Organophosphates and the Heart*

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Organophosphates are widely used as agricultural pesticides, and some of these compounds serve as nerve agents for chemical warfare. They act as powerful inhibitors of acetylcholinesterase, resulting in accumulation of acetylcholine and overstimulation of cholinergic synapses in the central nervous system, somatic nerves, parasympathetic nerve endings, and sweat glands. The mode of contact in organophosphate poisoning varies, as these compounds are absorbed efficiently by oral, dermal, conjunctival, gastrointestinal, and respiratory routes. Poisoning commonly occurs as a result of agricultural use, accidental exposure, suicide, and, rarely, homicide. Mortality rates as high as 85 percent have been reported,1 generally due to respiratory insufficiency.

Although physicians have been aware of the ophthalmic, neurologic, and psychological complications of organophosphate poisoning,2,4 less importance has been attached to the cardiac aspects, until recently. Cardiac complications and late occurrence of sudden death may take place after initial clinical toxicity has abated1 and the patient seems to have recovered from the acute and dramatic respiratory and neurologic manifestations.

CLINICAL EXPERIENCE

Although the annual number of individuals intoxicated by organophosphates in the United States alone exceeds 30,000,5 there have not been many reports on the cardiac manifestations. Obviously, the experience that can be accumulated (and published) on clinical trials with organophosphates in humans is also limited.

In 1970, Chhabra et al6 reported on 35 patients who had ingested Diazole (malathion) in suicide attempts. Electrocardiographic abnormalities observed in 37 percent included intraventricular conduction disturbances (limited to the acute phase) and ST-T changes (detected even at 2 months’ follow-up). The postmor-

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ten reports on five of these patients (two of whom died due to fatal arrhythmias) revealed diffuse myocardial damage.

Russian investigators were the first to draw attention to the life-threatening late-occurring arrhythmias in the recovery period of acute intoxication. In 1975, Luzhnikov et al1 reported on 183 cases of severe intoxication with organophosphates (Theophos, Chlorophos, Carbophos) treated at the Institute for Intensive Care in Moscow. In 34 patients (18.5 percent), various arrhythmias and conduction disturbances were observed. All patients with arrhythmias had a prolonged QT interval (79 ± 16 percent more than the average), correlating with the severity of intoxication and decrease of cholinesterase activity in the blood. From the second and third days after exposure, 21 patients exhibited multiple multifocal premature ventricular beats, which degenerated rapidly into ventricular fibrillation. Ten patients had various degrees of atrioventricular and/or intraventricular conduction disturbances. Twenty-nine patients died within 6 days of admission due to cardiac arrest; ventricular fibrillation was the antemortem arrhythmia in most cases. Treatment with potassium supplements and beta-blockers for suppression of arrhythmias failed. Also, cardiac pacing attempted in five patients (indication unspecified) did not induce any improvement.

In four patients who were severely intoxicated and had ectopic ventricular activity, complete replacement of the blood volume was performed on the third day of hospitalization in order to provide acetylcholinesterase. Six to twelve hours following the procedure, arrhythmias and conduction disturbances disappeared, and within 20 h the prolonged QT interval normalized, and cholinesterase activity in the blood returned to normal. The clinical features of the intoxication disappeared completely on the second day following the procedure.

Another large series reported in Hungary by Kiss and Fazekas7 included 168 patients, aged 15 to 82 years (average, 41 years), who were intoxicated by the organophosphates methyl parathion and dimethoate. Suicide attempts were the main cause for exposure in 122 patients, 50 of whom died. Electrocardiographic changes, correlating with the severity of intoxication,
were observed in 134 patients within 1 to 20 days after exposure. These included prolongation of QT interval and ST-T changes. Of the 56 patients who experienced arrhythmias, 22 had multiple premature ventricular beats, 7 had ventricular tachycardia, and 6 had ventricular fibrillation. In addition, various degrees of bradycardia (including first degree atrioventricular [AV] block in 2 patients) were observed in 5 patients, idioventricular rhythms in 3, and asystole in 5. In the majority of patients (41/56) the aforementioned arrhythmias were recorded on days 3 to 15 after exposure. Atropine in a dose of 4 mg/h did not suppress or prevent these arrhythmias. Only in 12 patients (not specified) could these arrhythmias be attributed to electrolyte derangements, acidosis, or hypoxemia. Postmortem analysis revealed focal histologic changes typical of necrosis and regeneration.\(^8\)

