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REVIEW ARTICLE

Organophosphorus poisoning and anaesthesia

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Summary

Organophosphorus compounds, used as insecticides and agents of chemical warfare, are a major global cause of health problems. These irreversible inhibitors of cholinesterase produce three well-recognised clinical entities: the initial cholinergic phase, which is a medical emergency often requiring management in an intensive care unit; the intermediate syndrome, during which prolonged ventilatory care is necessary; and delayed polyneuropathy. In addition, disturbances of body temperature and endocrine function, electrolyte imbalances, immunological dysfunction and disorders of reproduction have been reported in animals and man. Vocal cord paralysis, pancreatitis, cardiac arrhythmias and a wide range of neuropsychiatric disorders are known to follow acute and chronic exposure to organophosphorus compounds. As a result of the inhibition of plasma cholinesterase, there can be increased sensitivity to drugs hydrolysed by this enzyme, e.g. suxamethonium and mivacurium. The inhibition of acetylcholinesterase causes dysfunction at the neuromuscular junction which can produce altered responses to nondepolarising neuromuscular blockers. Anaesthetists may encounter patients exposed to organophosphorus compounds either following acute poisoning, trauma (warfare) or as patients with a wide range of nonspecific disorders presenting for surgery. The traditional use of oximes and atropine in treatment has failed to reduce the morbidity and mortality associated with poisoning. The roles of agents that have reduced the toxicity of organophosphorus compounds in animal experiments are discussed as potential therapeutic agents. There is an urgent need for accurate information on the problems associated with exposure to organophosphorus compounds. This would best be achieved by collaborative research between technologically advanced countries and developing countries, where organophosphorus compounds are a leading cause of ill health.

Keywords *Chemicals*; organophosphorus compounds. *Complications*; poisoning.

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Organophosphorus (OP) compounds are usually esters, amides or thiol derivatives of phosphonic acid and form a large family (> 50 000 compounds) of chemical agents with biological properties that have important, and sometimes unique, applications for the benefit of mankind. There is considerable structural diversity among the commonly used OP compounds. The principal use of these is as pesticides in agriculture, mainly as insecticides. Some formulations are used in veterinary and human medicine, particularly as antiparasitics, e.g. against ticks, lice and fleas. In commerce, OP compounds have been used as lubricants, plasticisers and flame-retardants. The development and use of some of these compounds as very potent agents of chemical warfare is of global significance.

Organophosphorus compounds inactivate acetylcholinesterases by alkyl phosphorylation of a serine hydroxyl group at the esteratic site of the enzyme. The phosphorylated enzyme is inactive and thus unable to hydrolyse acetylcholine. The biological effects of OP compounds are a result of the accumulation of endogenous acetylcholine at sites of cholinergic transmission. Organophosphorus compounds are readily absorbed across respiratory and gastrointestinal mucosa, and the lipophilic OP compounds are very readily absorbed through the skin.

The relationship between the toxicity of OPs and their structures has been investigated using several approaches. One approach has been to examine the relationship between the *in vivo* toxicity (LD_{50}) and their *in vitro* ability to inhibit acetylcholinesterase. The species variation of the toxicity of OP compounds is illustrated by the data on malathion, which is a nonsystemic insecticide. The LD_{50} (topical) for a bee is 0.71 μg while the oral LD_{50} for rats is 1375–2800 $mg.kg^{-1}$. The oral LD_{50} in rats for the nerve agent sarin is 550 $\mu g.kg^{-1}$. The acceptable daily intake (ADI, the amount of a chemical which can be consumed every day for an individual's life span with the practical certainty based on all available evidence that no harm will result) for humans is 0.02 $mg.kg^{-1}$. The acceptable daily intake for parathion is 0.004 $mg.kg^{-1}$ and the acute percutaneous LD_{50} for rabbits is 71 $mg.kg^{-1}$. The percutaneous LD_{50} for rabbits for the nerve agent sarin is 925 $\mu g.kg^{-1}$ [1].

Malathion, parathion, dimethoate, dichlorvos, diazinon, methamidophos and monocrotophos are some of the commonly used insecticides, while tabun, sarin and soman are used as nerve agents.

Pesticides cause $\approx$ 3 million poisonings and 200 000 deaths world-wide every year [2]. Organophosphorus-based pesticides are widely used globally and have emerged as the major pesticide contributor to ill health [2]. Ill health related to these irreversible inhibitors of acetylcholinesterase has been reported recently in studies from China [3], India [4–6], Brazil [7], Mexico [8], Canada [9], Costa Rica [10], Columbia [11], Puerto Rico [12], France [13], Spain [14, 15], Poland [16], Italy [17, 18], Belgium [19], Romania [20], Portugal [21], Greece [22], Germany [23], Japan [24], Jordan [25], South Africa [26], Turkey [27], Taiwan [28] and Sri Lanka [29, 30]. In 1996, the American Association of Poison Control Centers reported 86 914 human exposures to pesticides in the US [31]. There were 50 000–70 000 cases of acute pesticide poisoning reported from the 27 provinces of China each year during the 1990s [3]. Among the total cases, occupational poisoning accounted for about one-fifth of reported cases, with a mortality of $< 1\%$. Self-poisoning with suicidal intent is a major problem in developing agricultural countries such as Sri Lanka, and is responsible for over 90% of exposures [29]. The majority of the patients in these countries are males with a mean age of 25 years [30]. The reported mortality following OP insecticide poisoning varies between 4 and 30% [32]. There is also a report of poisoning by the intravenous route [27].

