Review Article

Different approaches to acute organophosphorus poison treatment

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Abstract

Organophosphorus compounds (OPCs) have a wide variety of applications and are a serious threat for self-poisoning, unintentional misuse, terrorist attack, occupational hazard and warfare attack. The present standard treatment has been reported to be unsatisfactory. Many novel approaches are being used and tested for acute organophosphorus (OP) poison treatment. The bioscavenger concept captured high attention among the scientific community during the last few decades. Other approaches like alkalinisation of blood plasma/serum and use of weak inhibitors against strong inhibitors, though it showed promising results, did not get such wide attention. The introduction of a novel broad-spectrum oxime has also been in focus.

In this mini-review, an update of the overview of four different approaches has been discussed. The standard therapy that is atropine+oxime+benzodiazepine along with supportive measures will continue to be the best option with only the replacement of a single oxime to improve its broad-spectrum efficacy.

Keywords: OPCs poison treatment, Bioscavenger, Oxime, OP antidotes.

Introduction

Organophosphorus group of poison exist since the 19th century. The first OP poison was discovered and reported by German scientist Philippe de Clermont and M Moschnine in 1855. The compound was a mono ester of organophosphorus compound and named tetraethyl pyrophosphate (TEPP). The first OP was developed as an insecticide for agriculture and now more than 100 kinds of OP pesticides are available in the market, each having different toxicity levels. Other OP compounds include Tabun, a deadly compound that was developed in 1936 by German scientists during World War II, followed by Sarin (1938), Soman (1944), Cyclosarin (1949) and VX (1952) respectively. The last compound was developed

in the UK. These compounds are called nerve agents, G-agents and warfare chemicals The first warfare use of Tabun was reported during the Iran-Iraq war in 1983, and then Sarin was used by Iraq in Halabjeh (Kurdistan) in 1988. The terrorist attack in Motsomoto in 1994 and Tokyo subway 1995 with Sarin and VX also caused many deaths and casualties.

The agriculture use of OP is widespread. Acute OP pesticide poisoning is common in developing countries because of insufficient control, storage, easily availability and less awareness among poorly educated farmers. Hundreds of thousands of people die each year around the world from OP poisoning, mostly in developing countries like India, Pakistan, and Sri Lanka. OP self-poisoning alone is responsible for 200,000 deaths a year in the world.[1] Occupational exposure, unintentional use and misuse are other factors in addition to the threat of terrorist activities. OP nerve agents are structurally different than the organophosphorus compounds used in pesticides, but the toxicological effects of both the groups are almost entirely due to the inhibition of acetylcholinesterase, a neurotransmitter enzyme. Signs and symptoms of OP poisoning can be divided into three categories; muscarinic, nicotinic and central nervous system effects. SLUDGE and DUMBELS are the two mnemonic used to remember the muscarinic effects. SLUDGE stands for salivation, lacrimation, urination, diarrhoea, GI upset and emesis, while DUMBEL means diaphoresis, urination, miosis, bradycardia, bronchospasm, bronchorrhea, emesis, excessive lacrimation and salivation. Nicotinic signs and symptoms include muscle fasciculation, cramping, weakness, and diaphragmatic failure. Autonomic nicotinic effects include hypertension, tachycardia, mydriasis, and pallor. CNS effects include anxiety, emotional labiality, restlessness, confusion, ataxia, tremors, seizures and coma. Death occurs due to respiratory failure.

The standard therapeutic treatment of the OP poisoning is atropine+oxime+benzodiazepines along with supporting measures, which include the proper ventilation and decontamination of the skin and body parts whether by alkali solution or by specific decontamination kits etc. Petroianu[2] described the treatment of OP poisoning as AFLOP — means atropine, fluid, oxygen, pralidoxime (oxime). Clinically atropine relieves muscarinic signs and symptoms and oxime (pralidoxime/obidoxime/HI-6 etc) is supposed to shorten the duration of the respiratory muscle paralysis by cholinesterase reactivation. Benzodiazepines are used to control OP-induced seizures. Pre-treatment with pyridostigmine along with regular therapy is recommended in warfare condition. Some of the non-regular antidotes include clonidine, fresh frozen plasma, magnesium sulphate, activated charcoal, milk and some other home remedies.[3] Other experimental approaches are the use of NMDA receptors antagonist such as gacyclidine[4] and haemoperfusion.[5]

The standard treatment which includes oxime is not satisfactory in all cases with every organophosphorus poison. It is rather considered disappointing by many scientists and clinicians.[6,7] The non-regular antidotes did not get attention from the scientific community for some reasons and scientific reports are negligible. Scientific work to countermeasure the organophosphorus poisoning is mainly done for warfare OP compounds and then secondarily for civilian purposes.

