The New England
Journal of Medicine

Volume 316 MARCH 26, 1987 Number 13

NEUROTOXIC EFFECTS OF ORGANOPHOSPHORUS INSECTICIDES

An Intermediate Syndrome

NIMAL SENANAYAKE, M.D., AND LAKSHMAN KARALLIEDDE, M.B.B.S.

Abstract Acute neurotoxic effects during the cholinergic phase of organophosphorus insecticide poisoning and delayed neurotoxic effects appearing two to three weeks later are well recognized. We observed 10 patients who had paralysis of proximal limb muscles, neck flexors, motor cranial nerves, and respiratory muscles 24 to 96 hours after poisoning, after a well-defined cholinergic phase. The compounds involved were fenthion, monocrotophos, dimethoate, and methamidophos. Four patients urgently required ventilatory support. The paralytic symptoms lasted up to 18 days. A delayed polyneuropathy later developed in one patient. Three patients died. Electromyographic studies showed fade on tetanic stimulation, absence of fade on low-frequency stimulation, and absence of post-tetanic facilitation, suggestive of a postsynaptic defect. This neuromuscular junctional defect may have been the predominant cause of the paralytic symptoms, with neural and central components contributing to various degrees. Our patients appeared to have a distinct clinical entity (a so-called intermediate syndrome) that developed after the acute cholinergic crisis and before the expected onset of the delayed neuropathy. (N Engl J Med 1987; 316: 761-3.)

ACUTE neurotoxic effects during the cholinergic phase of organophosphorus poisoning are well known. Also recognized are the delayed neurotoxic effects usually manifested as distal motor polyneuropathy.[1] This paper describes an intermediate syndrome of neurotoxic effects that appear after the acute cholinergic crisis but before the expected onset of delayed neuropathy. The cardinal feature of the syndrome is muscular weakness, affecting predominantly the proximal limb muscles and the neck flexors. Cranial-nerve palsies are common. Unlike the delayed polyneuropathy, this syndrome carries a risk of death because of the associated respiratory depression. The pathophysiologic process underlying this syndrome seems to be different from that of the cholinergic crisis and the delayed neuropathy, and the three clinical situations suggest a triphasic effect of organophosphorus compounds after human intoxication.

CASE REPORTS

This report concerns 10 patients observed in the University Medical Unit at Peradeniya during the past three years. All 10 were dark skinned and of Asian origin. Nine were men. The age range was 22 to 60 years (median, 24). In nine patients, poisoning was due to ingestion with suicidal intent; the other (Patient 8) presented after spraying. The organophosphorus compound was known with certainty in nine patients (Table 1).

All 10 patients had a well-defined cholinergic phase, with physical signs that included miosis, salivation, sweating, and fasciculations. Consciousness was impaired in one (Patient 7). The initial treatment included pralidoxime (1 g every 12 hours for 24 to 48 hours) and atropine (up to 40 mg in 24 hours). Atropine therapy was continued to maintain mydriasis and a pulse rate of at least 100 per minute. Four patients received these drugs within one to two hours of being poisoned. In 24 to 48 hours, all the patients recovered from the cholinergic crisis and were free of muscle fasciculations, miosis, and sweating. The patient who was unconscious on admission (Patient 7) became conscious and rational. One (Patient 3) was discharged to his home because he was free of symptoms and signs.

On recovery from the cholinergic crisis, usually 24 to 96 hours after the poisoning, an "intermediate syndrome" developed in all the patients. In seven patients, respiratory insufficiency drew attention to the onset of the syndrome. Four of these, including Patient 3, required immediate endotracheal intubation and intermittent positive-pressure ventilation. Various degrees of weakness of the muscles innervated by one or more cranial nerves were present in eight patients. Marked weakness of neck flexion to the extent that the patient was unable to raise his or her head off the pillow was a constant feature in all 10 patients. The other constant feature was weakness of proximal limb muscles. All the patients had moderate to severe weakness of shoulder abduction and hip flexion demonstrable on physical examination. However, normal strength in the distal muscles gave a false impression that the limbs were spared. In all but one (Patient 4), the knee and ankle reflexes were absent or markedly decreased. The upper-limb reflexes were also decreased to various degrees. In Patient 4, the reflexes were exaggerated and the muscle tone was increased, particularly in the lower limbs. The plantar responses were flexor. None of the patients had sensory impairment. An unusual feature was transient dystonic movements of the limbs, noted early in the course of the illness in two patients after fenthion poisoning (Patients 5 and 6). Patient 7, as he was recovering from the intermediate syndrome 18 days after being poisoned by methamidophos, went on to have delayed polyneuropathy.

