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Review

ANTIOXIDANTS IN ORGANOPHOSPHORUS COMPOUNDS POISONING

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Oxidative stress has recently been implicated as a factor in the mortality and morbidity induced by organophosphorus (OP) compound poisoning. An overwhelming number of research papers are based on studying at the cellular and organ level. Such studies have concluded that antioxidants can be used as an adjunct compound in the treatment of both chronic as well as acute OP poisoning. Still, the role of antioxidants in reducing the mortality and morbidity induced by OP compounds has scarcely been verified, as well as their role as adjunct treatment compounds for both structurally and functionally different OP compounds. The present review of the literature was undertaken to establish the role of antioxidants in survival studies following acute exposure to OP compounds. The review found no substantial evidence that antioxidants demonstrate any positive effect following extremely toxic poisoning. However, for a more comprehensive and rational conclusion, further research needs to be conducted.

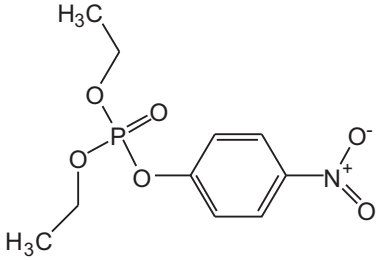
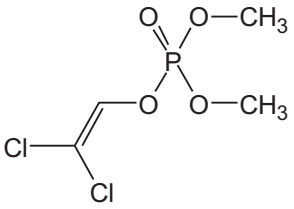
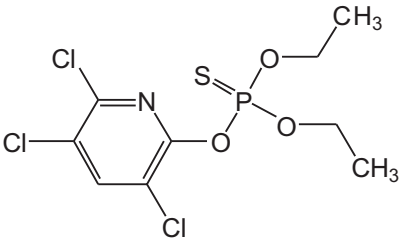
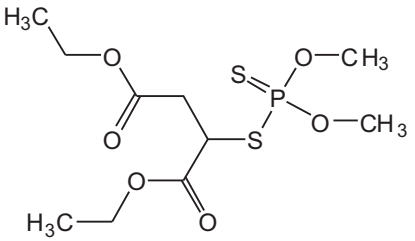
KEY WORDS: *acute poisoning, oxidative stress, survival study*

Intoxication by organophosphorus compounds

The history of organophosphorus compounds (OP) and their poisonous effect stretches throughout more than a century. These compounds manifest their toxicity by irreversibly inhibiting the enzyme acetylcholinesterase at the nerve synapse. Despite decades-long research, mortality caused by acute OP poisoning continues to be high (1), while no new standard therapies are being introduced. There are over 150 different types of synthesized OPs, though their generalized structure is much the same. Each OP has a unique profile of toxicity and behaviour. For instance, death due to dichlorvos poisoning occurs very rapidly, while dimethoate toxicity takes several hours to develop (2), even though both belong to the same OP class. From the standpoint of chemistry, OP compounds comprise organophosphates, organophosphonates and organophosphinates, each of which is further divided into sub-groups. Other classifications of OPs are based on the lethality of a compound. According to the classification of the World Health Organisation (WHO) (3), Class Ia belongs to extremely toxic OPs, Ib are highly toxic, Class II comprises moderately toxic, whereas Class III consists of mildly toxic OP compounds. Some examples are shown in Table 1. In addition, there are also the deadly organophosphorus chemical weapons (OPWs), called nerve agents.

Acute organophosphate insecticide poisoning manifests itself through three different phases of toxicity; namely, acute cholinergic crisis, which occurs from within a few minutes to twenty-four hours;

Table *1 Structure of organophosphorus compounds belonging to different class of OP insecticides*

Organophosphorus compounds (WHO's hazardous level)	Structures
Paraoxon- ethyl (Extremely hazardous; Class Ia)	
Dichlorvos (Highly hazardous; Class Ib)	
Chlorpyrifos (Moderately hazardous; Class II)	
Malathion (Slightly hazardous; Class III)	

intermediate syndrome (IMS), which sets in 48 h to 96 h after exposure; and delayed neuropathy (4). Acute cholinergic crises and IMS have been considered a major contributing factor in organophosphate-related morbidity and mortality because of their frequent occurrence and probable causative role in respiratory failure. Appropriate therapy leads to a complete recovery within 5 to 18 days (4).