Ludomirsky et al\(^9\) summarized their experience in 15 patients intoxicated by parathion phosphamidone and other organophosphates, pointing out the relatively high occurrence of torsade de points in this group and demonstrating the advantage of treatment with isoproterenol/pacing, as compared with other medical measures. In 14 patients with ECG recordings, QT interval prolongation was observed. In 6 of these, torsade de points was traced within 5 h of admission until 5 days following exposure.

A computerized study of 255 hospitalized patients exposed to organophosphates (mostly parathion and malathion) and to carbamates was conducted in eight hospitals in Israel.\(^10\) Five of the surviving patients died suddenly, some days after they were already clinically stable and signs of intoxication had subsided. In one of these patients there was evidence of ventricular fibrillation following torsade de points on the third day after admission.

**ANIMAL EXPERIENCE**

As early as 1948, Dayrit et al\(^11\) described severe cardiovascular phenomena in dogs, both anesthetized and awake, following exposure to the organophosphates hexaethyltetraphosphate and diethylpropanediol. They observed changes in blood pressure and heart rate and in the ECG, which varied in correlation with increasing dosage of the organophosphate.

Foxhounds were examined by Hassler et al\(^12\) to determine the effect of the chemical warfare agent soman, 10 \(\mu\)g/kg administered intravenously, (equivalent to twice the median lethal dose) on the electrical and mechanical properties of the heart. Eight of the 15 study animals served as the electrophysiologic model and 7 as the hemodynamic model. A significant and dramatic increase in electrical ectopic activity, which extended over 30 days following exposure, was observed. The first week was characterized by the appearance of idioventricular rhythms and recurrent episodes of life-threatening arrhythmias consisting of ventricular tachycardia and long pauses in the electrical activity of the sinus node. His bundle recordings showed a slight but nonsignificant delay in conduction velocity, compared with measurements taken at baseline.

In the hemodynamic model, the acute effects included dramatic increase in heart rate, cardiac contractility, intraventricular pressure, and coronary flow, which resolved within 15 to 60 min from onset.

These initial findings may indicate an enhanced sympathetic tone but also some decrease in cardiac mechanical performance, similar to the findings reported by Kiss and Fazekas\(^7\) and Ludomirsky et al.\(^9\)

As in another study on rats,\(^13\) no arrhythmias were detected within the first hour of observation. Torsade de pointes was not observed, although there are reports of its appearance in dogs following administration of the organophosphate compound VX (nerve agent). The authors mention that only a small percentage of the experimental population manifested the arrhythmic events. This seems to indicate that only a limited sector of individuals are susceptible to soman-induced arrhythmias, which may, however, be extremely severe. Amelioration of these arrhythmias was attained with phenobarbital treatment.

Robineau and Guittin\(^4\) examined the effects of the nerve agent VX on ECG and hemodynamic parameters in dogs challenged with increasing subcutaneous doses (1.5 to 6.0 \(\mu\)g/kg). Prolongation of the QT interval correlated with the dose applied, and a concomitant mild decrease in blood pressure was recorded. In dogs that received 6.0 \(\mu\)g/kg, these changes became more substantial and were associated with a significant decrease in left ventricular performance. In addition, sinus bradycardia, first-degree AV block, ventricular extrasystoles, and events of polymorphous ventricular tachycardia were common.

