Organophosphate and Carbamate Poisoning: Review of the Current Literature and Summary of Clinical and Laboratory Experience in Southern Israel

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Abstract
Organophosphate and carbamate are mainly used to kill insects, thereby protecting livestock, crops, homes and communities. Yet, these compounds also convey great danger. OP and CRB poisoning is an important clinical problem, often life-threatening, especially in the pediatric population in rural areas where reaching a physician or hospital on time is difficult. We present a summary of accumulated toxicological knowledge as well as clinical and laboratory experience from a medical center serving a relatively vast rural area and pediatric population. We stress the importance of knowing how to recognize the classic signs of OP and CRB poisoning and when it is appropriate to investigate for such poisoning even in the absence of those signs. Like any medical emergency, OP and CRB poisoning requires prompt resuscitation and use of antidotes. Atropine, oxygen and fluids are the mainstay of therapy. Oximes, which were found useful in some cases of OP poisoning and useless in some cases of CRB poisoning, are absolutely safe as empiric treatment, which is often needed since the major differential diagnosis of OP poisoning is CRB poisoning, which is clinically indistinguishable. We hope that continuing research will offer further insights into the management of such events, and we are confident that improved medical management of OP and CRB poisoning will result in a reduction of morbidity and other complications associated with intensive care procedures and hospitalization.

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Organophosphate and carbamate are insecticides used against insects in all developmental forms, but mainly to kill mature insects. Common OP compounds used in agriculture are para-thion, malathion, chlorpyrofos and dichlorvos. They are used to protect livestock, crops, homes and communities from the direct and indirect effects of insects and the diseases they carry [1,2]. But these compounds convey great danger. Each year, 500,000 deaths occur in rural Asia due to suicide. It is estimated that 200,000 of these deaths are due to self-OP poisoning [3]. Unintentional exposure is much more common, but almost never lethal [1,2].

Organophosphate compounds exist in a military setting as well. OP-based nerve gas was introduced in several military conflicts and acts of terror in the last few decades [1,2]; common names are sarin, tabun, soman and VX. Discussion of these compounds is beyond the scope of this review.

Organic phosphorus compounds are irreversible cholinesterase inhibitors that are frequently associated with human toxicity due to acetylcholinesterase inhibition [1]. These compounds are chemically defined by a P atom surrounded by four groups or chains of atoms; most of them are O atoms, but S, F, C and N may be found as well. The central P atom is always involved in P=O or P=S bonds; two more side chains, R1 and R2, may be aromatic or aliphatic groups. The fourth group is referred to as “X” or the “leaving group,” which determines many of the characteristics of the compound and serves as a basis for classification of these materials [4].

Diagnosis is made on the basis of clinical suspicion, the characteristic clinical signs, and reduced activity in the blood of butyrylcholinesterase (also known as pseudocholinesterase – PchE, or plasma cholinesterase due to its presence in the plasma) or AChE (also known as true cholinesterase, or red blood cell cholinesterase due to its presence in red blood cells). Patients with severe OP poisoning typically present with signs of muscarinic and nicotinic stimulation and central nervous system toxicity.

The major differential diagnosis is carbamate poisoning, which is clinically indistinguishable [3]. Carbamates are derivatives of carbamic acid. They have the same mechanism of action as OP, but the chemical bond is completely reversible; therefore, when considering non-lethal doses, the assumed duration of the toxic effect is expected to be significantly shorter than that of OP.

Pathophysiology
The primary mechanism of action of OP and CRB is inhibition of ester hydrolases, particularly AChE and PChE. AChE is an enzyme that degrades the neurotransmitter acetylcholine into choline and acetic acid. ACh is found in the central and peripheral nervous system, neuromuscular junctions, and red blood cells. OP inactivates AChE by phosphorylating the serine hydroxyl group located at the active site of AChE. The phosphorylation occurs by loss of an OP leaving group and establishment of a covalent bond with AChE. Once AChE has been inactivated, ACh accumulates throughout the nervous system, resulting in overstimulation of muscarinic and nicotinic receptors. Clinical effects are manifested...
via activation of the autonomic and central nervous systems and at nicotinic receptors on skeletal muscle.