Organophosphorus pesticides have also caused ill health following occupational exposure during application, e.g. spraying [33] and in sheep dips [34–36]. Further anecdotal evidence suggests that low-grade exposure to OP pesticides gives rise to a neurological syndrome characterised by headache, fatigue, skeletal muscle weakness and nausea, which is recognised in the farmlands of the USA as 'orange pickers flu'. In the 1930s, an OP derivative contaminated bootleg whisky and caused a neurological syndrome ('Jamaican ginger paralysis') in drinkers of the illicit alcohol [37]. In Israel, a study of pilots and ground crews of aircraft used for spraying, of field workers who were exposed at work to OP pesticides, of nonworkers (including children) who were subjected to drift exposures, and of the residents of houses treated with pest exterminators was carried out. In all these groups, evidence of an association between exposure and illness was identified, even though individuals with acute poisoning were not found. Complaints of headache, dizziness, fatigue, nausea, abdominal cramps and tingling in the extremities were associated with decreases in cholinesterase activity. Low-grade changes in nerve conduction and transient neuropsychological changes were associated with exposure [38]. A study from South Africa suggested that at least 17.5% of male rural workers engaged in crop spraying suffer from chronic OP poisoning [39]. Misapplication of OP pesticides commonly used in households has caused poisoning [4]. The OP compounds soman, sarin and tabun have been used as chemical warfare agents and continue to feature in threats to world peace. These nerve agents have been used in subways by terrorist groups and in the suppression of communities within countries [40]. Exposure to nerve agents, and possibly to some compounds used for protection against such agents, have been held responsible for a nonspecific clinical disorder commonly referred to as 'Gulf War Syndrome' [41].

Behan [42] observed that the clinical features of the neurobehavioural syndrome occurring after chronic exposure to OPs are identical to those described in patients with chronic fatigue syndrome (CFS). Severe mental and physical fatigue was a common complaint of patients with OP exposure as reported by the joint working party of the Royal College of Physicians and Royal College of Psychiatrists of London [36].

Following classical OP poisoning, three well-defined clinical phases [43] are recognised: the initial cholinergic phase, the intermediate syndrome and delayed polyneuropathy (OP-induced delayed polyneuropathy, OPIDN), illustrating a triphasic effect of OP compounds in man. Equally important are the effects of OP agents on specific physiological systems of the body, as reported in both man and in animals. The systems affected include the central nervous system (CNS), cardiovascular system and metabolic and endocrine systems, including reproduction and the neuromuscular junction [44]. The initial cholinergic phase is a medical emergency that requires treatment in an intensive care unit. The intermediate syndrome is marked by respiratory failure that may require prolonged ventilatory

assistance. Death from cardiorespiratory causes can occur during either of these phases. Animal experiments and observations in humans suggest that a wide range of disordered function in several systems in the body may follow OP poisoning and that these could affect the conduct of an anaesthetic.

The key dysfunction following OP exposure is the inhibition of cholinesterases, which are widely distributed throughout the body and participate in a variety of physiological functions, while being responsible for the metabolism of many drugs. Plasma cholinesterase recovers quickly, usually within 4 weeks. Red blood cell acetylcholinesterase takes longer and may not be restored to normal function for several months. Affected acetylcholinesterase recovers at the rate of $\approx 1\%$ per day. Restoration of acetylcholinesterase activity occurs by slow *de novo* synthesis of fresh enzyme and also to some extent as a result of spontaneous dephosphorylation of the inhibited enzyme. The rates for inactivation (phosphorylation) and reactivation (dephosphorylation) vary considerably for different OP agents and this accounts for the differences in toxicity of the various OP agents. The loss of a radical (ageing) makes the inactivated enzyme more stable so that spontaneous dephosphorylation does not occur. Ageing has an important bearing on toxicity. With chemical warfare agents such as soman, ageing occurs very quickly.

In 1955, Belling & Booth [45] considered the danger associated with the administration of suxamethonium to horses exposed to OP compounds. Their work listed some of the effects at a variety of doses, e.g. the time to recumbence after administration, the duration of the effects and the duration of artificial ventilation required after exposure. Later, Short *et al.* [46] reported on OP-induced complications during anaesthetic management in the horse. In 1966, Gesztes [47] reported prolonged apnoea in man after the administration of suxamethonium associated with the use of eye drops containing the OP compound ecothiopate iodide. In 1969, Seybold & Brautigam [48] described prolonged apnoea (in excess of 12 h) after the administration of suxamethonium to a patient poisoned by an OP agent. Sporadic reports of OP poisoning followed in the anaesthetic literature [49, 50]. In 1989, Weeks & Ford [51] reported prolonged suxamethonium-induced neuromuscular block associated with OP poisoning in man. More recently [52, 53], increased sensitivity to mivacurium in states of cholinesterase deficiency has been reported.

Baraka *et al.* [54] found a negative correlation between cholinesterase activity and the duration of suxamethonium neuromuscular blockade. An inverse relationship was found between a patient's cholinesterase activity and the time to the reappearance of the first response to a train-of-four (TOF) stimulus after the administration of mivacurium [55]. The half-life of mivacurium *in vitro* was found to increase as cholinesterase activity decreased [56]. Surprisingly, inhibition of cholinesterase activity (by 93% and 89%, respectively) increased the onset time of suxamethonium from a median of 40 s to 131 s, and of mivacurium from a median of 52 s to 105 s. As a result of the inhibition of degradation, the effective dose of suxamethonium that resulted in 70% depression of the initial twitch height was reduced from $900\,\mu g.kg^{-1}$ to $150\,\mu g.kg^{-1}$ and of mivacurium from $100\,\mu g.kg^{-1}$ to $35\,\mu g.kg^{-1}$ [57]. Cholinesterases also hydrolyse the local anaesthetic derivatives of para-amino benzoic acid, e.g. procaine and the β-adrenergic blocker esmolol. Furthermore, a hyperthermic syndrome similar to neuroleptic malignant syndrome occurred 13 days after acute OP poisoning for which dantrolene proved to be useful [58].

Clinical manifestations

The cholinergic phase

The accumulation of acetylcholine at muscarinic sites produces an increase in secretions (bronchorrhoea, salivation, tearing and sweating), bronchoconstriction (tightness in the chest and wheezing), bradycardia, vomiting and an increase in gastrointestinal motility (abdominal tightness and cramps). In the eye, OP agents cause the diagnostic miosis that results in blurring of vision. After exposure to sarin, an OP chemical warfare agent used in a terrorist attack in a Japanese subway, pain in the eye was a prominent symptom [40]. The effects of increased acetylcholine at nicotinic sites, e.g. the neuromuscular junction, causes muscle fasciculations and then a flaccid paralysis as a result of depolarising block. Inhibition of acetylcholinesterase in the brain leads to headache, insomnia, giddiness, confusion and drowsiness. After severe exposure, slurred speech, convulsions, coma and respiratory depression occur.

