning is known by the acronym A FLOP = Atropine, FLuids, Oxygen, Pralidoxime (Petroianu, 2005). The mnemonic is an oversimplification in as much as it does not include the GABA-A receptor agonists (benzodiazepines) used to control convulsions. A more comprehensive version would be A FLOOD = Atropine, FLuids, Oxygen, Oxime, Diazepam. The latter version of the mnemonic has the added advantage as to remind the clinical symptoms of organophosphorus inhibitors of cholinesterase exposure: the ''flood'' of secretions generated by cholinergic excitations.

The attempt to reactivate an inhibited enzyme using pyridinium oximes is meaningful only before ''ageing'' [of the phosphylated enzyme] sets in. While the molecular mechanism of ''ageing'' is not entirely understood it is associated with dealkylation of the alkyl-phosphylated enzyme. From a clinical perspective the half-life [t1/2] of the alkyl-phosphylated enzyme is therefore relevant and defines the window of opportunity for the use of pyridinium oximes.

Although, the mechanism of action of oximes is relatively well characterized in theory, their practical value remains uncertain and oximes have disappointed clinically (Buckley et al., 2011). Due to the presence of a positively charged nitrogen atom, oxime molecules are polar, have a negative log P and are hydrophilic. Since only small lipophilic compounds easily penetrate the blood brain barrier, oximes barely enter the brain (Lorke et al., 2008). The peak brain concentration ($C_{max}$) of the monopyridinium aldoxime pralidoxime is only about 10% of its blood $C_{max}$ and penetration of bispyridinium aldoximes is significantly lower (Lorke et al., 2007; Petroianu et al., 2007).

The relationship between oxime efficacy and their entry into the brain is a contentious issue. Is the restricted brain

penetration of oximes the reason for their limited efficacy? Could superior efficacy be achieved by an increase in brain penetration?

One school of thought is that even with limited oxime brain penetration some cholinesterase reactivation is achieved and considering the very high turn-over rate of the enzyme this is sufficient as to have a clinical impact. The corollary of this assumption is that more brain penetration would translate in more cholinesterase reactivation and better clinical outcomes.

The development of a less hydrophilic oxime was attempted: a dihydropyridine derivative of pralidoxime, pro-2-PAM was designed. This pro-drug should enter the brain more easily, and 2-PAM brain levels were indeed considerably higher when using this brain penetrating pro-drug (Bodor et al., 1976; Shek et al., 1976). However, overall results were disappointing leading to the following conclusion in a recent review: ''*Increasing the BBB penetration by oximes does not actually lead to significant benefits of survival rate, but certainly amplifies the neurotoxic risks*'' (Voicu et al., 2010).

After correlating in vivo toxicity of various oximes with different in vitro parameters (Lorke and Petroianu, 2009), our own experimental studies indicate that a negative log P (strong hydrophilicity) is a good predictor for low oxime toxicity (as assessed by survival). In addition, oximes with very negative log P (strong hydrophilicity) were significantly more efficacious in reducing DFP-induced mortality than more lipophilic ones.

This would suggest that limited brain penetration is actually desirable.

One possible basis for this paradigm-offending view is the formation of phosphylated oximes, which are generated by the reaction of oximes with organophosphorus-inhibited enzymes and which can be highly toxic (Kiderlen et al., 2005; Becker et al., 2007). Many phosphylated oximes are themselves potent inhibitors of AChE, sometimes much more potent than the initial offending organophosphate or organophosphonate, which generally translates into very high toxicity. Considering that phosphylation generally increases lipophilicity and thus brain penetration these possibilities make necessary a reassessment of our views of the ''perfect oxime'' (Petroianu et al., 2014).

Desirable properties of this elusive cholinesterase reactivator might be:

1. Hydrophilicity (limited brain penetration).
2. No major shift towards lipophilicity subsequent to phosphylation (still limited brain penetration).
3. No increase in toxicity subsequent to phosphylation.

If one throws in the ability to reactivate cholinesterases more or less independently of the inhibiting agent the picture of the ''perfect oxime'' becomes much sharper. However heretic these views might appear it is only via further in silico, in vitro and in vivo research that it can be refuted or confirmed.

## Conflict of interest

The author could not identify any real or potential conflict of interest.

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