In the present minireview, the four different approaches to OP treatment have been briefly reviewed to conclude which approach may prevail in the future for the treatment of organophosphorus poisoning and what may be the alternatives.

1. Alkalinisation of blood plasma/serum:

The rationale behind this approach is that alkalinization of blood will cause the hydrolysis of organophosphorus molecule. The approach was postulated by Placcio[8] and Cordoba et al.[9] The mechanism for this approach is the hydrolysis of the organophosphate, which has been claimed to increase10-fold for each pH unit towards alkalinity[6] and the hydrolysis of OP molecule, increases with higher PH. Alkalinisation of the blood to pH of more than 7.50 by sodium bicarbonate facilitates destruction of OP molecules.[10] However, the procedure does not cause the increase in acetylcholinesterase (AChE) activity[11] which is the biomarker of OP poisoning. Many of the workers reported sodium bicarbonate as an adjunct to standard therapy and found promising therapeutic effects.[10,11]

Now the question arises whether or not alkalinisation of blood by any compound is enough. Relevant literature shows that researchers are advocating the use of sodium bicarbonate for alkalinisation of blood for OP poison treatment. Sodium bicarbonate is used for cardiac sodium channel poisoning and sodium channel effects in clinical practice. The effectiveness of this sodium bicarbonate is a result of both the increased sodium concentration produced and increased serum alkalinisation.[12] Alkalinisation of blood with sodium bicarbonate might increase the hydrolysis of the esteratic portion of organophosphate molecule, thus decreasing its toxicity. Most of the OPCs are hydrolysed more rapidly at an alkaline pH and beneficial action of sodium bicarbonate could be at least explained by the change in the rate of hydrolysis of OPC relative to blood pH, thus inducing increase of elimination rate.[11]

Although the hypothetical mechanism is the hydrolysis of OP molecule by alkalinisation, but the exact mechanism of sodium bicarbonate action or alkalinisation for OP treatment is still not established. On the basis of available literature, the following mechanism of actions may be proposed. It is also possible that the mechanisms other than those proposed are involved.

◆ Hydrolyse i.e. breakdown of the OP molecules. Structurally different OP shows different stabilities in acidic conditions.

Some are more stable than others. Disturbance in acid-base balance will promote the breakdown of OP molecule.

◆ Achieving a urinary pH of 7.5 and above promotes excretion of drugs that are weak acids. Enhanced pesticide clearance from the body through non enzymatic and/or enzymatic hydrolysis has been reported.

◆ Controls the cardio toxicity via sodium pump channel. Arterial pH 7.45-7.55 reverses cardiac membrane depressant.

◆ Preventing the cardio-respiratory arrest due to OP poisoning.

◆ Improves efficacy of oximes by increasing the bio-availability.

◆ Potentiates therapeutic activity of atropine in acute organophosphate poisoning.

◆ There may be direct effect on neuromuscular functions.

◆ Bicarbonate induces release of lactate into circulation.

However, it is still unclear if this approach is good to all structurally different organophosphorus compounds. As a matter of fact, different chemical structures of OPCs show different stabilities in acid solutions and react differently in alkali solutions. Dimethoate, methyl parathion, malathion and trichlorfos in particular were found to be more stable in acidic conditions while diazinon was less stable in a similar environment. So it is important to determine the effectiveness against all structurally different organophosphorus poisons. Presently most of the work has been done on moderate toxic OPs like diclorvos.

Secondly, it is also not clear whether remedy is due to bicarbonates-induced alkalinisation or effect related to the sodium component. Serial blood gas analysis and other biochemical parameters like bicarbonates status etc. monitoring is a must during therapy. There must be proper arrangement for hyperventilation to blow off carbonic dioxide. The OP toxicity is directly related to the enzymatic activity of neurotransmitter enzyme acetylcholinesterase which breaks down into acetyl and choline before reformation. We also know that the activity of enzymes is dependent upon and specific to a particular pH. Even if it increases the bio-availability of enzyme reactivators (oximes) in combined therapeutic regimen, will the reactivators work?