Death is likely during this initial cholinergic phase due to effects on the heart (bradycardia and other arrhythmias), respiration (central or peripheral ventilatory failure) and on the brain (depression of vital centres). The cholinergic phase usually lasts 24–48 h and constitutes a medical emergency that requires treatment in an intensive care unit. Owing to cholinesterase inhibition, there is an increased sensitivity to any drug hydrolysed by this enzyme during the cholinergic phase [59].

The intermediate syndrome [60]

The intermediate syndrome is characterised by the onset of muscle weakness, including the muscles of respiration (particularly the diaphragm), and cranial nerve palsies. There is a rapid onset of difficulty in breathing associated with the use of the accessory muscles of respiration and, if untreated, death follows rapidly as a result of ventilatory

failure. The intermediate syndrome begins ≈ 1–4 days after poisoning and occurs after the cholinergic phase. Complete recovery occurs within 4–18 days if adequate ventilatory support is provided.

Leon-s Fidias *et al.* [61] performed a Medline search of studies of insecticide poisoning published between 1965 and 1995, and found that the intermediate neurotoxic syndrome, or similar manifestations, occurred in 20–68% of affected patients. Parathion was the causative agent in up to 75% of these cases.

Neuromuscular function in the intermediate syndrome

In OP poisoning, single evoked compound muscle action potentials (CMAPs) were followed by repetitive discharges and a decrement–increment (D–I) phenomenon with 10, 20 and 50 Hz supramaximal stimulation [23, 62]. The decrement response seen initially during the intermediate syndrome is similar to TOF fade and tetanic fade, which is usually attributed to a decrease in the effectiveness of the presynaptic cholinergic feedback mechanism and is associated with partial or recovering nondepolarising block. It is also observed in phase II suxamethonium block. Train-of-four fade has also been demonstrated after low doses of suxamethonium or after the administration of suxamethonium in the presence of a nondepolarising drug [63]. In myasthenia gravis, repetitive nerve stimulation at low frequencies produces a decrement that increases up to the fourth or fifth response. In the Eaton–Lambert myasthenic syndrome, the amplitude of compound muscle action potentials after a single stimulus is severely reduced, whereas an increment occurs at high-frequency repetitive stimulation [64]. Bowman has summarised the evidence for a presynaptic nicotinic receptor that responds to acetylcholine and is blocked by nondepolarising relaxants [65]. The repetitive firing following a single evoked compound muscle action potentials is considered to be due to excessive acetylcholine in the presence of an anticholinesterase, causing antidromic firing due to stimulation of the axonal (presynaptic) nicotinic receptors [66]. Besser *et al.* [23] showed that pancuronium 1 mg, which acts both pre- and postsynaptically, abolished the D–I phenomenon and partially reduced the repetitive discharge of the compound muscle action potentials in two patients with OP poisoning [23].

Presynaptic nicotinic receptors are presumed to be composed of alpha and beta units and to be similar to the nicotinic receptors in the CNS, which are also unaffected by alpha bungarotoxin. They are readily desensitised by increased levels of acetylcholine. It has been suggested by Feldman & Hood [67] that this desensitisation occurs earlier than postsynaptic depression and is of particular significance in the production of phase II block. It is also known that excessive Ca^{2+} mobilisation, which occurs in the presence of anticholinesterase agents, can cause downregulation or desensitisation of postsynaptic nicotinic receptors [66]. Kimura *et al.* [68, 69] reported the simultaneous release of noncontractile and contractile Ca^{2+} at the neuromuscular junction following nerve stimulation in the presence of anticholinesterase agents. Noncontractile Ca^{2+} mobilisation was shown to occur under desensitising conditions, depending upon the amount of acetylcholine accumulated in the synaptic cleft. The mechanism of noncontractile Ca^{2+} release requires prolonged activation of postsynaptic receptors and is blocked by low concentrations of tubocurarine and pancuronium. This phenomenon may also be a factor in the production of muscle weakness during the intermediate syndrome.

Unfortunately, there are no studies on responses to neuromuscular blocking agents during the intermediate syndrome, although a marked increase in sensitivity to nondepolarising neuromuscular blockers may be anticipated. This would be similar to the increased sensitivity to nondepolarising neuromuscular blockers after recovery of depolarising block. The increased sensitivity after depolarising block may be up to seven-fold and can occur between 3 and 4 h after suxamethonium block [70].

Baker & Sedgwick [71] carried out single fibre electromyographic (SFEMG) studies in subjects exposed to OP agents. A phenomenon referred to as 'jitter' was observed. This phenomenon originates largely at the neuromuscular junction and is dependent upon the rise time of the end-plate potential to the firing potential in muscle fibres. Jitter increase is the most sensitive indicator of impending failure of transmission at the neuromuscular junction and occurs before the traditional decrement response to tetanic stimulation. Small doses of nondepolarising neuromuscular blockers have been shown to increase jitter. Jitter may be due to an effect on the postjunctional nicotinic receptors or to blockade of the feedback loop at the nerve terminal controlling acetylcholine release. The increased jitter observed in subjects after OP poisoning may persist for up to 2 years and may not be accompanied by any clinical neuromuscular symptoms or signs. Although there is uncertainty as to the exact mechanism of muscle weakness in the intermediate syndrome, altered function at the neuromuscular junction may persist for up to 2 years after its occurrence, and during this period an increased sensitivity to nondepolarising neuromuscular blockers (as is seen after depolarisation block) may be anticipated. It is likely that the increased sensitivity to nondepolarising neuromuscular blockers would start immediately after the depolarisation block of the initial cholinergic phase.

Delayed polyneuropathy

Delayed polyneuropathy usually sets in 7–14 days after exposure to an OP agent and although not associated with

death, it results in disability due to symmetrical peripheral muscle weakness. There may also be disturbances in sensation. The sensory component, if present, is milder than the motor component [18].

