

REVIEW ARTICLE

ANTI-HISTAMINES: PROMISING ANTIDOTES OF ORGANOPHOSPHORUS POISONING

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Summary

Organophosphorus (OP) is a large group of compounds with a wide variety of applications. The group comprises insecticides, pesticides and nematocides etc. in addition to deadly poison OP warfare chemicals like sarin and tabun. Thousands of casualties have been reported globally each year by the unintentional and intentional use of OP compounds. Uses of deadly poison OP like sarin by terrorists groups and irresponsible regimens have been documented as well. The threat always exists. The mainstream therapy includes administration of atropine, pralidoxime and benzodiazepines in addition to general supportive measures. Despite this standard therapy, the mortality rates of OP poisoning are still high. Different approaches and methodologies have been postulated and introduced as an alternative to standard therapy but none could replace the existing standard therapy. The present short review examined the possibility of usage of antihistamines as alternate to atropine. Pros and cons have been discussed. The study suggests that some of the first generation antihistamines like promethazine and diphenhydramine may be effectively used as antidote for OP poisoning depending upon the degree of poisoning. They may have several advantages like inexpensive, systematically and centrally acting anticholinergic antihistamines, readily crosses blood-brain barrier, and large quantities of the drug exist in most hospitals and pharmacies, providing a reservoir in the event of a mass casualty event. However, further clinical studies and evidences are warranted.

Key words: Antihistamines; organophosphorus compounds; antidotes; promethazine; diphenhydramine

INTRODUCTION

Organophosphorus (OP) compounds usage cause poisoning whether intentional or unintentional and leads several thousands of deaths each year across

the world. The OP compounds directly or indirectly constitute a significant share of all the pesticides available in the market. Based on present extensive practice of these compounds, it has been extrapolated that an increased demand for their use in agriculture is likely to continue into the future. A recent report from the global market research and Consultancy Company in the USA (M&M) states that 'organophosphate pesticides are expected to have a high market share by 2015'. Exposure to OP based pesticides are associated with the populations such as agricultural workers, crop duster pilots, ground crews, florists, gardeners, exterminators, pesticide manufacturers,

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pet groomers and workers working in several sectors like nursery, Greenhouse, mosquito abatement, pest control and veterinary care etc. The unintentional or suicidal uses of OP compounds are frequent in developing countries which accounts thousands of deaths each year. The exposure of the compound is not limited to certain sectors of the population. On the contrary, almost every section of society, including those serving in defense and military are at the risk of exposure too.

This is further complicated by the newly emerging security threats for terrorist use and the irresponsible use of these compounds by certain regimes as reported very recently [1]. The present study was aimed to screen the potency of antihistamines as effective antidotes for poisoning of OP compounds. The available evidences are summarized in table 1. The review will provide an insight into the future direction and development of antihistamines as antidote of OP poisoning.