Alkainisation is not widely used for the treatment of OP poisoning mainly due to lack of confidence by clinicians in its efficacy. Literature search reveals little and inconclusive study on this approach. Balali-Mood et al.[10] conclude that sodium bicarbonate could be useful as a part of the therapeutic regimen in human organophosphate poisoning. For the assessment of oxime and bicarbonate therapeutic regimen, Vucinic et al.[13] conducted a clinical trial and suggested that oximes and bicarbonate should not be used together. In some centres, however sodium bicarbonate is routinely used for severe poisoning. According to Roberts and Buckley,[14] routine use of this approach to treatment cannot be recommended. The authors believe that it is under experimental stage and much more study is needed to reach a conclusion and recommend it for regular therapeutic use.

2. Bio-scavenger Approach:

The enzymes which are inhibited by OPCs or detoxify OPCs in the body, if administered exogenously, may decrease the endogenous enzyme inhibition level by OPCs or enhance the detoxification rate of OPCs. The exogenous enzymes which are used/meant to detoxify/sequester the organophosphorus compounds are termed bioscavangers. These are mainly esterases. Two names, A-esterase and B-esterase have been widely used in the literature to differentiate between the enzymes that hydrolyze organophosphorus compounds (A-esterase) and the enzymes that are progressively inhibited by organophosphorus compounds (B-esterases). Both names comprise groups of enzymes and not individual enzymes. Examples of B-esterases are Cholinesterases and Carboxylesterase. Examples of A-esterases are phosphotriesterase (PTE), anhydrolase, anhydrases, hydorolase, paraoxonase and DFPase etc. These enzymes may be produced and obtained from equine, bovine or other sources such as from bacteria through recombinant biotechnology principles/protein engineering techniques, and introduced into the OP-affected subject. The basic principle for the use of these enzymes is based on the role of the individual enzyme in the body. Nowadays, some use the terminology of stoichiometric bioscavenger as a first-generation concept, and catalytic bioscavenger as the second-generation approach.[15]

The use of exogenous enzymes in OP antagonism may be traced back to the late 1950s. The concept was reintroduced during the late 1980s. Wolfe et al.[16] worked on mice against nerve agents with foetal bovine serum acetylcholinesterase (FBS-AChE) and suggested a new approach for OPC treatment. Exogenously administered cholinesterases (ChE) can effectively sequester/detoxify in vivo OPCs before they reach their physiological targets.

The approach relates the ChE as anti-OP instead of OP as anti-ChE. OPC toxicity is caused by the irreversible binding to and inactivation of acetyl cholinesterase (AChE), the enzyme that normally catalyses the hydrolysis of acetylcholine at neuromuscular junction and other cholinergic synapses. It has been shown that the administration of foetal bovine serum AChE, or equine serum butyrylcholinesterase (EqBuChE), or human serum butyrylcholinesterase (HuBChE) protected the animals from multiple LD50s of a variety of highly toxic OPCs.[17] Recombinant human acetylcholinesterase (rHuAChE) has been reported better than HuBuChE. The efficacy of ChEs as biological scavengers to protect against OP poisoning has been demonstrated in mice, rats, guinea pigs and rhesus monkeys, and well documented during the last few decades.[18-20] Since its inception in 1987, BuChE has been preferred over AChE as a bioscavanger. There are a good number of

publications during the last few years showing the plasma-derived BuChE as the next generation OP antidote.[15,21]

HuBChE binds in an essentially irreversible fashion at a ratio of one molecule of OP bound to one molecule of HuBChE (i.e. stoichiometric binding) rendering AChE free for acetylcholine at neuro junctions. The preferred substrate for AChE and BuChE are acetylcholine (ACh) and butyrylcholin (BuCh) or propionylcholine respectively. Moreover, the enzyme is substrate specific. Besides, the following points are noteworthy.

1. Acetyl and butyrylcholinesterase are produced in very minute quantities in the human body. For production in large quantities, we have to look at the latest molecular techniques like recombinant technology and the capacity of production has to be checked.