The phosphorylation of an enzyme (neuropathy target esterase; NTE) in nerve tissue is considered to be responsible for the polyneuropathy [72, 73]. Neuropathy target esterase is a membrane-bound protein with high esterase catalytic activity whose physiological function is not known. The catalytic activity of NTE is not essential to the health of nerve axons. However, modification of the structure of NTE initiates an irreversible polyneuropathy. This phosphorylated enzyme also undergoes ageing [73]. As the differential inhibition of the target esterases (acetylcholinesterase and NTE) by OP compounds is followed by distinct neurological consequences in exposed subjects, it is useful to distinguish between the neurotoxic (inhibitors of acetylcholinesterase) and neuropathic (inhibitors of NTE) OP agents. Mouse or human neuroblastoma cell lines are considered to be useful *in vitro* models in distinguishing between the esterase-inhibiting OP agents [74].

Other effects of organophosphorus insecticides

Effects on the CNS

Eyer [75] concludes that neuropsychological effects can occur after OP poisoning and that the most frequently reported symptoms include impaired memory and vigilance, reduced information processing and psychomotor speed, memory deficit, linguistic disturbances, depression, anxiety and irritability. There is some concern at present that exposure to OP agents may precipitate psychosis and that chronic psychiatric effects of varying intensity may persist for years [76]. Duffy *et al.* [77] studied the brain electrical activity of workers exposed to the OP compound sarin after a period of 1 year free from exposure. Statistically significant differences from the control group included increased beta activity, increased delta and theta slowing, decreased alpha activity and increased amounts of rapid eye movement (REM) sleep. The findings represented an unexpected persistence of known short-term OP actions and, taken in parallel with the reported long-term behavioural effects, indicate that OP exposure can produce long-term changes in brain function. Perfusion defects, especially in the parietal lobe, have been detected on brain single photon emission computerised tomography (SPECT) after OP poisoning [78]. Acetylcholinesterase, in addition to being an acetylcholine hydrolysing enzyme, is also a neuromodulator that participates in the phenomenon of neuronal plasticity, i.e. the induction of long-term changes in synaptic function. The loss of this nonenzymatic neuromodulatory role of acetylcholinesterase is considered by some to be the basis for the long-term alterations in cognitive function that may follow long-term occupational exposure to OP compounds [79].

Extrapyramidal manifestations (dystonia, rest tremor, cogwheel rigidity and choreo-athetosis) [80] may occur 4–40 days after OP poisoning. These symptoms may disappear spontaneously in 1–4 weeks in those who survive. This phenomenon has been attributed to the inhibition of acetylcholinesterase in the human extrapyramidal system, which is rich in cholinergic neurones and acetylcholinesterase. Recent studies suggest that Parkinson's disease is more common in patients who report previous exposure to pesticides. The role of glutathione transferases, a ubiquitous group of detoxification enzymes involved in the metabolism of pesticides and other toxins, is probably important in the pathogenesis of pesticide-related disease. Glutathione transferase polymorphisms may influence the body's ability to detoxify pesticides and may increase patients' susceptibility to Parkinson's disease after pesticide exposure [81].

A possible association between CFS and chronic low-dose OP poisoning was strengthened by the observation that neuroendocrine disorders (augmentation of prolactin release in response to buspirone, increased sensitivity of central 5-hydroxytryptamine systems, augmented growth hormone response to pyridostigmine and impaired growth hormone release after exposure to dexamethasone) were similar in the two disorders. Furthermore, some patients with the neurobehavioural syndrome after OP exposure had oligoclonal bands in their cerebrospinal fluid; exposure to OPs has been implicated in the pathogenesis of multiple sclerosis, where fatigue is a chronic feature [82].

Altered immunity to infection

In 1974, Bellin & Chow [83] suggested that OP agents might have an effect on the human immune system. Casale *et al.* [84] demonstrated that parathion suppressed both the primary IgM and IgG response to sheep erythrocytes in inbred and outbred mice. The suppression occurred after a dose that produced cholinergic effects but was absent after a lower dose that did not produce cholinergic effects. Thus, OP-induced immunosuppression was associated with severe cholinergic stimulation, either from a direct action of acetylcholine on the immune system or secondary to the toxic chemical stress associated with cholinergic poisoning. Further work by the same group [85] showed that parathion induced suppression of humoral immunity in mice. A marked impairment of neutrophil chemotaxis stimulated with zymosan-activated serum and a greater frequency of upper respiratory tract infection were demonstrated in workers occupationally exposed to OP pesticides in whom a decrease in both serum and red blood cell cholinesterase (acetylcholinesterase) activity was observed [86]. In 1983, Zackov [87] reported that many

OP pesticides elicit autoimmune reactions and suppress the production of antibodies against vaccines. Newcombe [88] showed that patients exposed to OPs developed a number of abnormalities, including an increased incidence of lymphoproliferative disorders associated with impaired natural killer cell and cytotoxic T-cell function. He suggested that these patients might be prone to persistent viral infections, including Epstein–Barr virus and human herpes virus type 6. Murray *et al.* [89] reported 'influenza-like' symptoms probably associated with OP toxicity in 23 patients after occupational exposure.

Changes in metabolism and endocrine activity

In animal experiments, changes in the diurnal pattern of plasma adrenocorticotrophic hormone have been reported following OP insecticide poisoning [90]. Nicotinic receptors also function in brain pathways that increase the release of several pituitary hormones, including vasopressin, adrenocorticotrophic hormone and prolactin. In man, nonketotic hyperglycaemia and glycosuria may occur [91, 92]. Significant decreases in serum concentrations of thyroxine and triiodothyronine and an increased secretion of thyroid-stimulating hormone were observed after malathion treatment in rats [93]. Dose-dependent inhibition of phospholipase A_2 by paraoxon has been demonstrated *in vitro* [94]. Hyperamylasaemia and acute pancreatitis have been reported after oral or dermal exposures in man [27, 95, 96]. Dagli & Shaikh [96] found elevated amylase levels in 47% of patients poisoned with malathion. Lee *et al.* [27] found hyperamylasaemia to be closely related to clinical severity and the presence of shock. However, they considered hyperamylasaemia not to be synonymous with acute pancreatitis following OP poisoning. Lipase assay was felt to be indicated for the early diagnosis of acute pancreatitis. It has also been suggested that an elevation of serum amylase on the day of admission is predictive of subsequent respiratory failure [97]. Hypokalaemia (2.6 and 2.7 $mmol.l^{-1}$) and hypomagnesaemia (1.4 and 1.7 $mg.dl^{-1}$) have been reported after poisoning with the OP agent Diazinon [91].