Another experiment was carried out with the carbamate physostigmine.\(^15\) The cardiovascular and pulmonary parameters were monitored in domestic swine that received an intrapulmonary arterial infusion of physostigmine, 5 \(\mu\)g/kg/min for 2 h (total dose of 12 mg per swine). There were statistically significant increases in heart rate, cardiac output, mean aortic pressure, and both pulmonary artery and pulmonary artery wedge pressures. Analysis of the ECG changes indicated occasional premature ventricular contractions and an inverted T wave, as well as a few instances of AV block. Bradycardia was not observed.

In recent years, reports have also been published describing histopathologic changes in experimental animals exposed to organophosphates. Singer et al\(^16\) treated 71 rats with various subcutaneous single doses (111 to 221 \(\mu\)g/kg) of the organophosphorous nerve agents soman and sarin, and examined them periodi-
cally from day 2 through day 35 after injection; surviving rats were subsequently killed. Necropsy analysis of the heart revealed myocardial lesions similar to those reported previously by Gebbers et al. and Salpeter et al. in skeletal muscles and the diaphragm. There was focal myocardial damage that varied, depending on the interval between dosing and time of necropsy. The distribution of the lesions in all cases appeared to be random, but most lesions were located in the left ventricular myocardium and were more severe in the subendocardial region. Animals examined on day 2 after intoxication showed multifocal areas of acute myolysis. Animals examined on day 9 after exposure showed the beginning of resolution of necrotic areas. Cardiomyopathy was seldom observed beyond day 14. An interesting observation was the high occurrence of cardiac damage (50 percent) in a subgroup that also exhibited neurologic lesions.

McDonough et al. examined the histologic changes in the hearts of surviving rats that had been exposed to soman (85 μg/kg) subcutaneously and subsequently treated with the combination of atropine and diazepam in various doses. Of the 258 animals that survived the soman challenge, 16 percent had cardiac lesions. They were found only in the ventricular tissue, predominantly in the left ventricle. The lesions were random and multifocal, and consisted of either fibrosis or mineralization within the myocardial musculature, representing a final stage of resolution and healing. In addition, 87 percent of the animals with heart lesions for which detailed data were available had concomitant neuropathologic findings, suggesting some relationship between the presence of brain lesions and the occurrence of myocardial injury.

Both diazepam and atropine blocked the development of cardiac lesions in a dose-dependent fashion; the combination of diazepam, 3.2 mg/kg, and atropine, 10 to 32 mg/kg, was more effective in preventing cardiac morphologic damage than the combination of 0.1 and 1.0 mg/kg, respectively. In addition, there was good correlation between the clinical severity of intoxication and the appearance of cardiac lesions. These results are also the first to demonstrate that both drugs are effective in altering myocardial necrosis associated with nerve agent intoxication.

It was also found that cholinesterase inhibitors from the carbamate groups can cause histologic damage to the heart if administered in large doses. Kato et al. investigated the possible mechanism for genesis of cardiomyopathy in a group of rats treated with high doses of pyridostigmine (60 mg/kg) and compared the findings to those in another group, in which atropine (2 mg/kg) was administered 5 min later. The animals were killed 3 h after pyridostigmine administration, and their hearts were isolated. Structural changes, as observed with electron microscopy in the nontreated group, included contraction band necrosis, dilated T tubes, and mitochondrial swelling. In addition, heart mitochondrial electron transport activity and respiratory rates were measured. Activities of nicotinamide adenine dinucleotide-cytochrome c reductase and succinate-cytochrome c reductase were unaffected by pyridostigmine administration; however, cytochrome c oxidase activity was significantly reduced in the pyridostigmine group. In the atropine-treated group, the morphologic changes and the reduction in cytochrome c oxidase activity were less prominent.

Pathophysiology

The mechanism by which organophosphates induce cardiotoxicity has not been elucidated thus far. According to Ludomirsky et al., three phases of cardiac toxicity can be described: (1) a brief period of intense increase in sympathetic tone manifested by sinus tachycardia, (2) a prolonged phase characterized by extreme parasympathetic “overflow,” usually accompanied by hypoxemia and often manifested by ST-T segment changes, AV conduction disturbances of varying degrees, and rhythm disturbances that can deteriorate to ventricular fibrillation; and (3) a phase in which QT-interval prolongation, pleomorphic tachycardia, and sudden cardiac death are characteristic. The third phase can appear early, shortly after intoxication, but sometimes does not appear until several days after exposure, when the signs of clinical intoxication have already subsided. It is difficult to pinpoint one mechanism as being the cause of arrhythmias, especially in the late stage. Indeed, the clinical and laboratory evidence indicate a complex physiologic and histopathologic interaction.