Although OP are usually considered irreversible cholinesterase inhibitors, the OP-AChE bond becomes irreversible only after a second side reaction called “aging” [9], in which one of the R groups leaves the phosphate molecule at a characteristic rate. Different OP compounds have various aging times ranging from 2 minutes for the nerve agent soman to 72 hours for certain insecticides [1,6].

Organophosphates and carbamates can be absorbed cutaneously, ingested, inhaled, or injected. Although most patients rapidly become symptomatic, the onset and severity of symptoms depend on the specific compound, amount, route of exposure, and rate of metabolic degradation. Possible neurological complications are:

- Intermediate syndrome – proximal muscle weakness, respiratory muscle weakness and facial muscle weakness, which usually occurs days to a few weeks after the poisoning.
- Delayed neuropathy – distal muscle weakness, usually occurs weeks to months after the poisoning.

Carbamates inhibit AChE by depositing a carbamyl group on the enzyme, which is then completely inactivated; thus the clinical effect is exactly like OP toxicity. Unlike OP, though, carbamyl groups are weakly bound to AChE, which is believed to spontaneously reactivate rapidly, accounting for the short duration of intoxication [7].

**Cholinesterase assays**

Diagnosis of suspected OP or carbamate poisoning is usually confirmed by an assay to measure cholinesterase activity (both AChE and PChE may be used) in plasma. Currently, most of the laboratories in Israeli hospitals are equipped to reliably measure PChE level in about one hour. However, except for three hospitals, the results of AChE assays are not available in time to assist the diagnostic plan or the choice of medication. Yet, the PChE assay is far from serving as a gold standard, and the AChE assay is not error proof. An understanding of their limitations is essential for monitoring a patient’s cholinesterase status after OP or carbamate poisoning [3]. Some compounds inhibit PChE more effectively than they inhibit AChE. It should be stressed that PChE activity does not always relate to the severity of the poisoning, but it can be used as a sensitive marker of exposure to OP or CRB [8].

Activity between the cholinesterase-toxin complex and the oximes continues if the sample is left at room temperature for even a few minutes, and a sample taken from patients treated with oximes may yield a false negative result (normal level of cholinesterase activity in the laboratory, while plasma level is significantly low). To obtain reliable results, the reaction must be stopped immediately by cooling and dilution of the sample as soon as it is taken from the patient.

**Clinical features of OP and CRB poisoning**

- Expression of muscarinic overstimulation: bradycardia, chorrea, bronchospasm, diarrhea, hypotension, lacrimation, miosis, salivation, urination and vomiting.
- Expression of nicotinic overstimulation in the sympathetic system: hypertension, mydriasis, sweating and tachycardia.
- Expression of nicotinic overstimulation in the central nervous system: agitation, coma, confusion and respiratory failure.
- Expression of nicotinic overstimulation at the neuromuscular junction: fasciculations, muscle weakness and paralysis.

**Principles of therapy**

As in any medical emergency, airways must be secured, respiratory function is assisted according to the severity of the intoxication, and cardiovascular monitoring and support are warranted. Clothes should be removed as part of the primary survey, and eyes and skin should be irrigated if they were exposed to the toxic material.

Basic life support treatments include suction of oral secretions, intubation, and positive pressure mechanical ventilation. Intravenous fluids are usually given as soon as there is venous access and blood is drawn for laboratory investigation.

Control of excessive neurostimulation is accomplished by administration of atropine sulfate – an ACh muscarinic receptor antagonist. Reactivation of AChE is sometimes possible by administration of oxime; these compounds can reactivate acetylcholinesterase by attaching to the phosphorus atom and forming an oxime-phosphonate which then splits away from the acetylcholinesterase molecule. Having mentioned the suggested molecular mechanism of CBM intoxication, it seems quite sensible not to treat a known CRB poisoning with oximes, as the carbamyl residue should dislodge itself spontaneously, with or without additional pharmacotherapy. Interestingly, the same was concluded by other investigators [9].