Effects on the cardiovascular system

Cardiac complications often follow OP poisoning and the disorders reported range from hypotension or hypertension to arrhythmias and cardiac arrest [98]. Kiss & Fazekas [99] reported QT prolongation and ST segment and T-wave anomalies, along with various forms of arrhythmias in 56 of 134 patients poisoned with OP pesticides. Recurrent ventricular tachycardia with the torsade de pointes phenomenon was seen in seven patients. Complete atrioventricular block may occur [100]. A case of congestive cardiomyopathy following long-term OP exposure was recorded in 1980 [101]. After OP insecticide poisoning, QTc prolongation indicates a poor prognosis (mortality rate of 19.6% compared with 4.8% in those without QTc prolongation) and a higher incidence of respiratory failure [102]. Isoprenaline and electrical pacing were effective in shortening the QT prolongation. Lignocaine was found to be ineffective and in some instances caused ventricular fibrillation. Arrhythmias were also aggravated by large doses of atropine. In the series reported by Kiss & Fazekas, most fatal arrhythmias occurred some days after OP exposure when the patient's toxic clinical symptoms and signs were moderate or absent. Hypoxia, metabolic acidosis and electrolyte changes may compound the cardiovascular effects. A 'toxic myocarditis' was found in 76 postmortem examinations carried out after death resulting from OP exposure [103]. Focal myocardial damage (pericapillary haemorrhage, micronecrosis and patchy fibrosis) has also been observed. It has been suggested that the accumulation of acetylcholine at synaptic sites in the myocardium may produce negative inotropy due to interaction with the M_2 muscarinic receptors [104]. However, experimental work in animals suggests a direct action of OP agents on the heart. The ECG changes after human poisoning did not show close correlation with the decrease in enzyme activity and cannot be influenced by atropine. The ECG alteration reproduced in animal experiments precedes the toxicologically relevant cholinesterase depression. These effects are probably pesticide dose dependent and cannot be induced by cholinergic or adrenergic drugs [105].

Gastrointestinal effects

Patients treated in Sri Lanka after ingestion of OP insecticides developed profuse and offensive diarrhoea 2–5 days after poisoning [29]. Similar observations were made by Hayes *et al.* [106] in Rhodesia. Severe fluid and electrolyte losses may occur, in addition to physical difficulties associated with the nursing care of such patients.

Effects on reproduction

In experimental animals, OP poisoning during pregnancy causes pre- and postnatal death and congenital abnormalities such as vertebral deformities, limb defects, polydactyly, intestinal herniae, cleft palate and hydroureter [107]. Dichlorvos, an OP agent, causes damage to seminiferous tubules [108]. Phosphamidon appears to affect the principal cells in the caput epididymis through its toxic effect on the Leydig cells, and the clear cells of the cauda epididymis also appear to be vulnerable to the toxic effects of the pesticide [109]. There is a report of termination of pregnancy following OP poisoning during the first trimester [110]. Karalliedde *et al.* [111] reported normal childbirth in two patients who had required prolonged ventilatory support after severe poisoning during the second and third trimesters of pregnancy.

Vocal cord paralysis

A new variant of life-threatening OP toxicity that produces a brief bilateral vocal cord paralysis was reported recently [112]. A 2-year-old boy developed progressive respiratory distress and stridor without generalised muscle weakness that progressed to complete airway obstruction for which tracheal intubation was necessary. The vocal cord paralysis lasted 2 days.

Temperature regulation

The control of body temperature uses cholinergic pathways in the integration and central processing of thermal information, as well as in the control of thermo-effector responses [113]. After exposure to most OPs, rodents and other small species undergo a marked hypothermic response lasting up to 24 h. Hypothermia has been noted in several case studies and was observed to have an incidence of 7% in Hayes *et al.*'s series [106]. The precise aetiology of the hypothermia has not been determined and may be due to a combination of central neurological changes, muscle paralysis obliterating the shivering response and excessive diaphoresis resulting from overstimulation of the sympathetic cholinergic receptors. Some humans exposed to OP pesticides experience a fever that may last many days. One patient manifested a biphasic thermoregulatory response to OP poisoning: a rectal body temperature of 33 °C 1 h after ingestion that returned to normal after passive rewarming and a hyperthermic response after 18 days that lasted for 48 h [114]. In rats, the hyperthermic response can be blocked by administration of salicylates. Thus, the effect of OPs on body temperature cannot be explained solely on the basis of inhibition of acetylcholinesterase.

Effects on the eyes (myopia and pigmentary degeneration of retina) [44], joints (arthritis) [44] and cerebellar ataxia [44], along with interference with mitochondrial oxidative metabolism [44], have also been reported in animals and man but these observations have not been substantiated.

Effects on other enzymes

Organophosphorus agents are known to inhibit other enzyme systems, the consequences of which are as yet unknown. A variety of tissue carboxyesterases abound in serum, liver, intestine and other tissues. Although inhibition of one specific carboxyesterase, i.e. NTE, has toxic sequelae, no direct deleterious effects of inhibition of other carboxyesterases have been demonstrated. However, carboxyesterases may contribute markedly to the metabolic degradation of OP insecticides, such as malathion, and inhibition of these enzymes may potentiate the toxicity of some OP compounds.

Organophosphorus poisoning in children

Sofer *et al.* [115] described 25 infants and young children poisoned by carbamates and OP compounds. The presenting signs and symptoms differed from those described in adults and were mainly related to severe CNS depression, coma, stupor, dyspnoea and flaccidity. Miosis, excessive salivation, tearing, sweaty cold skin and gastrointestinal symptoms were less frequent, and bradycardia and fasciculations were quite uncommon on arrival in hospital.