Standard and non-standard therapy

Standard therapeutic treatment of OP poisoning includes atropine, oximes, and benzodiazepines accompanied by supporting measures (5). The use of oximes has frequently been deemed controversial (6). Supporting measures include proper ventilation and the decontamination of skin and body parts by an alkali solution, by specific decontamination kits, etc. Petroianu (5**)** named the treatment of OP poisoning AFLOP; an abbreviation for atropine, fluid, oxygen, and pralidoxime (oxime). Atropine relieves muscarinic signs and symptoms, while oximes (pralidoxime/ obidoxime/HI-6, etc.) shorten the duration of respiratory muscle paralysis through acetylcholinesterase reactivation. Benzodiazepines are used to control OP-induced seizures. In warfare, alongside regular therapy, pre-treatment with pyridostigmine is recommended (7). Some of the non-regular antidotes include clonidine, fresh frozen plasma, magnesium sulphate (8), N-acetylcysteine (9), activated charcoal, milk and certain other home remedies (10, 11), but their

effectiveness has not yet been sufficiently established (12). Other experimental approaches include the use of NMDA receptor antagonists such as gacyclidine (13), haemoperfusion (10) and the nanocarrier of magnetic magnesium (14). Non-regular antidotes for some reason usually do not receive attention from the scientific community, so the related scientific reports are negligible. Approaches such as the alkalization of blood plasma, use of weak inhibitors against strong inhibitors or use of bioscavengers are very popular but have not gained validity.

Oxidative stress and use of antioxidants in OP poisoning

The imbalance between the production of free radicals and antioxidant defences in the body is called oxidative stress and has significant health implications. Oxidative stress is a major mechanism in the pathophysiology of several toxins and diseases. In addition, oxidative stress is also a process related to xenobiotic exposure and different levels of environmental contamination. It has recently been

Table 2 *The oxidative stress in chronic/sub-chronic OP poisoning at organ level studies.*

Reference	OP compounds	Organ studied
Srivastava and Shivanandappa 2011 (37)	Dichlorvos (Highly toxic)	Rats brain
Bhatti et al., 2011 (38)	Ethion (Moderately toxic)	Erythrocytes
Amara et al., 2011 (39)	Dimethoate (Moderately toxic)	Liver
Dwivedia and Flora 2011 (40)	DDVP and monocrotophos (Highly toxic)	Blood, brain, liver
Dirican and Kalender 2011 (41)	Dichlorvos (Highly toxic)	Testes
Ojha et al., 2011 (42)	Chlorpyrifos, malathion, methyl parathion (Moderately/mildly/extremely toxic)	Liver, brain, kidney, spleen
Ehrich et al., 2011 (43)	Paraoxon and DDVP Extremely/highly toxic	Human neuroblastoma SH-SY5Y cells
Lua et al., 2010 (44)	Omethoate (Highly toxic)	Liver
Lukaszewicz-Hussain 2010 (24)	Review: oxidative stress and its role in toxicity of organophosphate insecticides	Oxidative stress by OP leads to organ damage.
Cemek et al., 2010 (45)	Fenthion (Moderately toxic)	Different rats tissues
Shah and Iqbal 2010 (46)	Diazinon (Moderately toxic)	Kidney
Kose et al., 2010 (33)	Dichlorvos (Highly toxic)	Blood and Cardiac muscle
Uzun et al., 2010 (47)	Chlorpyryfos (Moderately toxic)	Lung
Kalender et al., 2010 (48)	Malathion	Liver
Mansour and Mossa 2010 (49)	Chlorpyrifos (Moderately toxic)	Suckling pups
Togun et al., 2010 (50)	Dichlorvos (Highly toxic)	Cardiac tissues

Note *Only two reports are related to extremely toxic OPs, whereas the majority of the study covers moderately or highly toxic OP compounds*

Table 3 *Some of the references of acute OP poisoning and status of antioxidants.*

Reference	Type of study / article Tested compounds Organ studied	Conclusion
Dandapani et al., 2003 (17)	Clinical study	Severe and prolonged AChE inhibition is associated with oxidative stress and may contribute to the development and severity of intermediate syndrome.
Kovacic, 2003 (22)	Review	Toxic manifestations of OP are apparently due in part to oxidative stress.
Vidyasager et al., 2004 (18)	Clinical study	The increased level of MDA in OP poisoned patients who failed to survive was probably reflective of oxidative stress, but the patients who did survive after specific treatment did not show change in antioxidant status.
Sharma et al., 2005 (51)	Dimethoate Rat liver and brain	The organophosphate increases the generation of certain free radicals in the liver and brain by alterations to antioxidant status.
Ranjbar et al., 2005 (20)	Clinical study	Oxygen free radicals and their related interactions like lipid peroxidation are present in acute OP poisoning.
Cankayali et al., 2005 (28)	DDVP Rat serum	In addition to classic treatments, drugs with antioxidants might be promising in the treatment of OP poisoning.
Fortunato et al.,2006 (52)	Malathion Rat brain	Malathion induced oxidative stress and modulated SOD and CAT in selective brain regions.
Venkatesh et al., 2006 (35)	Clinical study	Occurrence of oxidative stress in severe acute OP poisoning was evident; however the development of type II paralysis is not associated with the level of oxidative stress.
Gunay et al., 2007 (32)	Survival study on rats DDVP	There was no evidence for increased oxidative stress due to DDVP.
Possamai et al., 2007 (19)	Malathion Rat organs, muscle and serum	Oxidative stress, particularly lipoperoxidation, is involved in OP toxicity.
Yurumez et al., 2007 (30)	Survival study on mice Fenthion	NAC used as an antioxidant improved the survival rate in mice.
Lukaszewicz-Hussain, 2008 (24)	Review OP insecticides	Supplementation with antioxidants may be beneficial in OP poisoning however the rat models do not completely reflect clinical trials.
Jiang et al., 2010 (53)	Methyl parathion Rat plasma and liver	It is also important to administer antioxidants in acute OP toxicity, in addition to standard therapy.
Zhang et al., 2010 (54)	Clinical study	Effective antioxidant therapy may be a therapeutic option following acute organophosphorus poisoning.
Kose et al., 2010 (33)	DDVP Serum Rat cardiac cells	Acute DDVP administration did not cause marked oxidative stress.
Rastogi et al., 2009 (55)	Epidemiological study	Pesticide sprayers exposed to insecticides including OP display more oxidative stress.
Hundekari et al., 2011 (56)	Clinical study	Antioxidant supplementation may be useful to reduce toxic effects in acute OP poisoning in addition to regular therapy.