2. Retention of the exogenous enzyme in circulation is very short as they are rapidly eliminated from the body within 5-15 minutes.

3. Introduction of foreign protein into the living body may produce different immunological responses upon administration or repeated administration, a point which is scarcely addressed.

4. Since cholinesterases works on stoichiometric principles, 17,21 this may create a problem in dosing as well as may need large quantities of exogenous enzyme to produce a therapeutic effect.

Two patents have been filed[17,22] and a company in Canada, Nexia Biotechnologies Ltd, developed recombinant rBuChE with the trade name ProtexiaTM in 2005 for OP intoxication. ProtexiaR is now sold to PharmAthene, USA, which will produce it for the American army. A commercially produced recombinant form of human butyrylcholinesterase (r-HuBuChE; PharmAthene Inc.) expressed in the milk of transgenic goats has become available recently. This material is biochemically similar to plasma-derived HuBuChE in in vitro assays.[21] Two industrial good manufacturing practice (GMP) processes exist for mass production of human BChE. The first one is purification of the natural enzyme from the Cohn Fraction IV of human plasma. This process has been developed by Baxter Healthcare Corporation in the USA (www.baxter.com). Highly purified human plasma BuChE was granted the status of Investigational New Drug by the Food and Drug Administration in 2006 for protection against nerve agents in the USA.[20,21]

The limitation of the approach is that the concept is basically related with prophylactic treatment which is a war-condition treatment. Secondly, the impact of introduction of foreign protein (enzyme) into immunological system of subject is less focused. Besides, mass production of stable and purified human enzyme is also an issue. The data on pharmacokinetics, toxicokinetics and immunological studies is also scarce. Stability for long-term storage in solution or in lyophilised forms, and in vivo operational stability, and bioavailability are other major issues to be addressed.

Effectiveness against all groups of organophosphorus compounds is not yet established. Peter et al.[5] in the review of adjunct and alternative to oximes therapy in organophosphorus poisoning are not optimistic of the success of this approach at large. Pichamuthu et al.[23] did not find favourable trends in their pilot randomised controlled study on humans. However, in spite of all the concerns and doubts, there is impressive evidence and enthusiasm in favour of this approach.

3. Weak inhibitors vs. strong inhibitors:

The approach is basically tested as pre-treatment protocol which is a wartime use for OP nerve agent exposure. The concept is to block the cholinesterase reversibly using carbamate (pyridostigmine) in order to deny access to the active site of the enzyme to the irreversible inhibitor (OP nerve agent) on subsequent exposure. Based on animal experiments, the FDA approved military combat medical use of oral pyridostigmine (PSTG) as prophylactic treatment at least 30 minutes before nerve agent exposure. However, there is a difference in opinion in the scientific community. Most authors consider PSTG pre-treatment to be effective only when followed by standard treatment that is atropine+oxime+diazepam, while others do not agree with the opinions.[24] Based on the hypothesis and speculation that a weaker inhibitor of cholinesterase applied at higher dose than PSTG might offer similar or superior benefits with fewer side effects, Prof George Petroianu and his team tested a number of weak inhibitors like tiapride, ranitidine, metoclopromide, tacrine, methylene blue etc. with paraoxon and methyl paraoxon[25] etc. In vitro and in vivo results supported their speculation with promising results in some cases and may provide alternative to pyridostigmine to some extent, but overall could not get wider attraction. Moreover, experiments performed by others using nerve agents instead of organophosphates were less promising.[26]

It may be noticed that the approach is not valid for general therapeutic treatment which a clinician may generally encounter. Rather the concept may be useful only in case of tentatively known OP exposure or as a military combat medicine. Secondly, the pre-treatment alone is not sufficient and standard therapeutic treatment may still be needed which includes atropine and oxime.

4. Oxime therapy:

Oximes are powerful nucleophilic agents used as adjunct treatment in organophosphorus poisoning for reactivation of inhibited acetylcholinesterase, a neurotransmitter enzyme and primary toxic target of organophosphorus poisoning. There is no universal broad-spectrum oxime which may be effective against all kinds of OPCs. Pralidoxime chloride was the first reported oxime, developed in 1956, and is

Table: Life preserving properties of some oximes in comparison to candidate oxime K-27 for structurally four different kinds of OPCs.