It becomes apparent that the morphologic and electrophysiologic disorders caused by organophosphates (and high doses of carbamates) are similar, yet unrelated, to the differences in the chemical structure of the various compounds. It may be postulated that organophosphates exert a direct toxic effect on the heart. According to Marosi et al., the pathologic electrophysiologic changes are related to the severity of intoxication, but not to the decrease in enzyme activity, nor are they influenced by atropine. The ECG alterations can be reproduced in animal experiments, precede the toxicologically relevant cholinesterase depression, and are dose-related. Thus, it can be deduced that in organophosphate intoxication, the QT-interval lengthening reflects a direct myocardial pesticide effect and is independent of cholinergic mediation.

Another possibility lies in the basic architecture of cardiac innervation. The heart receives its nerve supply from both the sympathetic and the parasympathetic arms of the autonomic system. We suggest that the action of organophosphate on both these

578 Organophosphates and the Heart (Roth et al)
systems acutely distorts their functional balance.

There are studies that suggest that the morphologic damage can be caused by continuous vagus nerve stimulation (due to the liberated acetylcholine). Manning et al.\(^{17}\) described ECG changes consisting of T-wave alterations in vagus-stimulated dogs and occasional ventricular extrasystoles. Autopsy examination revealed the hearts to be dark and mottled in a few animals, with infarcted areas in some of the papillary muscles. The magnitude of the myocardial damage correlated with the duration of stimulation. However, animals that received atropine not only survived the treatment twice as long as the others, but also showed no evidence of myocardial damage. These results, identical with those reported by Hall et al.,\(^ {28}\) further strengthen the hypothesis that parasympathetic overexcitation causes myocardial damage through liberation of acetylcholine.

Although the exact pathogenesis of the cardiac lesion is unestablished at this time, its association with brain lesions is too strong to be dismissed. A neurogenic background for cardiac lesions can be suggested by the high incidence detected in rats suffering neurologic damage,\(^ {16}\) similar to that described in the central neurologic process.\(^ {29}\) Moreover, there is evidence that both branches of the autonomic system may play a major role in the cardiac pathogenesis. On one hand, sympathetic overactivity resulting in local catecholamine release is implicated as the cause of myocardial damage.\(^ {30}\) This was confirmed by the observation that short-term administration of high doses of norepinephrine induced focal myocardial necrosis in dogs, cats, and rabbits\(^ {31}\) and that this pathologic process could be prevented by sympathetic antagonists.\(^ {32}\) On the other hand, parasympathetic overactivity has also been implicated in myocardial damage,\(^ {30}\) being the same mechanism as that suggested by Gebbers et al.\(^ {17}\) for peripheral myopathy.

Moreover, it was found that intracoronary injection of acetylcholine may induce vasoconstriction in a substantial number of adult humans with healthy or atherosclerotic coronary arteries.\(^ {33,34}\) Thus, in addition to a general state of hypoxemia characteristic of organophosphate poisoning, there may be a further burden on the heart due to derangement in coronary perfusion. This may be one of the possible mechanisms responsible for the frequent occurrence of ST-T changes observed in the acute stage. It could be that this condition of hypoxia, which may be accompanied by derangements in myocardial perfusion that cause release of oxygen-free radicals, which in turn induce necrosis of myocytes, is important in the development of cardiomyopathy. It should be stressed, however, that the mechanisms of the ST-T changes described, which suggest an acute ischemic event, cannot explain why these ST-T changes remain after the disappear-

ance of the acute signs of intoxication.\(^ {6,25}\) unless we assume long-lasting myocardial damage.