postulated that OPs produce oxidative stress through the formation of reactive oxygen species (ROS) (15). ROS such as hydrogen peroxide, superoxide anions and hydroxyl radicals are produced in a number of

Table 4 *The antioxidants investigated (last column) against acute/sub-acute OP toxicity for oxidative response in rodents for survival and cellular & organ level studies (25).*

Name of OP compounds	OP class	Type of study	Antioxidant used in the study
Paraoxon-ethyl	Ia; extremely toxic	Survival study	NAC, Glutathione (reduced)
Parathion-methyl	Ia; extremely toxic	Cellular/organ-level study	Not available for acute study
Chlorfenvifos	Ib; highly toxic	Cellular/organ-level study	Not available for acute study
DDVP	Ib; highly toxic	Cellular/organ-level study	NAC
Metasystox	Ib; highly toxic	Cellular/organ-level study	Vitamin E
Methidathion	Ib; highly toxic	Cellular/organ-level study	Vitamin C and E
Monocrotofos	Ib; highly toxic	Cellular/organ-level study	Not available for acute study
Anilophos	II; Moderately toxic	Cellular/organ-level study	Not available for acute study
Chlorpyrifos	II; Moderately toxic	Cellular/organ-level study	Vitamin C, E, melatonin
Diazinon	II; Moderately toxic	Cellular/organ-level study	Vitamin C, E, theophylline, pentoxifylline
Dimethoate	II; Moderately toxic	Cellular/organ-level study	Vitamin C and E
Ethion	II; Moderately toxic	Cellular/organ-level study	Not available for acute study
Fenthion	II; Moderately toxic	Cellular/organ-level study	Vitamin C, E, NAC, melatonin
Fenthion	II; Moderately toxic	Survival study	NAC
Sumithion (Fenitrothion)	II; Moderately toxic	Cellular/organ-level study	Not available for acute study
Malathion	III; Slightly toxic	Cellular/organ-level study	Vitamin E, Ginger, $ZnCl_2$
DFP	Not listed	Cellular/organ-level study	Vitamin E
Menazon	Not listed	Cellular/organ-level study	Not available for acute study

Note *It is evident from the table that* in vivo *survival studies were conducted only with paraoxon-ethyl and fenthion. All the other studies were carried out to evaluate the oxidative responses at cellular and organ level only, which may or may not have implications in pathophysiological conditions but cannot be correlated with mortality/morbidity. There is no correlation study to predict the oxidative response by OP at cellular level and mortality/morbidity.*

cellular reactions by enzymes such as lipoxygenases, peroxidases and dehydrogenases (16). ROS are part of the normal oxidative metabolism, but when produced in excess, they cause tissue injury. The role of oxygen-free radicals has been established in many chronic disorders, but their significance in acute conditions has not been given much attention.