The four patients who required ventilatory care subsequently underwent tracheostomy and received mechanical ventilation for 5 to 15 days. The rest of the management was addressed to symptoms.

From the Departments of Medicine and Surgery, Faculty of Medicine, University of Peradeniya, Peradeniya, Sri Lanka. Address reprint requests to Professor Senanayake at the Department of Medicine, Faculty of Medicine, Peradeniya, Sri Lanka.

Table 1. Characteristics of 10 Patients with the Intermediate Syndrome.

Patient No.	Age (Yr)/ Sex	Organophosphate	Time to Onset of Weakness (Days)	Cranial-Nerve Palsies	Respiratory Difficulty*	Duration of Weakness (Days)	Other Features
1	22/M	Dimethoate	2	iii, iv, vi, vii, x	−	5	—
2	60/M	Dimethoate	2	?	+	3 (Died)	—
3	24/M	Fenthion	2	iii, vii	+ (IPPV)	15 (Died)	—
4	26/F	Fenthion	<6	iii, iv, vi	−	18	Pyramidal signs
5	25/M	Fenthion	2	iii, iv, vi, vii, x	+	5 (Died)	Dystonia
6	55/M	Fenthion	<6	x	−	8	Dystonia
7	22/M	Methamidophos	<4	—	+ (IPPV)	32†	Delayed neuropathy
8	23/M	Monocrotophos	1	vi, vii	+	16	—
9	27/M	Monocrotophos	<4	iii, iv, vi, v, x	+ (IPPV)	18	—
10	27/M	Unknown	2	v, vi, vii	+ (IPPV)	16	—

*IPPV denotes intermittent positive-pressure ventilation.
†Overlapped onset of polyneuropathy.

Methods

Routine urinalysis and biochemical and hematologic investigations revealed no serious abnormality. Examination of cerebrospinal fluid in three patients was also normal.

Assay of cholinesterase activity was not available. It would have been useful, not in the diagnosis of the cholinergic crisis, which was clinically obvious, but in determining whether the degree of cholinesterase inhibition in plasma or red cells was correlated with the symptoms of the subsequent intermediate syndrome.

Nerve conduction (median nerve, motor and sensory; and common peroneal nerve, motor) in six patients during the intermediate syndrome was normal. The results of routine electromyography of the distal and proximal limb muscles were also normal. However, tetanic stimulation of the abductor pollicis brevis 24 to 48 hours after the onset of the intermediate syndrome showed a marked fade at 20 and 50 Hz. The muscle was stimulated with surface electrodes on the median nerve at the wrist, and the muscle action potentials were recorded with surface electrodes placed on the muscle. At 50 Hz, a fade of 30 to 75 percent was observed at five seconds; at 20 Hz, one patient had an 80 percent fade in 10 seconds, and the others had a fade of 20 to 30 percent in 10 seconds. A train of four supramaximal stimuli at 2 Hz did not produce a change in the amplitude of the motor action potential. There was no post-tetanic facilitation.

Clinical Course

There was no definite pattern in the development of the neurologic manifestations. Nevertheless, the regression of signs followed a characteristic pattern in those who survived. Cranial-nerve palsies — palatal, facial, and external ocular, in that order — were the first to regress. This regression was followed by improvement of the respiratory difficulty and recovery of strength in the proximal limb muscles. Neck flexion was the last function recovered. The period of recovery ranged from 5 to 18 days after the onset of weakness, except in Patient 7, who subsequently had delayed polyneuropathy. In this patient, the weakness of neck flexion lasted 32 days. By that time, he already had weakness of the distal muscles of the limbs due to the delayed neuropathy. Two patients died of respiratory failure, on the third and fifth days, respectively. Patient 3 died on the 15th day, because of a technical failure while he was receiving ventilation.