Biochemistry

Acetylcholinesterase present in human red blood cells is the same as that found in the target synapses, and changing concentrations of red blood cell acetylcholinesterase are assumed to mirror the effects of OP agents in the target organs, provided the OP agent has equal access to the blood and synapses. It cannot be assumed that the dysfunction at a cholinergic junction is linearly dependent upon the amount of acetylcholinesterase present as there are considerable reserves of the enzyme at all sites and the amount required for efficient functioning is very small in comparison with the total amount available. The range of decreases in activity of acetylcholinesterase or plasma cholinesterase in patients with identical symptoms and signs may be very large [116]. Furthermore, the sensitivities of acetylcholinesterase and cholinesterase to OP agents differ and the use of whole blood for estimations of cholinesterase activity may therefore prove inaccurate. However, in many field situations and in clinical practice, tests using whole blood are more practical than those using separated red blood cells. The usefulness of cholinesterase level estimations is further limited by the physiological variations that occur within and between individuals in health, and the influence of disease states, medication and genetic variations in the enzyme. Thus, serial measurements are of greater benefit than a single estimation. Further caution is required as there is no uniformly accepted standard technique – each method has its own 'normal' range. In chronic exposure, depression of normal cholinesterase activity in blood by 80% is generally considered to be diagnostic of poisoning. When the depression is between 60 and 80%, there may be gastrointestinal symptoms. However, there is considerable individual variation. Fasciculations and other neuromuscular signs and symptoms may develop with depression of acetylcholinesterase in excess of 80% [116]. There is a risk of death with depression of 90% or more. However, animals can survive depression of 100% and humans have had 90–95% depression and recovered without treatment [116]. Clinical recovery correlates well with red blood cell acetylcholinesterase recovery to 30% of normal [117]. A study from Portugal [21] concluded that cholinesterase recovery to above 10% of normal correlates with a good prognosis.

Normal cholinesterase, but not several of its common genetic variants, serves as a scavenger for certain anticholinesterases such as OP compounds. Loewenstein-Lichtenstein *et al.* [118] reported an Israeli soldier homozygous for atypical cholinesterase who suffered severe symptoms following pyridostigmine prophylaxis during the Gulf War. His cholinesterase was far more sensitive than normal cholinesterase to inhibition by anticholinesterases. Thus, increased susceptibility to the toxicity of OP agents appears to be dependent on the quantitative and qualitative state of cholinesterase, as well as on factors that influence acetylcholinesterase values. Cholinesterase activity in red blood cells is low in the newborn and in patients with leukaemia and multiple myeloma, and is elevated whenever the proportion of reticulocytes and young erythrocytes in blood is increased, as in thalassaemia major and hereditary spherocytosis [119]. Plasma cholinesterase activity is depressed in liver disease (cirrhosis, chronic, toxic or viral hepatitis, malignant metastases), hepatic jaundice, obstructive jaundice, decompensated heart disease, allergic diseases, malignant neoplasms and pregnancy [119]. Recent work has shown that protein and calorie malnutrition is associated with a reduction in cholinesterase, which might be a significant factor affecting the severity of OP poisoning in developing countries [120].

Methods used to assay cholinesterase activity vary in sophistication [121]. They include electrometric, colorimetric and titrometric assays. Field methods and fast methods (using paper tests) are also available. Among the disadvantages of the currently used methods are that they cannot detect low-level exposures, the structure of the agent used or the extent of the poisoning. In principle, OP-inhibited cholinesterase in human plasma is the most persistent and abundant source for biomonitoring of exposure to OP agents. Fluoride ions reactivate the inhibited enzyme readily at pH 4, converting the OP moiety into the corresponding phosphofluoridate. Subsequent quantification of the latter product provides a reliable and highly sensitive method for detection of exposure to, or handling of, OPs such as nerve agents or pesticides [122]. This procedure was applied to serum samples from the victims of the Tokyo subway attack by the AUM Shinriyko sect and in an earlier incident at Matsumoto. Surveillance of occupational, accidental and incidental exposure to OP pesticides using urine alkyl phosphate and phenolic metabolite measurements [123], and the application of high-performance thin layer chromatography [124], have been discussed recently.

Management

First aid

1 Remove patient from the contaminated environment.
2 Remove contaminated clothing.
3 Wash skin with soap and water, and eyes with water.
4 Assess breathing and circulation.
5 Resuscitate if necessary.
6 Support vital functions if necessary: oxygen therapy, lung ventilation, inotropes.
7 Control of convulsions.
8 Monitor: ECG, blood pressure, oxygen saturation, ventilation, level of consciousness.

Prevent further absorption of insecticide

1 Gastric lavage: protect airway in patients with impaired consciousness.
2 Administer activated charcoal even though the capacity of activated charcoal to adsorb most OP compounds is not established. In acute fenthion poisoning, evacuation of the gastrointestinal tract, followed by activated charcoal administration, repeated until the absence of anticholinesterase capacity in the gastrointestinal fluid is demonstrated, was advocated by clinicians in Belgium [125]. However, a rectal ulcer causing massive haemorrhage due to activated charcoal treatment in oral OP poisoning has been reported from Japan [126].

Investigations

1 Arterial blood for oxygen and carbon dioxide partial pressures.
2 Venous blood for estimation of red cell acetylcholinesterase and concentration of the OP compound.
3 Venous blood for estimation of biochemistry (electrolytes, glucose, amylase, lipase, creatinine) and haematology.
4 Chest X-ray.
5 Ultrasound scan of the abdomen (pancreatic status).