	Paraoxon-ethyl	Paraoxon-methyl	Diisopropylflouro-phosphate (DFP)	Azinfos-methyl
Oxime		**Relative risk of death (RR)**		
Pralidoxime chloride	0.78	0.88	0.62	0.23
Obidoxime	0.64	0.93	0.26	0.37
HI-6	0.36	0.96	0.39	N/A
Trimedoxime	0.40	0.76	0.46	N/A
K-27	0.20	0.58	0.21	0.26
K 48	0.32	0.60	0.30	0.33

OPCs: Organophosphorus Compounds.

still the most widely used oxime particularly in developing countries despite the fact that it is the least-effective among therapeutically available oximes like obidoxime, trimedoxime and HI-6. Obidoxime has been reported the best for insecticide/pesticide OPCs and HI-6 is considered good for nerve agent OP.

The concept for oxime use in OP poisoning, as proposed by Wilson in 1959[27] for the first oxime pralidoxime, was that organophosphorus poisoned acetylcholinesterase is not completely dead. Instead, the poisoned enzyme retains the catalytic ability to transfer its blocking organophosphorus group away from its enzyme's active site and on to pralidoxime. Oximes reactivate phosphylated cholinesterase by displacing the phosphoryl moiety from the enzyme by virtue of their high affinity for the enzyme and their powerful nucleophilicity.

Clinical view on the value of oximes as adjuncts in the therapy of OPC poisoning of human remains divided. It has been argued that oximes are unnecessary when intoxication is not severe.[6]

Clinical experience with oximes as a whole was reported disappointing by some clinicians and researchers.[28,29] etc. The negative results of oximes have been reported by clinicians mainly from Asian countries and their opinion is based on poorly designed studies like suboptimal dose, short duration of treatment etc. and some of the studies did not follow WHO recommendations.[30]

In fact, there are some limitations with oxime therapy. An oxime may be effective against specific organophosphorus anticholinesterase and ineffective for others. For instance, obidoxime is good for most of the OPCs used in pesticides, but not for all the structurally different OPCs. Hence, there would be very limited basis for choosing an effective oxime for unknown OPC exposure. Secondly, AChE inhibited by OPC anticholinesterase undergoes process of ageing and the oximes do not work on aged or inactive enzymes. Different OPCs have different time periods or half-life for ageing ranges from a few minutes to many days. Dosing and time of treatment also play a role in a successful oxime therapy. In short, there are many factors that influence oxime efficacy and the studies earlier mentioned with negative reports may not have considered all the factors for the success or failure of oxime therapy.

During the last two decades hundreds of new oximes were synthesised in different parts of the world. Kamil Kuca group in the Czech Republic are synthesising K-series of oximes with different structural molecules. The K-oximes were basically targeted for Tabun and other OP nerve agents,[31] but tests were extended for pesticides-induced AChE inhibition and found promising potential. More than 200 structurally different K-oximes have been synthesised since 2003, the most promising among them is K-27 which worked well against nerve agents[32] as well as pesticides[33,34] (Table). K-27 is a promising candidate to replace therapeutically available oximes with respect to insecticide and pesticide organophosphorus poisoning.[35]

Conclusion

The overview corroborates that the bioscavenger approach is meant and developed for pre-treatment in case of nerve agent exposure in a military combat. Its full benefits depend upon follow-up with standard treatment, which includes atropine and oxime. Moreover, it may be speculated that the method may be confined to certain advanced countries because of its cost and technique. Secondly, OP nerve agent exposure is not a global problem like OP pesticide misuse which every year claims hundreds of lives particularly in the third world. However, the success of this approach in its specific environment may not be under-rated.

The alkainisation approach seems effective and is also being used in many medical setups, but it is still inconclusive whether only sodium chloride should be used for alkalinisation or any other compound may be equally effective. Secondly, the use of standard therapy in conjunction has been recommended which means standard therapy remains the gold standard and has wider benefits.

The use of reversible weak inhibitors against strong irreversible inhibitors theory has not shown a striking achievement other than the fact that the pyridostigmine as pre-treatment drug is in use as a military combat medicine, and is the only FDA-approved drug based on the concept.

