

## Organophosphate neuropathy

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### Introduction

This article includes discussion of organophosphate neuropathy, organophosphate-induced delayed neuropathy, and OPIDN. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

### Overview

In this article, the author details the clinical manifestations resulting from organophosphate poisoning. Although there has been great concern about the effects of “nerve gas,” definite exposure to these chemicals in combat has been limited and the manifestations have not been well studied. This article focuses on the clinical features of acute and intermediate syndromes of organophosphate poisoning and also the organophosphate-induced delayed polyneuropathy, which develops only after exposure to certain specific chemicals.

### Key points

- Organophosphate poisoning occurs because of exposure to pesticides, either through occupational contact or intentionally in suicide attempts.
- The neuropathy associated with organophosphate intoxication is delayed in onset and may occur even when initial symptoms from exposure are mild.

### Historical note and terminology

Organophosphate compounds are used as chemical warfare agents (nerve gas), petroleum additives, insecticides, lubricants, antioxidants, flame retardants, and plastic modifiers. The best characterized peripheral neuropathy caused by these compounds in humans is that due to triorthocresyl phosphate, although exposure to other organophosphates such as chlorpyrifos, mipafox, trichlorfon, and leptophos may cause a similar neuropathy. In spite of the multiple uses of these compounds, group exposure in the occupational setting is rare. Intoxication typically occurs due to accidental pesticide exposure from agricultural spraying. This may occur in those individuals mixing or applying the pesticide or through dermal exposure from those working in the fields shortly after spraying (Metcalf and Holmes 1969). Exposure to and possible toxicity from organophosphorus compounds have also been reported in sheep dippers (Jamal et al 2002). Most organophosphate esters are quickly degraded in the environment. Pesticides containing organophosphate are also intentionally ingested in suicide attempts, and in some locations are the most common cause of organophosphate poisoning (Adinew et al 2017). In 1 case, attempted injection of malathion seemed to cause focal injury of the median nerve in a delayed fashion (Ergun et al 2009). A report indicated that intentional subcutaneous injection of chlorpyrifos caused a severe case of organophosphorous poisoning (Soummer et al 2011).

### Clinical manifestations

#### Presentation and course

The type 1 organophosphate syndrome (Wadia et al 1974) is primarily due to excessive muscarinic stimulation. These effects are always present within 1 day of exposure and frequently within hours. The specific organophosphate and the degree of exposure determine the intensity of the acute syndrome. Typical muscarinic symptoms include nausea and vomiting, diarrhea, sweating, salivation, micturition, and tachycardia or bradycardia. Extreme cases may cause CNS involvement with nervousness, emotional lability, fatigue, decreased alertness, cognitive impairment, convulsions, and coma. Rarely, the behavioral change may be the only manifestation. Previous exposure to organophosphate with resultant decrease in functional acetyl cholinesterase may increase the susceptibility, on subsequent exposure, to

developing the acute syndrome.

The intermediate or type 2 organophosphate syndrome (De Bleecker 1995; Abdollahi and Karami-Mohajeri 2012) is due to the overstimulation of nicotinic acetylcholine receptors in skeletal muscle and occurs within 12 to 96 hours of exposure. It is termed intermediate because it follows the muscarinic symptoms and precedes the peripheral neuropathy. There may be an interval of 1 to 4 days between the acute and intermediate syndromes during which the patient is symptom free. Although the neuropathy is discussed more frequently, it probably occurs less often than the type 2 syndrome. Respiratory insufficiency is usually the initial feature. This is followed by proximal muscle and neck flexor weakness. Distal extremity strength is usually preserved but there may be involvement of the cranial muscles (including extraocular muscles). Sensory function remains intact but dystonic posturing is occasionally seen. Recovery starts to occur 5 to 15 days after exposure and proceeds from the cranial muscles to the respiratory muscles, proximal limb muscles, and lastly to the neck flexors. Atropine does not prevent or treat the intermediate syndrome (Wadia et al 1974) as the drug is specific for muscarinic receptors. There is no correlation between the development of the type 2 syndrome and the later appearance of neuropathy.