Atropine or glycopyrrolate

Atropine acts as a physiological antidote, effectively antagonising the muscarinic receptor-mediated actions of excessive acetylcholine (increased tracheobronchial secretions, bradycardia, salivation, bronchoconstriction). It is not known to have any beneficial effect at the neuromuscular junction. Unlike glycopyrrolate, atropine crosses the blood–brain barrier and counteracts the effects of acetylcholine accumulation in the CNS that may cause convulsions and extrapyramidal symptoms. The initial dose should be 2 mg intravenously, repeated at 5–10 min intervals until signs of atropinisation occur: a pulse rate > 80 beat.min^{-1} and dilatation of the initially constricted pupils. Atropine therapy should be maintained until there is complete recovery. Paediatric treatment comprises doses of 0.02–0.05 mg.kg^{-1} every 10–30 min [127]. Infusions of atropine (0.02–0.08 ml.kg^{-1}.h^{-1}) [128] have produced significant reductions in mortality in some centres when compared with conventional intermittent therapy. Atropine has been

shown to enhance neuromuscular transmission and transmitter release, possibly by acting on muscarinic presynaptic inhibitory receptors, which are involved in the feedback mechanism of transmitter release [129, 130]. This observation is of relevance in OP poisoning, as the pathological basis is the accumulation of acetylcholine at the neuromuscular junction. It has been shown that a smaller than traditional dose of atropine used over a shorter duration at a hospital in China was associated with lower complication and mortality rates [131]. A case of OP poisoning refractory to atropine, and in which glycopyrrolate was used to reduce cholinergic symptoms, was reported recently [9].

Magnesium

Kiss & Fazekas [99] reported that in their series, ventricular premature contractions were successfully eliminated with intravenous magnesium sulphate. The magnesium was thought to counteract the direct toxic inhibitory effect of OPs on sodium–potassium ATPase.

Valero & Golan [132] suggested control of atropine-induced massive tachycardia in OP insecticide poisoning by means of β adrenoceptor blockade. Others suggested that using a combination of atropine and glycopyrrolate might offer an advantage over atropine alone, as tachycardia might be avoided. However, tachycardia in OP poisoning is at times not solely due to therapeutic atropine. Catecholamine release from the adrenal medulla is under cholinergic control. Work in pigs has shown that bradycardia due to muscarinic acetylcholine effects occurred only at a low dose or a slow application rate of OP. At higher dosage and faster application rates there was a tendency for hypertension, accompanied by tachycardia, to occur. Thus, it was argued that if β-blockade is used to control the tachycardia, there could be a risk of severe hypertension due to unopposed α activity. In these experiments in pigs, magnesium infusions were used with excellent results. An additional benefit in this setting may be magnesium's inhibitory effect on acetylcholine release [133]. Singh *et al.* [134] administered magnesium sulphate 4 g intravenously to patients intoxicated with OP and observed that the neuro-electrophysiological defects that had been observed earlier were reversed.

Oximes

Three actions have been attributed to pralidoxime [107]:
1 reactivation of cholinesterase by cleavage of phospshorylated active sites;
2 direct reaction and detoxification of unbonded OP molecules;
3 endogenous anticholinergic effect in normal doses.

In animal experiments, a plasma concentration of $4\,mg.ml^{-1}$ was required to counteract neuromuscular block, bradycardia, hypotension and respiratory failure [135]. Suggested therapeutic concentrations have been achieved for 6 h by intravenous administration of pralidoxime chloride (2-PAM) in $15–30\,mg.kg^{-1}$ doses given intravenously. A continuous infusion with a dose of $550\,mg.h^{-1}$ would provide similar therapeutic levels and has been advocated for severe poisoning. However, it should follow two intravenous bolus doses of $30\,mg.kg^{-1}$ 4 h apart. Pralidoxime mesylate (P2S) is less effective in producing sustained oxime concentrations and requires 4-hourly dosing [136]. It is believed that when effective concentrations of oxime are achieved, the balance between ageing and reactivation reaction rates for the inhibited acetylcholinesterase is altered in favour of the latter. Thus, benefit will accrue even if oxime therapy is commenced or continued several days after poisoning.

Traditional dosing for pralidoxime in OP poisoning is 1 g every 8–12 h intravenously in adults and $25–50\,mg.kg^{-1}$ in children. Continuous infusion protocols have been used safely and effectively in children and adults, consequent to the recognition that intermittent bolus doses do not maintain serum pralidoxime concentrations above the minimum effective concentration as suggested by animal data. Thompson *et al.* [137] demonstrated by pharmacokinetic simulation that intermittent dosing in adults of 1 g every 8 h would maintain the desired target concentration for < 5 h in a 24-h period. The volume of distribution and the plasma clearance of pralidoxime is greater in children and the recommended regime is a loading dose of $20–50\,mg.kg^{-1}$ based on symptom severity, followed by a continuous infusion of $10–20\,mg.kg^{-1}.h^{-1}$ [138]. Therapeutic concentrations of the oxime should be maintained to regenerate as much active enzyme activity as possible until the OP compound has been eliminated.

The reactivation action of pralidoxime is most marked at the neuromuscular junction. It does not reverse the muscarinic manifestations of OP poisoning and has a short half-life (1.2 h) when administered intravenously. Oximes, being ionised compounds, do not cross the blood–brain barrier easily and the $\approx 10\%$ reactivation of brain acetylcholinesterase claimed following oxime therapy is thought to be an overestimation [139]. However, some workers believe that the limited passage of the oxime to the brain may have a significant, albeit small, effect and prompt improvement has been reported in the level of consciousness and in the EEG of a poisoned child with an intravenous infusion of pralidoxime chloride [140]. Intramuscular injections of pralidoxime chloride of 7.5 or $10\,mg.kg^{-1}$ have produced plasma concentrations exceeding the therapeutic level of $4\,mg.l^{-1}$ [43]. In large doses, pralidoxime can produce neuromuscular block and even inhibition of acetylcholinesterase [141, 142]. There exists

some controversy regarding the use of pralidoxime in OP poisoning [50, 143, 144] and the timing and sequence of the administration of atropine and pralidoxime [117]. *In vitro* studies with human sera by Ganendran *et al.* [145] showed that pralidoxime produced no significant improvement in overall outcome after OP insecticide poisoning and that there was a risk of producing harmful and more potent phosphorylated oximes. In one study using pralidoxime methylsulphate, it was found that following methyl and ethyl parathion poisoning, enzyme reactivation could be obtained in some patients at oxime concentrations as low as 2.88 $mg.l^{-1}$. However, in others, oxime concentrations as high as 14.6 $mg.l^{-1}$ did not produce an effect. These workers concluded that the therapeutic effect of oximes seemed to depend on the plasma concentration of the OP agent, with the benefits being minimal at high blood levels of OP [146]. A high incidence of arrhythmia was observed in patients who received large cumulative doses of atropine and obidoxime. Impairment of liver function was significantly higher in patients who received high cumulative doses of obidoxime [147]. Scott [148] reporting repeated asystole following pralidoxime administration in OP self-poisoning and concluded that the 'time-honoured eminence of pralidoxime as an antidote in OP poisoning is undeserved'.