During recent years, oxidative stress has been described as a co-lethal factor in OP-induced poisoning (17-21). Many reviews have stressed the role of oxidative stress in OP poisoning (15, 22-26). Bayrami et al. (27) found oxidative stress and acetylcholinesterase inhibition, along with many other parameters, in farmers chronically exposed to OP, but the name and class of OP exposure was not mentioned and the observed effect was asserted to be due to chronic exposure. Antioxidants have been suggested as adjunct to OP antidotes (28, Tables 2 to 4). One oxime has been reported to possess antioxidant property (29), but among the impressive volume of published articles, only two survival studies documented the benefits of antioxidants. Most of the studies were done on moderately or highly toxic compounds. One paper published in 2007 by Yurumez et al. (30) determined the beneficial effect of *N*-acetylcysteine (NAC) in counteracting the organophosphate fenthion (a moderately toxic OP according to the classification of the WHO) in mice, and demonstrated that NAC has prophylactic as well as therapeutic activity in OP poisoning and clearly improves survival rates in mice. Pena-Llopis et al. (31) showed that NAC increased fish survival following exposure to lethal doses of dichlorvos. These papers described the effectiveness of the antioxidant NAC in acute poisoning. It is also possible that NAC improved the survival rate for another reason; it may have prevented lung-related pathological conditions such as shortness of breath or obstructive pulmonary conditions. Possami et al. (19) showed that the most sensitive targets of oxidative damage after acute treatment with malathion (a mild toxic OP) were the kidneys, lungs and diaphragm, as well as the liver, quadriceps and serum after sub-chronic treatment. Moreover, mortality by OP intoxication is mainly caused by respiratory obstruction,

while most of the mortality in acute OP poisoning results from acute respiratory failure due to central respiratory depression, respiratory muscle weakness, and/or direct pulmonary effects (bronchospasm and bronchorrhea) (2). NAC may also have other roles which can contribute to improving the survival of animals. The protective effect of NAC may only extend to experimental OP fenthion and not to other structurally different OPs. In an acute study on rats, Gunay et al. (32) reported no evidence of oxidative stress due to dichlorvos. Kose et al., (33) concluded that acute dichlorvos administration does not cause marked oxidative stress and probably does not play a major role in dichlorvos-induced poisoning. Nurulain et al. (34) found no survival effect for glutathione reduced (GSH) and NAC with an acute dose of paraoxon (extremely hazardous OP) induced intoxication in Wistar rats. It was evident that NAC and GSH had a negative effect, instead of being protective (unpublished data). In a clinical trial, Venkatesh et al. (35) corroborated that the in-hospital morbidity and mortality of OP poisonings are mostly associated with type II paralysis (intermediate syndrome) and the development of type II paralysis is not associated with the level of oxidative stress. However, there was an early occurrence of oxidative stress in severe acute OP poisoning. This shows that an antioxidant has no role at phase II of acute toxicity. Indirect evidence of oxidative stress in IMS has been reported in a review by Abdollahi and Karami-Mohajeri (36). Other antioxidants used for OP-induced toxicity include vitamin C and E, date palm, etc. (Table 4), but where mixed results were noted, the outcomes describe only the cellular-level damage and biochemical estimation of oxidative stress parameters.

SUMMARY

1. It is evident from the literature that oxidative stress occurs in acute organophosphorus poisoning, but there is no convincing evidence that antioxidants may prevent mortality in acute OP poisoning.
2. Whether all antioxidants are beneficial or merely NAC in certain acute OP poisonings is unclear.
3. Can antioxidants be effective for all classes of OPs? This is an issue that has been completely ignored.
4. Can antioxidants be effective for all phases of acute toxicity? This issue has also been completely ignored.
5. The use of antioxidants might be effective (speculation) in long-term pathophysiological conditions induced by OP compounds through chronic or sub-chronic exposures, or even in the delayed phase of acute OP poisoning.
6. Since antioxidants might not be useful for survival, their inclusion into standard therapy cannot be warranted.

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Sažetak

ANTIOKSIDANSI I TROVANJE ORGANOFOSFORNIM SPOJEVIMA

Oksidacijski stres u novije je vrijeme označen kao faktor pri mortalitetu i morbiditetu uzrokovanom trovanjem organofosfornim spojevima. Sve veći broj studija zasnovan je na proučavanju na razini stanice i organa i takve su studije većinom zaključile da se antioksidansi mogu rabiti kao dodatne tvari pri liječenju kroničnog, ali i akutnog trovanja organofosfornim spojevima. No uloga antioksidansâ u smanjenju mortaliteta i morbiditeta izazvanog trovanjem organofosfornim spojevima još nije u dovoljnoj mjeri potvrđena. Štoviše, funkcija antioksidansâ kao dodatnih tvari pri liječenju i dalje je uvelike nerazjašnjena za strukturalno i funkcionalno različite vrste organofosfornih spojeva. Ovaj pregledni rad napisan je s namjerom određivanja uloge antioksidansâ u studijama preživljavanja zbog akutne izloženosti organofosfornim spojevima. Pregledom se nije utvrdio nijedan čvršći dokaz da antioksidansi imaju pozitivan učinak nakon ekstremno toksičnog trovanja. Međutim za sveobuhvatniji i racionalniji zaključak nužno je dalje proučavanje.

KLJUČNE RIJEČI: *akutno trovanje, oksidacijski stres, studija preživljavanja*

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