Independent of the development of the type 1 or type 2 syndromes, a central-peripheral axonopathy may develop with exposure to some organophosphates. A case report of intentional chlorpyrifos ingestion highlighted that the CNS effects may be prominent and overshadow the neuropathy (Thivakaran et al 2012). The neuropathy is not related to the inhibition of acetyl cholinesterase. Neuropathy may not occur until 7 to 21 days after exposure and, therefore, has been labeled the organophosphate-induced delayed polyneuropathy. Although it occurs less frequently than the cholinergic syndromes, it causes significant morbidity. Most organophosphates used in agriculture do not cause the organophosphate-induced delayed polyneuropathy. Compounds that frequently cause subtle or unappreciated cholinergic symptoms are the ones that seem to cause the most dramatic cases of neuropathy. Such cases frequently involve low-level chronic exposure.

In contrast to most toxic central-peripheral axonopathies, the onset of organophosphate-induced delayed polyneuropathy is subacute. The patient usually reaches the nadir by 2 weeks after onset and sometimes sooner. The initial manifestations of organophosphate-induced delayed polyneuropathy include painful paresthesias in the feet and cramping pain in the calf muscles; however, motor symptoms and signs are predominate. There is early weakness of the leg muscles with foot drop. Later, the intrinsic hand muscles are affected, and the proximal muscles are spared until later in the disease course. There is typically evidence of sensory loss with careful examination. There may be gait ataxia that is disproportionate to the degree of weakness or sensory loss. The Achilles reflex is always absent but the degree of CNS dysfunction determines the activity of the other reflexes. Autonomic or cranial nerve dysfunction is rarely present.

There are reports of an association between chronic, low-level organophosphate exposure (in the absence of cholinergic toxicity) and a sensory neuropathy distinct from organophosphate-induced delayed polyneuropathy (Jamal et al 2002). However, in a well-designed study that carefully looked at exposure to chlorpyrifos and evaluated clinical and electrophysiologic parameters, no association with sensory neuropathy was discovered (Albers et al 2004).

### **Prognosis and complications**

Recovery from the acute and intermediate syndromes is usually complete as long as there is good supportive care. By 1 week after organophosphate exposure, only 40% to 60% of acetyl cholinesterase content is regenerated. However, this is usually adequate for functional recovery. The cognitive and behavioral abnormalities may persist after recovery from the acute syndrome.

Good recovery usually occurs in those patients with mild organophosphate-induced delayed polyneuropathy. With more severe deficits, residual foot drop, claw hand deformity, or atrophy may persist. The effects on central (distal dorsal column and corticospinal) axons are frequently revealed after recovery from the peripheral neuropathy. Long-term deficits include ataxia and spasticity and these are more frequent than persistent dysfunction from neuropathy.

## **Biological basis**

### **Etiology and pathogenesis**

Intoxication typically occurs due to accidental pesticide exposure from agricultural spraying. This may occur in those individuals mixing or applying the pesticide or through dermal exposure from those working in the fields shortly after

spraying (Metcalf and Holmes 1969; Lotti et al 1993). Exposure to chemical warfare agents has been proposed to be associated with development of peripheral neuropathy, but the evidence is very limited (Holisaz et al 2007).

Absorption of organophosphates may take place through the respiratory and gastrointestinal tracts as well as through the skin. Once absorbed, the action of organophosphate is to irreversibly inhibit acetyl cholinesterase in erythrocytes and nervous tissue by phosphorylation. Acetylcholine cannot be degraded and builds up, resulting in excessive stimulation of both muscarinic and nicotinic receptors. There are acute (type 1) and intermediate (type 2) syndromes that are based on the receptor preferentially affected.

