SPECIAL ARTICLE

Nicotinic antagonists in the treatment of nerve agent intoxication

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J R Soc Med 2005;**98**:114–115

Organophosphorus (OP) nerve agents are potent inhibitors of human acetylcholinesterase and butyrylcholinesterase. Although some OPs may induce delayed toxic effects on muscle and nerve,[1] it is the inhibition of acetylcholinesterase that accounts for the acute life-threatening toxicity of soman, sarin, VX, tabun and similar OP compounds. This acute toxicity, which arises from the uncontrolled accumulation of acetylcholine (ACh) at peripheral and central muscarinic and nicotinic ACh receptors (mAChRs and nAChRs), gives rise to the so-called cholinergic syndrome, which comprises symptoms and signs attributable to inappropriate stimulation of mAChRs (airway hypersecretion, bronchoconstriction, bradycardia, gut hypermotility, sweating, pupillary constriction) and nAChRs (muscle fasciculation and weakness, tachycardia, hypertension, pupillary dilatation). Despite this involvement of mAChRs and nAChRs in nerve agent and OP pesticide toxicity, pharmacotherapy focuses only on the mAChR component, the mainstay of treatment being the competitive mAChR antagonist atropine, which is given together with an oxime reactivator of OP-inactivated acetylcholinesterase, such as pralidoxime. Given that the effects of ACh are mediated by both mAChRs and nAChRs, Smythies and Golomb[2] posed the perfectly logical question of why nAChR antagonists are not incorporated in the therapeutic approach to nerve agent intoxication.

nAChRs may be grouped into two broad classes—neuronal and muscle. Although there is evidence that dysfunction of brain nAChRs may have a role in the pathogenesis of certain types of human epilepsy,[3] evidence for anticonvulsant efficacy of centrally active nAChR antagonists in animal models of OP intoxication is lacking.[4,5] However, our understanding of the pharmacology and function of brain nAChRs is still sketchy and it is conceivable that nAChR antagonists may be developed in the future that could be useful in the treatment of seizures associated with severe OP intoxication. At present the agent used to control nerve-agent-induced seizures is diazepam, its efficacy having been clearly established in numerous animal studies (see, for example, Ref. 6) and in a limited number of reports of human exposure to sarin and VX.[7,8]

Neuronal nAChRs also mediate neurotransmission in sympathetic and parasympathetic ganglia and in the adrenal medulla. Nicotinic effects in parasympathetic ganglia are already addressed postganglionically by the antimuscarinic therapy routinely given to OP-intoxicated patients. The question then arises: would nAChR blockade in sympathetic ganglia and the adrenal medulla be therapeutically beneficial? There is clinical evidence that a proportion of individuals poisoned with a range of OP pesticides can present with tachyarrhythmias and hypertension.[9,10] Severely poisoned victims of the Tokyo sarin incident commonly presented with tachycardia and hypertension.[11] These observations imply that a sympathetic ganglion blocker might be of use in the therapy of nerve agent and OP pesticide poisoning in those individuals displaying nicotinic-dominant signs. Nevertheless, we can find no reports in the clinical sphere where a ganglion blocker has formed part of the therapy of OP poisoning. We suspect this is partly because clinicians are cautious about using drugs that exert a potent hypotensive action—which may in itself induce a reflex tachycardia despite effective ganglionic blockade.[12] However, until such time as a randomized control trial of adjunctive ganglion blocker therapy in OP poisoned patients is conducted it would be premature to dismiss a therapeutic role for this class of drugs.

The remaining potential therapeutic target for nAChR antagonists in OP intoxication is the neuromuscular junction. Fasciculation and weakness due to overstimulation of nAChRs at the motor end-plate in respiratory and other muscles are common signs in OP pesticide and nerve agent poisoning in humans.[8–11] It would appear logical, therefore, to attempt to minimize these signs by use of a non-depolarizing neuromuscular blocker such as gallamine or pancuronium, which are competitive antagonists of ACh at the muscle nAChR. The concept of use is straightforward: administer a dose of competitive neuromuscular blocker that is sufficient to antagonize the effects of excessive ACh (and thereby normalize function at the neuromuscular junction) but which is not so great that the now normalized function itself becomes compromised by excess antagonism. And herein lies the problem. It is not difficult to envisage that the narrow therapeutic window for optimal antagonism

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by a competitive blocker would preclude use of such drugs except in circumstances where mechanical ventilation can be administered. While this may be realistic in isolated cases of OP poisoning, it is unlikely to be practicable where there are mass casualties (e.g. the Tokyo subway incident[11]).

An alternative approach to address the effects of OPs at the neuromuscular junction would be to use a non-competitive muscle nAChR antagonist whose effects would not be overcome by increasing concentrations of ACh. There is strong experimental evidence that certain bispyridinium compounds have a beneficial effect in OP poisoning through this type of action.[13–15] These compounds, which fortuitously include certain oxime reactivators of phosphorylated AChE such as HI-6 and toxogonin, can lead to recovery of function even in the absence of enzyme reactivation.[13–15] Effective compounds have been shown to block the open ion channel of the nAChR[15,16] and this blocking action correlates well with their ability to relieve tetanic block induced by soman.[14]

Open channel block, which is a form of noncompetitive antagonism of the action of ACh at the muscle nAChR, is an attractive concept because the block is use-dependent: antagonism becomes greater as activation of the nAChR increases. This is the converse of what happens with a competitive antagonist and, at least in principle, appears to be an ideal way of mitigating the effects of OP-induced overstimulation of muscle nAChRs.

The challenge now is to elucidate the structural requirements for muscle nAChR block in an effort to design molecules in which this action is optimized. This will then enable validation of this therapeutic approach in appropriate experimental models of OP intoxication. Unfortunately, the development of improved pharmacotherapies for OP poisoning is not high on the agenda of the major pharmaceutical companies, even though it is estimated that more than 300 000 people in Asia and the Western Pacific alone die each year from exposure to OP pesticides.[17]

Acknowledgments This work is supported by the Ministry of Defence, UK.

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