Histologically, it is possible that the derangement of cellular morphology is due to a massive influx of Ca\(^ {2+}\) into the cytoplasm. Normally, acetylcholine receptors have a high binding capacity for calcium ions,\(^ {36}\) and binding of acetylcholine to the receptor causes release of these Ca\(^ {2+}\) ions. Thus, the excessive depolarization of the end-plate receptors following intoxication may cause an enhanced Ca\(^ {2+}\) influx.

The studies of Salpeter et al.\(^ {18}\) on skeletal muscles suggest that a major role of acetylcholinesterase (by restricting the action of acetylcholine both in time and space) is to protect the muscle from short-term fatigue and long-term myopathy, which may result from extensive Ca\(^ +\) fluxes. The fact that late-onset arrhythmias can be successfully treated by the administration of intravenous magnesium-sulfate\(^ {8}\) may further support the theory that disturbances in calcium channels play a role in the pathogenesis of the cardiomyopathy.

The precise mechanism that generates torsade de pointes in organophosphate intoxication is unknown. However, in view of the mixed degenerative and regenerative processes observed during the late phase of intoxication, we suggest that focal areas interspersed with normal myocardium can produce many potential areas of reentry and nonhomogeneity of repolarization, and that this may result in arrhythmia, as already shown.\(^ {37}\)

The exact time lapse from organophosphate exposure to the manifestation of late cardiac complications is unpredictable, but it can be assumed that with some organophosphates used in chemical warfare (eg, soman), this period may be extended because spontaneous reactivation of the enzyme is limited due to rapid "aging" of the complex enzyme-poison. Thus, only the time-consuming mechanism of enzyme "de novo" synthesis exists.\(^ {30}\) It is also hard to predict in which of the intoxicated patients they will appear. However, the general impression is that in severe poisoning they are quite common and are a major cause of late mortality in organophosphate poisoning.\(^ {6,8,10}\)

In view of the aforementioned, it seems that in organophosphate poisoning there are complex and multifactorial reasons for the development of cardiac arrhythmias. The acute syndrome represents classical acetylcholinesterase inhibition and a state of extreme parasympathetic overactivity. The reasons for the late manifestations (characterized by uncommon and unexpected arrhythmias), which may appear as long as 15 days after exposure,\(^ {7}\) are unknown, but may be attributed to (a) direct cardiotoxic effect; (b) metabolic (acidosis) and electrolyte derangements; (c) recovery and healing mechanisms of the damaged myocardium; or (d) autonomic imbalance and insufficiency. Also,
the increase in free fatty acids described by some authors after intoxication with organophosphates may contribute to the arrhythmogenicity. Lastly, cholinergic stimuli may induce an increase in sympathetic tonus in the postganglionic fibers, compensatory reflexes, and a direct deleterious adrenergic effect on the heart.30

**Treatment**

The pharmacologic treatment of organophosphate poisoning has a long history and is relatively efficient if applied early. Successful treatment depends, *inter alia*, on the chemical properties of the poison. In cases of intoxication by rapid "aging" poisons, the rate of success is limited. In addition to the necessity of prompt intervention, treatment should not further compromise the victim's chances of complete and quick recovery. The global objectives of treatment should integrate three elements: (1) maximum protection of acetylcholinesterase (using car bamates, such as pyridostigmine); (2) treatment of the effects of acetylcholine excess (using atropine and other cholinolytes, which compete with acetylcholine on the muscarinic receptors); and (3) attempted restoration of acetylcholinesterase activity. In addition, anticonvulsants (eg, diazepam) are frequently used to counteract spasms induced by organophosphates.