Diazepam

Some reports have indicated that benzodiazepines are potentially useful as antidotes to poisoning by cholinesterase inhibitors [149–151]. Diazepam has been useful in the management of convulsions after OP poisoning and in the support of ventilatory care.

Clonidine

Clonidine inhibits the release of acetylcholine from central and peripheral cholinergic neurones. Clonidine pretreatment (0.3 $mg.kg^{-1}$) increased the onset latency to tremor from 5 to 20 min, increased the onset latency to death from 12 to 24 min and increased the percentage of survivors to 50% following poisoning with physostigmine. Yohimbine (1 $mg.kg^{-1}$) reversed these protective effects of clonidine. The physostigmine-induced accumulation of forebrain and hindbrain acetylcholine was also reduced by 50% in both brain regions in clonidine-pretreated mice. The respiratory paralysis induced by neostigmine, a selective peripheral anticholinesterase, was not affected by clonidine pretreatment. It was suggested that central cholinergic neurones involved in the regulation of respiration and fine motor control, but not peripheral motor neurones, are inhibited by the action of clonidine on α receptors [152, 153].

Mice pretreated with the centrally active α_2 adrenergic agonist clonidine (0.1–1 $mg.kg^{-1}$), were protected from several of the toxic manifestations of soman, an OP compound [152]. The protection resulted in increased survival rates and a reduction in centrally mediated symptoms of soman, including tremor and straub tail, as well as one peripheral muscarinic symptom, excessive salivation. Pretreatment with atropine (25 $mg.kg^{-1}$) also protected against soman toxicity. When atropine was combined with clonidine, the degree of protection afforded by the combination was greater than that predicted for a simple additive effect. The protective effects of clonidine are likely to involve multiple effects, including blockade of acetylcholine release and of postsynaptic muscarinic receptors, and transient inhibition of acetylcholinesterase. Clonidine administration may prove useful in the treatment of OP poisoning.

Fluoride

Pretreatment of mice with atropine (17.4 $mg.kg^{-1}$) and sodium fluoride (5 or 15 $mg.kg^{-1}$) had a significantly greater antidotal effect than atropine alone against the lethal actions of soman and sarin. Atropine and sodium fluoride (15 $mg.kg^{-1}$) was effective against tabun, whereas a lower dose of sodium fluoride was not [154, 155]. An effect of sodium fluoride on OP-inhibited acetylcholinesterase could not account for the antidotal action of sodium fluoride. It was hypothesised that the antidotal effect of sodium fluoride is due to its antidesensitising action at nicotinic receptors in the neuromuscular junction and sympathetic ganglia, in addition to the proposed increased hydrolysis of sarin and direct detoxification of tabun. Acetylcholinesterase and NTE that had been inhibited with either mipafox or with di-*N*-butylphosphorodiamidate could be reactivated by prolonged treatment with aqueous potassium fluoride [156]. It is interesting to note that increased cholinesterase levels were observed in workers in a plastic factory handling fluorine compounds [157]. The role of fluoride in OP poisoning merits further study.

Annealed red cells

Resealed cells containing a recombinant phosphotriesterase provided protection against the lethal effect of paraoxon. Phosphotriesterase hydrolyses paraoxon to the less toxic 4-nitrophenol and diethylphosphate. This enzyme was encapsulated into carrier erythrocytes by hypotonic dialysis with subsequent resealing and annealing. The encapsulated enzyme was found to persist longer and possess much greater efficacy. When these carrier cells were administered in combination with pralidoxime chloride and atropine, a marked synergism was observed [158]. The use of lyophilised human cholinesterase, fresh plasma and exchange transfusions are of little value [125].

Conclusions

Organophosphorus compounds provide the anaesthetist with demanding clinical challenges following acute exposure, during both the cholinergic phase and the intermediate syndrome. The use of nerve gases in armed conflicts may be associated with trauma for which anaesthetic services would be required. Occupational exposure to OP agents may manifest as nonspecific disorders in patients presenting for surgery. The effects of OP agents at the neuromuscular junction can alter the response to both depolarising and nondepolarising neuromuscular blockers. Altered neuromuscular function has been observed for up to 2 years after exposure. The activity of drugs hydrolysed by cholinesterase, e.g. local anaesthetics and esmolol, can be prolonged until total recovery of cholinesterase activity occurs. Disturbances in electrolyte balance, e.g. hypokalaemia, endocrine function, e.g. reduced adrenocorticotrophic hormone levels and hyperglycaemia, temperature regulation, immune responses, mental acuity and memory that could follow exposure to OP agents need to be considered during the conduct of an anaesthetic. Effects on the vocal cords are of particular relevance, as is the occurrence of pancreatitis and extrapyramidal disorders. Cardiovascular effects may be long-lasting and the risk of life-threatening arrhythmias provides challenging therapeutic scenarios during anaesthesia and in intensive care.

The mortality and morbidity following acute poisoning is unacceptable and therapeutic regimens that have remained unchanged for decades need to be re-evaluated. It is estimated that the global financial loss due to insect damage is around £6 billion per year. In the face of uncontrolled population growth in several regions of the world, pesticides have made an invaluable contribution to the continuing need for the production of more food. Insecticides have been responsible for the elimination and control of many insect-borne diseases. To maximise the benefits of pesticides to man, there is an urgent need for the collection of precise, accurate information on the range of problems that can occur after exposure to OP compounds in order that appropriate protective and preventive measures can be implemented. Furthermore, the magnitude of the health problems associated with OP agents necessitates collaborative multidisciplinary research between technologically advanced countries and developing countries, where most incidents of poisoning are encountered.

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