Table 1. Summary of investigated antihistamines against OP intoxication

Antihistamines	Treatment / subject; human or animal studies	Type of OP	Conclusion	References
Chlorcyclizine, Cyclizine	Pretreatment/mice	Parathion, paraoxon, TEPP, EPN, malathion	Marked survival protection	Welch and Coon 1964 [24]
Diphenhydramine	Sub-acute/dog	Fenthion	Effective in treating OP-induced neuromuscular weakness	Clemmons et al. 1984 [25]
Diphenhydramine	Pretreatment/mice	Fenamiphos, DDVP	Increased the percentage of survivors	Mohammad et al. 1989 [26]
Diphenhydramine	Mice	DDVP	Effective against DDVP poisoning	Faris and Muhammad 1996 [27]
Diphenhydramine	Pretreatment & simultaneous application /mice	DDVP	Pretreatment with DPH produced significant number of survival. Simultaneous treatment did not improve survivability	Faris and Muhammad 1997 [28]
Diphenhydramine	Pretreatment/rats	DDVP	DPH significantly reduced mortality in rats with acute, severe dichlorvos exposure	Bird et al. 2002 [29]
Diphenhydramine	Pretreatment/rats	DDVP	Effective in acute poisoning	Bird et al. 2003 [4]
Diphenhydramine	Post-treatments/rats	Fenthion	DPH significantly reduced myocardial injury, including edema, inflammation, vacuolization and necrosis	Yavuz et al. 2008 [30]
Diphenhydramine	Acute study/chicks	DDVP	DPH has protective effects against DDV poisoning in chicks	Mohammad et al. 2012 [31]
Chlorpheniramine	Acute study/chicks	DDVP	Chlorpheniramine have protective effects in case of DDVP poisoning in chicks resembling that of atropine	Mousa 2009 [32]
Diphenhydramine	Post-treatment/rats	DDVP	The antidotal effect of DPH appeared to be comparable with that of the atropine	Muhammad et al. 2002 [33]
Promethazine	Pre & post treatment/rats	Soman poisoning	Effective against soman poisoning	Kan et al. 2008 [21]
Flunarizine	Pretreatment/rats	Soman poisoning	No promising effect	Carpentier et al. 2004 [34]

Treatment options

The standard management of the poisoning by OP compounds involves a therapeutic regimen of atropine+oxime+benzodiazepines along with other symptomatic and supportive measures. Non-regular antidotes include clonidine, fresh frozen plasma, magnesium sulphate, activated charcoal, milk

and some other home remedies [2]. Other experimental approaches include the use of NMDA receptors antagonists, weak inhibitors vs strong inhibitors, alkalization of plasma and the use of bio-scavengers i.e. exogenous enzymes and hemoperfusion, etc. The non-regular antidotes did not garner much attention among the scientific community as well as clinicians for some unknown reasons.

Other investigational approaches are in infancy and did not reach a concrete conclusion and probably suffered with insufficient evidences from experimental studies. However, advances have been made on the use of exogenous enzymes but practically their use is not cost effective therefore it is of enormous concern and out of reach of mass population worldwide. There is a pressing need to find alternative, cheaper and easily available antidotes for OP poisoning. While antidotes for OP exposures exist, terrorist attacks and recent reports on the use of sarin against civilian [1] have raised the concerns for the availability of antidotes in the event of poisoning involving a large number of persons. In the event of antidote shortage or when there is an urgent unmet need of antidotes, it is important to have known alternative anticholinergic agents that may improve treatment efficiency at different stages of the OP poisoning.

Literature survey

To identify all published articles on the topic, we performed searches in Pub Med Central, Scopus, Medline Plus, Oxford journal online, Biomed Central, EMBASE, Science direct, Entrez PubMed, Cochrane library, DOAJ and Cambridge journal online and TOXNE. The keywords for search were antihistamines and organophosphorus poisoning, antihistamines and organophosphate poisoning, first generation antihistamines and organophosphorus poisoning, antihistamines, antidotes and organophosphates. The literature search was performed in March 2014. No specific period was specified to retrieve the published articles from the earliest possible dates. The results of the literature search were not restricted to any specific type of the article, however limited to the English language of the publication. Article title and abstracts which were judged to be devoid of any information on the subject were out of the scope of the review and excluded from further review.

The literature search retrieved thirteen articles on the subject with eight on diphenhydramine and five on other antihistamines. The earliest report became available in 1963 and the most recent available publication on the subject appeared in 2012, till date following the different search engines and data bases for information retrieval. Majority of the available studies were conducted on mice, rats, chicks, and dogs. Except one, all the available reports revealed the benefits of antihistamines in OP poisoning and concluded that antihistamines could be the potential antidotal agents and can be promising

based on their positive efficacy and anticipated safety. Results from these retrieved studies are summarized in synoptic table as represented in table 1.