It may, therefore, be concluded that the

atropine+oxime+benzodiazepine plus supportive measures will remain a golden treatment protocol with only a replacement of oxime with a broad spectrum and more effective oxime, like K-27, which is a candidate oxime to replace the existing therapeutically available oximes for adjunct treatment in pesticide poisoning. The compound may be easily available across the world, without any specialised technical requirement.

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References

1. Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. Lancet 2008; 371: 597-607.
2. Petroianu GA. Poisoning with organophosphorus compound (OPC): Mythology vs. Reality. The Middle East J Emer Med 2006; 6: 3-8.
3. Eddleston M, Gunnell D, Karunaratne A, de Silva D, Sheriff MH, Buckley NA. Epidemiology of intentional self-poisoning in rural Sri Lanka. Br J Psychiat 2005; 187: 583-4.
4. Lallement G. [Interest in an glutamate antagonistic compound for the treatment of organophosphate poisoning]. Ann Pharm Fr 2000; 58: 17-9.
5. Peter JV, Moran JL, Pichamuthu K, Chacko B. Adjuncts and alternatives to oxime therapy in organophosphate poisoning--is there evidence of benefit in human poisoning? A review. Anaesth Intensive Care 2008; 36: 339-50.
6. Johnson MK, Jacobsen D, Meredith TJ, Eyer P, Heath AJ, Ligtenstein DA, et al. Evaluation of antidotes for poisoning by organophosphorus pesticides. Emergency Medicine 2000; 12: 22-37.
7. Buckley NA, Eddleston M, Li Y, Bevan M, Robertson J. Oximes for acute organophosphate pesticide poisoning. Cochrane database of systematic reviews (Online). 2011(2):CD005085.
8. Placcio DC. New approach to treatment of OP poisoning. Ant Med Medelin 1982; 31: 1-2.
9. Cordoba D, Cadavid S, Angulo D, Ramos I. Organophosphate poisoning: modifications in acid base equilibrium and use of sodium bicarbonate as an aid in the treatment of toxicity in dogs. Vet Hum Toxicol 1983; 25: 1-3.
10. Balali-Mood M, Shahab-Ahmadi A, Salimifar M, Shariate M, editors. Effects of sodium bicarbonate in organophosphate pesticide poisoning. Proceedings of Chemical and Biological Medical Treatment Symposium (CBMTS) III; 2000; 7-12; Spiez, Switzerland.
11. Antonijvic B, Stefanovic D, Milovanovic ZA, Stojiljkovic MP, Bokonjic D, Dukic M, editors. Standard antidotes along with sodium bicarbonate in organophosphate poisoning. Proceedings of Chemical and Biological Medical Treatment Symposium (CBMTS) IV; 2002 April 28 - May 3; Spiez, Switzerland.
12. Betten DP, Vohra RB, Cook MD, Matteucci MJ, Clark RF. Antidote use in the critically ill poisoned patient. J Intensive Care Med 2006; 21: 255-77.
13. Vucinic S, Ercegovic G, Djordjevic D, Jovanovic M, Vukcevic-Perkovic N, Potrebic O, et al. What are the Clinical Significance of Oxime and Sodium Bicarbonate Therapy for Acute Organophosphate Poisoning? J Med Chem Biol Radiol Def 2010: 128.
14. Roberts D, Buckley N. Alkalinisation for organophosphorus pesticide poisoning. Cochrane Database Syst Rev 2005; 1.
15. Masson P, Rochu D. Catalytic bioscavengers against toxic esters, an alternative approach for prophylaxis and treatments of poisonings. Acta Naturae 2009; 1: 68-78.
16. Wolfe AD, Rush RS, Doctor BP, Koplovitz I, Jones D. Acetylcholinesterase prophylaxis against organophosphate toxicity. Fundam Appl Toxicol 1987; 9: 266-70.
17. Doctor BP, Saxena A. Bioscavengers for the protection of humans against organophosphate toxicity. Chem Biol Interact 2005; 158: 167-71.
18. Ashani Y. Prospective of human butyrylcholinesterase as a detoxifying antidote and potential regulator of controlled-release drugs. Drug Development Research 2000; 50: 298-308.