**Efficacy of treatment and outcome**

It is not yet possible to establish the efficacy of all the different treatments for organophosphate poisoning due to the lack of evidence-based data [3]. Some of the mainstay treatments were introduced long before it became mandatory to conduct a controlled trial, and what is known about these treatments comes from animal studies [1-3].

Atropine is considered the most acceptable and widely used treatment for OP and CRB poisoning. It is a competitive inhibitor of the muscarinic ACh receptor; therefore, it diminishes some of the pathological cholinergic effect but has no effect on the AChE-OP complex. Other muscarinic antagonists are available, but none has been evaluated by high quality randomized clinical trials [3].

Oximes, such as pralidoxime and obidoxime chloride (toxogonin), can reactivate AChE, thus attempting a reversal of the pathological biochemical mechanism in addition to symptomatic relief in the poisoned patients. The most widely used oxime is pralidoxime [3], and in Israel, obidoxime chloride (toxogonin) and other oxime salts are available but a thorough comparison between the different materials in terms of clinical effect and outcome was never performed. The World Health Organization
has published a recommendation to use oximes to treat all symptomatic patients who need atropine [3].

Benzodiazepine (diazepam) is considered the drug of choice to treat OP and CRB poisoning-induced convulsion or agitation. Although most patients will not need this treatment, it is sometimes recommended to administer prophylactic diazepam in cases of severe OP and CRB poisoning because of its documented synergism with other antidotes to improve survival and prevent CNS complications [2]. Attempts to enhance elimination of toxic material by hemoperfusion, hemodialysis or exchange transfusion have not proved effective so far [2].

Glycopyrrolate is a medication of the muscarinic anticholinergic group. It is a synthetic quaternary amine with no central effects and can be used to reduce salivary, tracheobronchial and pharyngeal secretions, as well as decreasing the acidity of gastric secretion and even preventing bradycardia especially in patients who had an adverse reaction to atropine [10]. However, its use as a symptomatic treatment for OP and CRB poisoning has not been extensively evaluated [2].

With regard to management, patients with OP and CRB poisoning must be kept under continuous observation even after atropinization. Levels of cholinesterase should be measured every 12–24 hours and less frequently later on. An exception to this is poisoning by a lipophilic OP, mainly in extremely high doses, which results in a vast distribution to the fatty tissue and a long duration of clinical effect, or abrupt recurrence after cessation of therapy due to redistribution of the poison. The discharge criteria are: an asymptomatic patient in whom atropine or oxime was not required for 1–2 days and whose AChE or PChE levels in plasma are stable [1].

OP as chemical warfare nerve agents

Although dozens of chemical OP-based compounds were produced as nerve agents, four agents (tabun, sarin, VX and soman) are at the core of this field – having been used in wars and in acts of terror [1,2].

Tabun, sarin and soman are considered volatile agents, hence after the release of these agents, with or without an explosive mechanism, they are vaporized and remain so for hours to days. Their main toxicity is via inhalation, as was the case in 1994 when the Japanese terrorist cult, Aum Shinrikyo, synthesized and then deployed sarin against civilians in Matsumoto, Japan, killing eight people. The following year, the same terrorist group released sarin again – in the infamous Tokyo Subway attack, killing 13 and sending 5500 persons to local hospitals. After intoxication, the average aging half-life is extremely short for these agents and they reach the hospital. Hospital treatment includes all of the above as well as decontamination and intravenous therapy, usually in the intensive care unit [1,2].

The pathophysiology of these nerve agents is the same as was described for OP and CRB. These compounds are much more toxic than insecticides, yet there seems to be no relation between the aging half-life and the lethal dose. It appears that nerve agents have an extraordinary affinity for the AChE molecule, and so, hours or even days before the chemical aging takes place, a relatively small amount of toxin achieves maximal binding of the AChE, facilitating respiratory failure and sometimes even death [11].

Therapy is a combination of atropine, oximes and benzodiazepines (especially diazepam), which some authors recommend for all victims of nerve agent toxicity, regardless of whether or not they have seizures. Most of these combination therapies are available as auto-injectors and can be given to victims before they reach the hospital. Hospital treatment includes all of the above as well as decontamination and intravenous therapy, usually in the intensive care unit [1,2].