HISTAMINES AND ANTIHISTAMINES IN BRIEF

Histamine, a biogenic monoamine was first synthesized in 1907 and released from mast cells. Upon activation mast cells can undergo an anaphylactic or piecemeal degranulation-dependent or -independent mediator secretion, resulting in rapid or slow release of soluble mediators, such as serine proteinases, histamine, lipid-derived mediators, cytokines, chemokines and growth factors. Mast cells express different receptors and ligands on the cell surface, molecules that can activate the cells of the immune system, such as different subsets of T cells. Histamine plays an important role in several physiological functions, including induction of inflammatory reactions. The elucidation of its role in health and disease and its molecular mechanism of action have been continuous, reflecting the application of advances in scientific knowledge, technology and therapeutics over the last 100 years. The diverse functions of histamine, which include neurotransmission, regulation of gastric acid production, vasodilation and smooth muscle contraction are mediated on the cellular level by four G-protein-coupled specific histamine receptor subtypes, referred to as histamine H1 receptor (H1R), H2R, H3R and H4R. The histaminergic system has a role in the treatment of allergic inflammatory disorders by the development of histamine receptor agonists, antagonists. Antagonists of histamine receptors (H1 and H2) are among the most prescribed drugs worldwide. Convincing number of studies demonstrate that the H1R and H4R are responsible for allergic inflammation, hence they could be an important and critical player in the OP poisoning where inflammation is one of the reasons of death and disability and it is desired to be treated in first instance following the antidotes.

ANTI-HISTAMINES IN ORGANOPHOSPHORUS POISONING

The present review evaluates the available literature for the use of antihistamines in OP poisoning. A number of alternative therapies for OP poisonings

have been well explored in the past that could potentially be useful in emergency situations of antidote shortages. For instance, it has been demonstrated that glycopyrrolate, an antimuscarinic agent, is equally effective with less central nervous system side effects and a greater control of salivary, tracheobronchial, and pharyngeal secretions [3]. However, glycopyrrolate does not cross the blood brain barrier and it is not expected to control central cholinergic toxicity. Moreover, early death due to OP poisoning appears to be a centrally mediated process [4]. The pharmacological evolution of antihistamines revealed three generations of products differing at the levels of specificity, half-life and duration of action, safety and toxicity. The first generation antihistamines have the advantages over the others due to their diverse pharmacological activities which are desirable in OP poisoning. The pharmacological benefits of first generation antihistamines are numerous like they are centrally acting, exhibiting antimuscarinic and anticholinergic activities, crossing the blood brain barrier, widely available, easily accessible and less expensive with time tested safety over other antidotes. They also commendably reduce edema, which is one of the major reasons in OP poisoning related death.

Furthermore, delayed adverse outcomes due to inflammatory responses are speculated to be improved by the use of antihistamines, owing to its effects on inflammation and role in regulation of inflammation and pain. Some of the first generation antihistamines, particularly belonging to phenothiazine group are found to be alpha-7 nicotinic acetylcholine (α -7nACh) receptor antagonists [5] which may contribute to the neuro-protective effect. Some of the first-generation H1 antihistamines like promethazine are non-selective in binding to the H1 receptors and have alpha-adrenergic blocking effects. Similarly, pyrilamine has been reported to inhibit catecholamine secretion as well as nACh inhibitor [6]. Currently, H1 antihistamines are the second most commonly prescribed class of medications after antibiotics. More than 40 different forms of H1 antihistamines are currently used in clinical practice worldwide [7]. However, the literature search did not reveal enough studies on application of histamines in OP compounds intoxication. Secondly, investigations were mainly focused on diphenhydramine, a H1 antihistamine.