The organophosphate-induced delayed polyneuropathy may be triggered by certain esterase enzymes but prevented by others. Neuropathy target esterase inhibition is felt to play a role in the genesis of organophosphate-induced delayed polyneuropathy. In fact, evaluation of the toxicity potential of organophosphorus pesticides is based on an assay that measures inhibition of chick neuropathy target esterase (Battershill et al 2004; Doherty 2006). Organophosphate-induced delayed polyneuropathy may be prevented in experimental animals by inhibiting neuropathy target esterase but promoted by inhibiting another esterase known as M200 (Moretto et al 2001). The activity of lymphocyte neuropathy target esterase has been followed serially in a case of organophosphate-induced delayed polyneuropathy and found to be reduced (McConnell et al 1999). Neuropathy target esterase localizes to the inner face of the endoplasmic reticulum (Glynn 2006). It has been shown to play a role in phosphatidyl choline homeostasis and derangement may have effects on membrane stability and contribute to the problems with axonal transport (Glynn 2006). Studies in hens have shown that changes in neurofilaments may be an early event in the evolution of organophosphate-induced delayed polyneuropathy (Song et al 2009b). The same investigators showed that the inhibition of organophosphate-induced delayed polyneuropathy correlated with lack of alteration in neurofilament proportions, suggesting a possible pathogenic role (Song et al 2009a). Although some organophosphorus compounds inhibit calcium-activated ATPases, this activity does not relate to induction of organophosphate-induced delayed polyneuropathy (Barber et al 2001). Investigators have demonstrated abnormalities of mitochondrial complex I activity that correlate with changes in neuropathy target esterase and clinical effects in the preferred animal model (Salama et al 2014).

## **Epidemiology"**

The annual incidence of pesticide intoxications is estimated to be 150,000 to 300,000. This is an estimate, as less than 2% of cases are actually reported to public health officials (Coye 1985). However, organophosphate-induced delayed polyneuropathy is much more commonly caused by tri-ortho-cresyl phosphate, which was used as a hydraulic fluid rather than a pesticide (Lotti and Moretto 2005).

Organophosphate exposures have been reported in Gulf War veterans as well as in sheep dippers. However, critical analysis of these reports shows that several of the cardinal features of toxicology, such as dose-response relationship, are missing (Lotti 2002). In the final analysis, no conclusive evidence exists that a distinct sensory neuropathy is caused by chronic, low-level exposure to organophosphates (Lotti 2002).

## **Prevention**

Education of those working with these compounds regarding the potential toxicity is the first step. Protective clothing, good hygiene, and monitoring for toxicity are all important. As noted above, after emergence of the acute syndrome, administration of atropine has no effect on the later development of the intermediate syndrome or organophosphate-induced delayed polyneuropathy. However, nerve conduction studies may reveal evidence of early, reversible neuropathy in exposed individuals (Misra et al 1988). Serum levels of cholinesterase have been demonstrated to be depressed in pesticide workers exposed to chlorpyrifos; this enzyme may be a useful marker for exposure (Dyer et al 2001). Finally, screening of compounds for their potential to cause organophosphate-induced delayed polyneuropathy may reduce the incidence of later toxicity (Battershill et al 2004).

## **Differential diagnosis**

The acute syndrome may have prominent mental status abnormalities, and other drug or toxin ingestion needs to be excluded. The intermediate syndrome with prominent muscular weakness that may present in a fulminant fashion can mimic Guillain-Barré syndrome, periodic paralysis, or a severe attack of myasthenia gravis. The delayed neuropathy needs to be distinguished from other causes of a central-peripheral distal axonopathy, which include numerous other

toxins as well as naturally occurring illnesses. It may also present in an earlier stage as a simple distal axonopathy, which has a broad differential diagnosis.

## Diagnostic workup

Although electrophysiologic testing is a sensitive indicator for organophosphate exposure, it does not accurately reflect the severity. Shortly after organophosphate exposure, spontaneous repetitive motor action potentials following the initial compound motor action potential are elicited by a single stimulus (Wadia et al 1987b; Rafai et al 2007). The ability to elicit spontaneous repetitive motor action potentials is a sensitive indicator of organophosphate exposure but does not reflect the degree of intoxication. With the onset of weakness, a decremental response to repetitive nerve stimulation is seen. The maximal reduction in motor potential amplitude typically occurs with the second potential, unlike myasthenia gravis in which the decrement is typically maximal by the fourth response. In the case of mild intoxication, rapid stimulation rates may be required to demonstrate decrement. In addition, decrement may be followed by increment, and spontaneous repetitive motor action potentials are usually present. With more severe exposure, spontaneous repetitive motor action potentials may be absent and decrement is evident even with slow rates of stimulation (Besser et al 1989).