Discussion

This series represents a group of patients who had muscular paralysis following poisoning by certain organophosphorus compounds, after apparent recovery from the cholinergic crisis but before the expected onset of delayed polyneuropathy. The characteristic pattern of muscle involvement and other associated features merit recognition of this disorder as a distinct clinical entity, which we call the "intermediate syndrome." The muscle weakness had an acute onset, was noted within 24 to 96 hours after poisoning, and affected conscious patients without fasciculation or other cholinergic manifestations. The early onset of the intermediate syndrome differentiates it from the delayed polyneuropathy that appears two to three weeks after poisoning.[2] There is also an obvious contrast between the patterns of muscular weakness in the two conditions. The intermediate syndrome predominantly affects muscles innervated by the cranial nerves — neck flexors, proximal muscles of the limbs, and muscles of respiration. In delayed polyneuropathy, the paralysis is usually limited to the distal muscles of the limbs; cranial nerves and respiratory muscles are spared. The clinical courses of the two entities also differ (Table 2).

Paralysis appearing within 24 hours of poisoning by organophosphorus compounds (ronnel, methyl parathion, or malathion) and lasting a few days or weeks has been described in hens.[3,4] In rats, intravenous injections of diisopropyl fluorophosphate and paraoxon have produced pathologic changes in the end-plate region of striated muscles that were fully developed in 12 hours. Recovery was shown to begin in 2 days,

Table 2. Comparison of the Intermediate Syndrome and Delayed Neuropathy.

Variable	Intermediate Syndrome	Delayed Neuropathy
Time of onset, after poisoning	1–4 Days	2–3 Wk
Sites of weakness		
Limb muscles	Proximal	Distal
Neck muscles	+	−
Cranial nerves	+	−
Respiratory muscles	+	−
Electromyogram	Tetanic fade	Denervation
Recovery, from time of onset	4–18 Days	6–12 Mo
Organophosphorus agents commonly involved	Fenthion Dimethoate Monocrotophos	Methamidophos Trichlorphon Leptophos

and it was almost complete in 10 days.[5] Pathologic changes in the motor end plate, particularly of external ocular muscles, have been described in rats killed 15 days after organophosphorus poisoning.[6] The intermediate syndrome described here probably represents the human equivalent of some of these observations in animals.

The agents most commonly responsible for organophosphorus intoxication in the 92 patients we have seen have been dimethoate in 16, methamidophos in 9, malathion in 8, monocrotophos in 6, and fenthion in 6.[7] The agents responsible for the intermediate syndrome have been fenthion in 4, monocrotophos in 2, dimethoate in 2, and methamidophos in 1. During the cholinergic crisis, there was no difference in the clinical picture between those in whom the intermediate syndrome subsequently developed and those in whom it did not. The treatment given and the response observed in the cholinergic phase were also similar in all patients. Atropine therapy did not seem to influence the development of the intermediate syndrome.

Fenthion, dimethoate, and monocrotophos are dimethoxy compounds. Dean et al.[8] and Mahieu et al.[9] have reported prolonged ventilatory depression in humans with fenthion poisoning. There has also been a report of two relapses in spite of apparently adequate therapy.[5] Relapse of symptoms with unconsciousness following dimethoate intoxication has also been reported.[10] Dicrotophos, a compound closely related to monocrotophos, has produced respiratory paralysis on the sixth day after intoxication.[11] Relapse with respiratory difficulty following intoxication with malathion, another dimethoxy compound, has also been reported.[12]

In a series of patients with delayed neuropathy described by one of us, methamidophos was the causative agent in 25 of the 27 cases.[13] Three of the patients had a history suggestive of the intermediate syndrome. In Patient 7 in the present study, unconsciousness due to methamidophos, lasting for 12 hours in the cholinergic phase despite supportive and specific therapy, suggested severe intoxication, which may have been a determinant in the development of the intermediate syndrome. The possibility that some of the unusual symptoms and signs were due to the presence of impurities or to interaction with other chemicals in the commercial formulations cannot be excluded.

Wadia et al.[14] have reported paralytic neurologic signs in patients after poisoning with diazinon, an oxygen–sulfur dimethyl compound. The signs were divided into Type I (those present on admission) and Type II (those appearing 24 hours after poisoning). Type I signs, which included impaired consciousness and fasciculation, responded to atropine therapy. Type II signs (proximal limb weakness, areflexia, and cranial-nerve palsies) were not influenced by atropine. Some patients with Type I paralysis who recovered with atropine therapy subsequently had Type II paralysis. A number of patients with Type II signs died of respiratory paralysis. We believe that the Type II signs fit the description of the intermediate syndrome.