The hallmark of OP toxicity is the inhibition of acetylcholinesterase. However, many other non-cholinergic co-lethal factors play role in mortality

and morbidity. One among the many effects of OP agents in intoxication is the modulation of early phase allergic reactions mediated by specific IgE antibodies and stimulation of mast cell degranulation, possibly causing the release of histamine or histamine-like compounds precipitate the inflammation [8]. Such biological effects could be translated in humans too and supposedly play a critical role in instituting the inflammatory reactions and resultant cascade. According to Cowan et al. [9] OP induced cholinergic crisis is often accompanied by toxicity induced by non-cholinergic mechanisms, including anaphylactic shock. OP-induced anaphylaxis is induced by autacoids, such as histamine and platelet activating factor (PAF), and serine proteases [9]. Activation and degranulation of mast cells and basophils release histamine, cytokines; tumor necrosis factor- α (TNF- α), interleukin-1beta (IL-1 β), eicosanoids (prostaglandin D2 and leukotriene C4), and other mediators into the extracellular environment which sets the development of anaphylaxis. Histamine released from mast cells binds to H1 histamine receptors and increase capillary permeability and initiate vasodilation and inflammatory responses [10]. There are substantial evidences that at least some OP compounds induce anaphylaxis by stimulating the release of autacoids from mast cells and basophils. Exposure of an OP compound, Soman has been shown to induce mast cell degranulation in rats in a dose-dependent manner [11] and also provoked a calcium-dependent release of histamine from rat peritoneal mast cells [12]. Whereas, another OP compound, Sarin reported to elevate histamine levels in the bronchoalveolar lavage of guinea pigs [13]. In another study, an agent malathion in mice following oral exposure shown to increase the macrophage function, measured by respiratory burst activity of peritoneal macrophages [14-15] and this malathion-induced macrophage activity was influenced by inflammatory mediators released from mast cells [16-17]. Moreover, malathion metabolites also induce histamine release from basophils and peritoneal mast cells [18]. Antihistamines also act as anti-inflammatory agents by preventing histamine release from mast cells and/or stabilizing histamine receptors in an inactive conformation. Additionally, antihistamines inhibit the expression of intracellular adhesion molecules (ICAM-1), prevent release of prostaglandins, and regulate release of pro-inflammatory cytokines from T lymphocytes and epithelial cells [19]. It is suggested that sufferers of OP poisoning may benefit from the potential anti-inflammatory properties of the antihistamines [10].

The OP poisonings are also associated with cardiac complications within few hours of exposure including myocardial infarction. The increase in catecholamines release and other vasoactive amines like neutral proteases along with histamines are one of the causative factors for myocardial infarction [20]. It is established that acute and chronic OP intoxication induces inflammation [10] which is neurotoxic as well as neuroprotective. The inflammation triggers the release of IL-1 β , which is also a stimulant to release histamines [18]. The acute inflammation may lead to sepsis and death and may act as a co-mortality factor in OP poisoning. Histamine, like many other transmitters, mediates responses via receptors like H1 receptors for first generation antihistamines. According to Nettis et al. [19] antihistamines may exert anti-inflammatory effects both ways, either receptor-dependent or -independent mechanisms.

Now, the question arises, which antihistamine is suitable among the four different groups/generations of antihistamines for OP intoxication. There is no clear answer and explanation available in the literature. However, the available literature review reveals that majority of the first generation antihistamines have been mainly investigated in OP poisoning. Even among the six sub groups of first generation antihistamines, diphenhydramine (ethanolamine) was investigated by a number of investigators. A group of researchers from army medical research institute of chemical defense, Aberdeen, UK found promethazine as an effective antidote for soman poisoning in rats [21]. Promethazine use as antihistamine is very old and used in the clinics since several decades. Its pharmacokinetics and toxicity are well documented and established. It is believed to be available in almost all the clinical settings or assumed to have easy availability and wide accessibility being an over the counter (OTC) drug. In addition to antihistaminic activity, it is being a potent anticholinergic (both muscarinic and nicotinic) and a centrally acting action as well as a tentative α -7 nicotinic acetylcholine channel inhibitor. The authors concluded this drug as an efficient antidote owing multifunctional properties for organophosphorus poisoning.