OP and CRB poisoning in southern Israel

During the past two to three decades, more than 100 infants and children were admitted to Soroka Medical Center and later diagnosed as suffering from either OP or CRB poisoning. The experience gathered by the pediatric emergency department and intensive care unit staff was published in three different reports [9,12].

Clinical presentation of OP or CRB poisoning in young children

Sofer et al. [12] described 25 infants and children aged 3 months to 7 years admitted to the pediatric intensive care unit with moderate to severe OP or CRB poisoning. The most common presentation (occurring in 96% of the children) was stupor or coma; 92% presented with muscle weakness and dyspnea. Bradycardia, fasciculations and gastrointestinal manifestations were the three least common presentations in those children.

Lifshitz and colleagues [13] described 52 children aged 2–8 years with OP (16 children) or CRB (36 children) poisoning, all of whom were admitted to the pediatric ICU. Among those who suffered CRB poisoning, 100% presented with stupor or coma and hypotonia, fasciculations was the least common sign (5.5%). Among those with OP poisoning, 100% presented with stupor or coma and hypotonia, and bradycardia was the least common sign (25%).

Oxime treatment for CRB poisoning

Lifshitz et al. [9] described 26 children aged 1–8 years with severe CRB poisoning. All were admitted with CNS depression and hypotonia and received both atropine and oximes. Later on, the poison was identified as CRB – either methomyl or aldicarb. All children fully recovered within 24 hours, and it was concluded that contrary to common practice and belief (at the time) there is no danger of clinical deterioration when victims of CRB poisoning are treated with oximes. Another interesting finding was that oxime therapy does not contribute to the recovery of CRB-
poisoned pediatric patients – proven in vitro AChE inhibited with CRB was not reactivated by pralidoxime and obidoxime, even in extremely high concentrations, while the AChE inhibited with OP compound (paraoxon) regained up to 95% of its activity [9].

Conclusions
OP and CRB poisoning is a common health problem in the developing world. OP poisoning and CRB poisoning are clinically indistinguishable, and when there is doubt as to the identity of the toxic compound the initial treatment is intended to cover OP poisoning. A recent molecular study further illuminated the nature of “aging” of the chemical bond between OP and AChE [5], a characteristic that does not exist in CRB poisoning due to the relative weakness of the chemical bond.

Analysis of more than 100 cases of OP and CRB poisoning treated at the Soroka Medical Center has given us insight into the different clinical presentations of pediatric toxicity compared to the classic descriptions of cholinesterase inhibitor toxicity that was documented in adults. Lack of history of exposure and absence of classical signs do not exclude the possibility of OP and CRB poisoning. These factors only stress the importance of a high index of suspicion required in endemic areas such as rural Asia and southern Israel.

It is important to bear in mind that OP and CRB poisoning is a life-threatening event, and that prompt resuscitation and usage of antidotes is the mainstay of current therapy. We hope that during the following decade continuing research and analysis will help improve the clinical outcome.

References

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Capsule

High levels of endoglin in systemic sclerosis

Vascular endothelia growth factor (VEGF) is a potent substance implicated in angiogenesis. Patients with systemic sclerosis have high levels and increased expression of this factor in their serum and tissue. The vascular effects of VEGF are mediated by endoglin, a co-receptor of transforming growth factor-beta expressed on endothelial cells. In this line, Wipff and colleagues studied serum levels of endoglin, by ELISA, in 187 systemic sclerosis patients compared with 48 controls. The authors found high serum levels of endoglin and basic epidermal growth factor in patients compared to controls.

Moreover, endoglin levels were associated in multivariate analysis with skin ulceration, positivity to anticientromere antibody, and abnormal relation of diffusing capacity for carbon monoxide per alveolar volume. This study showed that patients with systemic sclerosis and ischemic phenomena (pulmonary and cutaneous) have increased levels of endoglin, and this mediator may play a role in scleroderma pathogenesis.

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