Electrophysiologic testing in organophosphate-induced delayed polyneuropathy reveals evidence of a sensorimotor axonal neuropathy. Although motor symptoms are most prevalent, sensory conduction abnormalities are more dramatic and appear earlier. Sensory nerve action potentials are reduced in amplitude or absent, whereas the motor conduction studies are either normal or reveal minimal slowing of conduction velocity. Needle EMG reveals evidence of acute and chronic denervation in the distal and occasionally proximal limb muscles. EMG is normal in patients with the intermediate syndrome (Wadia et al 1987a).

Routine clinical laboratory values are typically unrevealing. Acetyl cholinesterase levels in erythrocytes are depressed with recent exposure to organophosphate and levels below 20% of normal are associated with severe weakness. However, the variability of normal erythrocyte acetyl cholinesterase levels makes a single determination difficult to interpret and serial measurements showing progressive decline in activity are most helpful. The acetyl cholinesterase level is not predictive of future development of organophosphate-induced delayed polyneuropathy, and levels may have returned to normal by the time testing is performed as enzyme regeneration occurs at the rate of 1% per day. There appears to be little diagnostic value in performing pseudocholinesterase levels. The CSF protein level is normal or slightly elevated and the fluid acellular.

## Management

Organophosphate poisoning is a medical emergency and can be fatal if not treated properly. Because there is significant risk of respiratory failure, maintenance of a good airway is paramount and intubation may be required. Excessive secretions and vomiting are often present with altered awareness, and intubation may be necessary even when respiratory function is preserved.

Immediately after recognition, the affected individual should be removed from further exposure. Contaminated clothing should be removed and the skin cleansed to prevent further absorption. In the case of ingestion, gastric lavage should be performed and cathartics administered. Reactivation of acetyl cholinesterase may be accelerated by the administration of pralidoxime, which is most effective if given early in the course. Pralidoxime may prevent the emergence of the intermediate syndrome. Although the World Health Organization recommends the use of pralidoxime for organophosphate poisoning, a Cochrane review did not find evidence to support its use, and there was suggestion that there may be harm, particularly in some cases (Buckley et al 2011). Fortunately, the muscarinic symptoms are typically relieved with atropine. However, the duration of atropine's action is short and it often must be readministered to prevent the recurrence of symptoms that may still be fatal. Because there is some evidence that administration of atropine to patients with respiratory insufficiency may be associated with an increased risk of ventricular arrhythmias, patients need to be adequately ventilated before it is given. Atropine is specific for muscarinic receptors and, therefore, has no effect on depolarizing neuromuscular blockade due to overstimulation of nicotinic receptors. A study found that administration of packed red blood cells is beneficial in acute organophosphate poisoning, and the benefit is more pronounced with freshly obtained (fewer than 10 days) packed red blood cells (Bao et al 2017).

## Special considerations

### Pregnancy

There is some evidence that organophosphate compounds may be able to pass to the fetus in utero. There is variability regarding the potential for teratogenicity of these agents in animal models.

### Anesthesia

Neuromuscular blocking agents that are typically used in preparing the patient for intubation should not be used because they may exacerbate the problem.

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\*\*References especially recommended by the author or editor for general reading.

### **Former authors**

Alan R Berger MD

### **ICD and OMIM codes**

## **ICD codes**

ICD-9:

Organophosphate neuropathy: 357.7

ICD-10:

Organophosphate neuropathy: G62.2

## **Profile**

### **Age range of presentation**

19-44 years

45-64 years

### **Sex preponderance**

male=female

### **Family history**

none

### **Heredity**

none

### **Population groups selectively affected**

none selectively affected

### **Occupation groups selectively affected**

agricultural workers

## **Differential diagnosis list**

other drug or toxin ingestion

Guillain-Barré syndrome

periodic paralysis

myasthenia gravis

other causes of central-peripheral distal axonopathy

simple distal axonopathy

## **Associated disorders**

Intermediate organophosphate syndrome

Type 1 organophosphate syndrome

## **Other topics to consider**

Clinical evaluation of peripheral neuropathies

Gulf War syndrome

Neurologic disorders related to chemical and biological warfare agents

Neuroprotection for CNS disorders

Toxic peripheral neuropathies