LIMITATIONS

There are several limitations with the use of antihistamines as an antidote of OP compounds toxicity or poisoning. They are enumerated below:

1. Cardiac complications of OP intoxication include tachycardia or bradycardia (depending on whether nicotinic or muscarinic effects predominate), and irregular beats represented by ventricular tachyarrhythmia. The rate-corrected QT interval (QTc) in electrocardiogram represents electrical depolarization and repolarization of the ventricles. A lengthened QTc interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. Some of the first generation antihistamines also exhibit prolonged QTc. However, it is not clear whether cardiac manifestation is the direct effect of OP intoxication or a secondary complication of OP toxicity due to release of catecholamines and histamines etc. Though, despite this fact, that antihistamines like promethazine and diphenhydramine are non-prescriptive and available as over the counter drug in most of the countries around the world. The easy availability, cost effectiveness and wide accessibility over the counter are suffice to demonstrate its time tested safety and efficacy over other antihistamines. However, the potential risks cannot be excluded, thus it is suggested that the use of antihistamines should not be underestimated for the effective and alternative treatment. Large scale studies particularly for this indication in OP poisoning should be undertaken to provide a proof of concept and unequivocal evidence.
2. The other major concern lies in the convenience of the route of drug delivery for a prompt action. The parenterals (i.e. injections) of the drugs are obviously preferred for a prompt action in case of urgent need under acute conditions. Though some of the antihistamines are available as injectable, all the antihistamines are not available in the injectable forms. In the context of different routes of drug delivery, Geller et al. [22] and Rajpal et al. [23] reports that alternative formulations may be used in case of need. For instance, reconstitution of powdered atropine is a workable option in mass-casualty settings [22]. Similarly, Rajpal et al. [23] revealed the clinical safety and usefulness of sublingual atropine in healthy volunteers. Another route of administration could be applied to other agents and may offer potential benefits for the OP poisoned patient, especially in a mass-casualty scenario.
3. The literature search revealed very meagre studies on animal models and provides only limited

mechanistic insight. Large randomized and systemic investigations are needed to translate the work for human use.

CONCLUSION AND FUTURE PROSPECTS

In the preview of the available limited literature, the randomized controlled trials are needed to demonstrate the anticipated efficacy of antihistamines and relative safety in OP poisonings. From the literature review, it appears that promethazine may have greater potential as alternative to atropine, presently used antidote for OP poisoning owing to the mainly antimuscarinic action of atropine. In addition to the antihistaminic actions, promethazine also possesses an antimuscarinic, antinicotinic and neuroprotective properties for delayed toxicities and improves well-being. The easy availability, accessibility and applicability along with relatively established safety profile may further prompt its utility as an antidote in OP poisoning. The scope of using antihistamines in OP poisoning is encouraging based on the evidences available from few studies. However, many more studies are warranted in order to provide experimental evidences and the translation of experimental findings in humans, considering the pharmacological efficacy and speculated benefits of antihistamines in OP poisoning. The major concern of use of antihistamines are the numerous mechanistic studies which reveal that some of the antihistamines exhibit cardiotoxic effects due to the inhibition of repolarization potassium channels, which leads to prolongation of the action potential, QTc interval. Therefore, the patients at risk such as those with congenital long QTc syndrome, cardiac disease, liver disease, electrolyte disturbance, or those taking drugs that can prolong QTc interval, should be cautious in using antihistamines. The evidence available with antihistamines so far indicates that the potential to cause ventricular arrhythmias is not a class effect rather an antihistamine specific effect. For instance, loratadine and metabolites of ebastine are devoid of QTc interval prolongation and other adverse electrocardiogram effects.

It is awaited that investigating the potential of many more available antihistamines in OP poisoning as well as investigating their arrhythmogenic potential will help to address the antidotal efficacy and safety of antihistamines in OP poisoning. Momentarily, similar to antihistamines, organophosphorus compounds differ in their

toxicodynamics and are diversified in their action, therefore, further studies on different groups of organophosphorus compounds as well as antihistamines will be able to address the concern of potential antidotal efficacy and safety.

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