The electromyographic findings (fade on tetanic stimulation, absence of fade on low-frequency stimulation, and absence of post-tetanic facilitation) were different from those seen in other neuromuscular disorders. Tetanic stimulation produces an enhancing response in botulism and myasthenic syndrome.[15] Fade on tetanic stimulation is seen in myasthenia gravis, but a decline in response at low frequencies of stimulation and post-tetanic facilitation are also observed.[15] In depolarization block as seen with acetylcholine and decamethonium, both fast and twitch rates of nerve stimulation are well sustained.[16] Thus, it is possible that the neuromuscular junctional dysfunction in the intermediate syndrome is post-synaptic. This would be in keeping with the pathologic changes described in laboratory animals.

In 9 of our 10 patients the ankle reflex was absent, suggesting a neuropathic element. Signs of pyramidal-tract dysfunction in Patient 4 suggest an additional upper motor component due to involvement of the cephalic part of the pyramidal system. The dystonia noted in two patients, though not directly related to the muscular weakness, further suggests a central involvement of the extrapyramidal system. It is likely that the neuromuscular junctional dysfunction is the predominant factor in the pathogenesis of the intermediate syndrome. However, the possibility of contributions to muscle weakness by neural and central components cannot be ruled out.

References

1. Lotti M, Becker CE, Aminoff MJ. Organophosphate polyneuropathy: pathogenesis and prevention. Neurology 1984; 34:658-62.
2. Senanayake N, Johnson MK. Acute polyneuropathy after poisoning by a new organophosphate insecticide. N Engl J Med 1982; 306:155-7.
3. Witter RF, Gaines TB. Relationship between depression of brain or plasma cholinesterase and paralysis in chickens caused by certain organic phosphorus compounds. Biochem Pharmacol 1963; 12:1377-86.
4. Gaines TB. Acute toxicity of pesticides. Toxicol Appl Pharmacol 1969; 14:515-34.
5. Hayes WJ Jr. Pesticides studied in man. Baltimore: Williams & Wilkins, 1982:284-413.
6. Asanuma S, Nakamura T, Suzuki A, Hirooka Y, Kurosawa K, Matsushima S. An experimental study on the organophosphorus pesticide residues in humans. Jpn J Ind Health 1974; 16:36-7.
7. Senanayake N, Karalliedde L. Pattern of acute poisoning in a medical unit in Central Sri Lanka. Second Indo-Pacific Congress on Legal Medicine and Forensic Sciences. Colombo: Medico-Legal Society of Sri Lanka, 1986:36. abstract.
8. Dean G, Coxon J, Brereton D. Poisoning by an organophosphorus compound: a case report. S Afr Med J 1967; 41:1017-9.
9. Mahieu P, Hassoun A, Van Binst R, Lauwerys R, Deheneffe Y. Severe and prolonged poisoning by fenthion: significance of the determination of the anticholinesterase capacity of plasma. J Toxicol Clin Toxicol 1982; 19:425-32.
10. Molphy R, Rathus EM. Organic phosphorus poisoning and therapy. Med J Aust 1964; 2:337-40.
11. Perron R, Johnson BB. Insecticide poisoning. N Engl J Med 1969; 281: 274-5.
12. Gadoth N, Fisher A. Late onset of neuromuscular block in organophosphorus poisoning. Ann Intern Med 1978; 88:654-5.
13. Senanayake N. Polyneuropathy following insecticide poisoning: a clinical and electrophysiological study. J Neurol 1985; 232:Suppl:203. abstract.
14. Wadia RS, Sadagopan C, Amin RB, Sardesai HV. Neurological manifestations of organophosphorous insecticide poisoning. J Neurol Neurosurg Psychiatry 1974; 37:841-7.
15. McComas AJ. Neuromuscular function and disorders. London: Butterworths, 1977:195-200.
16. Feldman SA. Neuromuscular block. In: Churchill-Davidson HC, ed. A practice of anaesthesia. 4th ed. London: Lloyd-Luke, 1978:829-64.