19. Broomfield CA, Maxwell DM, Solana RP, Castro CA, Finger AV, Lenz DE. Protection by butyrylcholinesterase against organophosphorus poisoning in nonhuman primates. J Pharmacol Exp Ther 1991; 259: 633-8.
20. Saxena A, Luo C, Chilukuri N, Maxwell DM, Doctor BP. Novel approaches to medical protection against chemical warfare nerve agents. In: Romano JA, Jr, Lukey BJ, Salem H, editors. Chemical Warfare Agents: Informa Healthcare; 2007; pp 145-73.
21. Lenz DE, Yeung D, Smith JR, Sweeney RE, Lumley LA, Cerasoli DM. Stoichiometric and catalytic scavengers as protection against nerve agent toxicity: a mini review. Toxicology 2007; 233: 31-9.
22. Cohen O, Kronman C, Chitlaru T, Velan B, Shafferman A. Uses of chemically-modified cholinesterases for detoxification of organophosporus compounds. US Patent 20,040,147,002; 2004.
23. Pichamuthu K, Jerobin J, Nair A, John G, Kamalesh J, Thomas K, et al. Bioscavenger therapy for organophosphate poisoning - an open-labeled pilot randomized trial comparing fresh frozen plasma or albumin with saline in acute organophosphate poisoning in humans. Clin Toxicol (Phila) 2010; 48: 813-9.
24. Gordon JJ, Leadbeater L, Maidment MP. The protection of animals against organophosphate poisoning by pretreatment with a carbamate. Toxicol Appl Pharmacol 1978; 43: 207-16.
25. Petroianu GA, Hasan MY, Nurulain SM, Nagelkerke N, Kassa J, Kuca K. New K-Oximes (K-27 and K-48) in Comparison with Obidoxime (LuH-6), HI-6, Trimedoxime (TMB-4), and Pralidoxime (2-PAM): Survival in Rats Exposed IP to the Organophosphate Paraoxon. Toxicol Mech Methods 2007; 17: 401-8.
26. Bartling A, Thiermann H, Szinicz L, Worek F. Effect of metoclopramide and ranitidine on the inhibition of human AChE by VX in vitro. J Appl Toxicol 2005; 25: 568-71.
27. Wilson IB, Ginsburg S, Quan C. Molecular complementariness as basis for reactivation of ackyl phosphate — inhibited enzyme. Arch Biochem Biophysic 1958; 77: 286-96.
28. Peter JV, Cherian AM. Organic insecticides. Anaesth Intensive Care 2000; 28: 11-21.
29. Buckley NA, Eddleston M, Dawson AH. The need for translational research on antidotes for pesticide poisoning. Clin Exp Pharmacol Physiol 2005; 32: 999-1005.
30. Jokanovic M. Medical treatment of acute poisoning with organophosphorus and carbamate pesticides. Toxicol Lett 2009; 190: 107-15.
31. Kassa J, Kuca K, Bartosova L, Kunesova G. The Development of New Structural Analogues of Oximes for the Antidotal Treatment of Poisoning by Nerve Agents and the Comparison of Their Reactivating and Therapeutic Efficacy with Currently Available Oximes. Curr Org Chem 2007; 11: 267-83.
32. Musilek K, Kuca K, Jun D, Dohnal V, Dolezal M. Synthesis of the novel series of bispyridinium compounds bearing (E)-but-2-ene linker and evaluation of their reactivation activity against chlorpyrifos-inhibited acetylcholinesterase. Bioorg Med Chem Lett 2006; 16: 622-7.
33. Petroianu GA, Nurulain SM, Nagelkerke N, Shafiullah M, Kassa J, Kuca K. Five oximes (K-27, K-48, obidoxime, HI-6 and trimedoxime) in comparison with pralidoxime: survival in rats exposed to methyl-paraoxon. J Appl Toxicol 2007; 27: 453-7.
34. Nurulain SM, Lorke DE, Hasan MY, Shafiullah M, Kuca K, Musilek K, et al. Efficacy of eight experimental bispyridinium oximes against paraoxon-induced mortality: comparison with the conventional oximes pralidoxime and obidoxime. Neurotox Res 2009; 16: 60-7.
35. Kuca K, Musilek K, Jun D, Pohanka M, Ghosh KK, Hrabinova M. Oxime K027: novel low-toxic candidate for the universal reactivator of nerve agent- and pesticide-inhibited acetylcholinesterase. J Enzyme Inhib Med Chem 2010; 25: 509-12.