**Pretreatment**

Pretreatment does not equate with prophylaxis, which unfortunately does not exist, even partially. However, it will significantly enhance the success of subsequent treatment. The logic behind the use of carbamate lies in its capacity to bind reversibly to acetylcholinesterase and to "protect" the latter from phosphorylation by organophosphates.40 The slow and spontaneous decarbamylation of the acetylcholinesterase, which parallels the clearance of organophosphates, can result in release of life-sustaining acetylcholine. Thus, the aim of treatment is to "protect" about 30 percent of the acetylcholinesterase. The recommended dose of pyridostigmine is 30 mg orally every 8 h. Following pretreatment, a decrease in heart rate by up to 5 beats per minute at rest and exertion may be observed, without causing any clinical incapacitation.41-45

One of the questions that may arise is what is the significance of a "double attack" on the enzyme acetylcholinesterase in the pretreatment phase (by pyridostigmine) and in the acute phase (by organophosphate). This is difficult to answer, considering the fact that while the dose and concentration of the chemical agent can be well planned and controlled in clinical trials, in mass disasters this is not the case. Animal studies did not confirm this fear. On the contrary, they proved that the addition of a carbamate not only did not enhance the intoxication effects, but decreased the toxicity of soman 4- to 15-fold (depending on the conditions of the trial). It was demonstrated that the protective effect increases in correlation to the percentage of carbamylated enzyme up to 70 percent.46 At very high doses, however, pyridostigmine might exacerbate the toxic effects.

**Acute Phase**

The specific supportive measures are the key to overcoming arrhythmias in the acute stage and should be instituted immediately on admission of the patient to the emergency room or earlier, if possible, by a first-aid team. Thus, atropinization after establishment of an airway and adequate ventilation to improve oxygenation, acid-base balance, and hemodynamics are the main objectives in treatment. At this point, it is important to highlight the potentially deleterious effect of atropine on the ischemic and bradycardic myocardium.47-50 Kiss and Fazelakos7 reported that arrhythmias continued despite administration of large doses of atropine. Consequently, they recommend not exceeding a daily dose of 100 mg, since an excessive dosage may increase the severity of arrhythmias.

Significant ventricular arrhythmias that are not responsive to lidocaine, bretyllium, and/or direct electrical cardioversion have been shown to be best treated with intravenous isoproterenol, overdrive pacing,9,26 and administration of magnesium. Although the exact mechanism is not yet known, the magnesium probably counteracts the direct toxic inhibitory effect of the organophosphates on Na+/K+-ATPase, by reactivating the membrane Na+/K+-ATPase.51

**Late Phase**

Prevention and treatment of late arrhythmias are more complicated. Susceptibility to late arrhythmias may be determined according to the history of severe poisoning and significant QT-interval prolongation on the ECG. The recommended treatment for arrhythmia suppression on the basis of prolonged QT interval is overpacing or the intravenous administration of isoproterenol or magnesium salts.52 The immediate treatment of sustained ventricular tachycardia accompanied by hemodynamic compromise is based on electrical cardioversion followed by an attempt to immediately shorten the QT interval. It is worth mentioning that although there are reports of successful termination of torsades de pointe due to prolonged QT interval with the use of lidocaine and derivatives, whether the condition is congenital or acquired,53 the efficacy of these drugs in organophosphate intoxication is limited, and they might even aggravate the arrhythmia.8

In summary, organophosphate intoxication may cause deleterious cardiac effects, including morpho-
logic damage, in the acute stage. Successful treatment of intoxication can reduce the extent of cardiac damage. Late arrhythmias are imminent even if the treatment in the acute phase is efficient (including treatment of early arrhythmias, characteristic at this stage) and may occur unheralded 1 to 15 days following exposure to the organophosphate. It is possible that in those compounds serving as nerve agents, especially soman, this period may be even further extended.

The frequency of these life-threatening arrhythmias, which can result in sudden death, increases in correlation with the severity of intoxication and the length of QT interval. Electrocardiographic monitoring in at least severe cases is warranted for early detection and for prompt and better management of dysrhythmias. After the acute insult has subsided, it may be advisable to continue monitoring severe intoxication victims in a convalescent facility, with telemetric cardia monitoring and resuscitation equipment, for at least 3 weeks, to allow prompt diagnosis and treatment of late-occurring arrhythmias.

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CHEST / 103 / 2 / FEBRUARY, 1993 581
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582
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