

Case Report

The “Intermediate Syndrome” as Critical Sequelae of Organophosphate Poisoning: The First Report of Two Cases in Thailand

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The authors report 2 cases of organophosphate poisoning which developed intermediate syndrome. The first case was a man who took an organophosphate insecticide, monocrotophos, and developed severe organophosphate poisoning. Respiratory support was needed. He was treated with atropine and 2-PAM. Weakness of neck muscles, proximal limb and respiratory muscle developed in the 3rd day after ingestion. By supportive treatment and careful monitoring, however, he recovered after 11 days of the poisoning. The second case was a lady who took dicrotophos. She developed severe organophosphate poisoning for which respiratory support was also needed. High dose of atropine, but without 2-PAM, was administered. She developed bulbar palsy, proximal muscle and respiratory weakness 3 day after the ingestion. Ventilation support was needed for 13 days before weaning was successful. This report did not support an efficacy of pralidoxime (2-PAM) in alleviation of the intermediate syndrome, but aims to alert physicians to recognize the intermediate syndrome for which adequate respiratory care is the crucial key for its management.

Keywords: Organophosphate, Pralidoxime, Bulbar palsy, Proximal muscle weakness, Respiratory failure

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The clinical feature of organophosphate poisoning is a combination effect of acetylcholine stimulation on various kinds of acetylcholine receptors such as muscarinic and nicotinic receptors. Patients who develop respiratory failure have less favorable prognosis and outcome. Many factors are responsible for respiratory failure such as respiratory muscle weakness, bronchospasm with bronchorrhea, and respiratory tract infection. Regarding muscle weakness, two kinds of clinical features during acute organophosphate poisoning are described. Fasciculation and weakness from direct stimulation of nicotinic cholinergic receptor is well known. Another clinical feature is “an intermediate syndrome”^(1,2). Although it has been described for a few decades, it remains commonly undiagnosed.

The objective of this communication, which is believed to be the first one in Thailand with regard to the intermediate syndrome after organophosphate poisoning, was to report on two interesting cases of neurotoxic manifestations from poisoning with dicrotophos and monocrotophos. It was hoped that this report would serve to alert physicians to early recognize the intermediate syndrome during the course of severe organophosphate poisoning. Respiratory care is specifically emphasized as the key of management for the intermediate syndrome patients.

Case Report

Case 1

A forty-two-year-old man was brought to the hospital after having developed progressive comatose. He had a history of hypertension with poor compliance. On admission, he was unconscious, not responsive to pain stimuli. Vital signs revealed BP 180/130 mmHg,

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P 103/min, RR 18/min. Pupils were 1 mm in diameter. Generalized sweating and coarse crepitation of both lungs were found. Muscle fasciculation was observed on both legs. He was intubated with and put on assisted ventilation. Anticholinesterase insecticide poisoning was then diagnosed. He was treated with 50 gram of activated charcoal via nasogastric tube feeding for gastrointestinal decontamination. Pralidoxime (2-PAM) and atropine were both administered. The dose of 2-PAM was 1 gram given intravenously every 6 hours. Atropine (1.2 mg) was administered intravenously every 5 minutes till atropinization. Because the total of 13.2 mg of atropine in 55 minutes was initially needed to dry the secretion, but the pupils remained 1-2 mm in diameter, atropine was continuously infused at the rate of 15 mg/hour to dry the secretion. The patient's consciousness was slightly improved. Secretion and sweating were minimal, heart rate ranged from 80-110/min, but the pupils were still 1-2 mm in diameter.

On the second day of admission, his consciousness improved and he was able to follow verbal commands. The secretion was dry, but tachycardia and miosis still remained. The 2-PAM and high dose of atropine were therefore continued.

He was fully conscious on the 3rd day but was not able to flex his neck. Physical examination revealed bilateral symmetrical weakness of the proximal upper and lower extremities as well as neck flexor muscles as shown in Table 1. Although the lungs were clear, mechanical ventilation was still needed. No sensory deficit was detected. The intermediate syn-

Table 1. The power of each limb muscle group at the time when intermediate syndrome was diagnosed in case 1

Muscle category		Right	Left
Shoulder	F/Abd	3/3	3/3
Elbow	F/E	4/4	4/4
Wrist	F/E	4 ⁺ /4 ⁺	4/4 ⁺
Handgrip		5/5	5/5
Hip	F/Abd	3 ⁺ /3	3 ⁺ /3
Knee	F/E	4/4	4/4
Ankle	DF/PF	4/4	4/4
Toe	EHL/FHL	5/5	5/5
Neck	flexion	not able to be against gravity	

Abbreviations:

F/Abd	flexion/abduction
F/E	flexion/extension
DF/PF	dorsiflexion/plantar flexion
EHL/FHL	extensor hallucis longus/flexor hallucis longus

drome was therefore diagnosed. The drugs remained necessary.

On the 4th day, he developed visual hallucination as he wrote to nurses that he saw a swarm of ants marching on a nearby bed. He was restless, and then self extubated. Shortly, shortness of breath resumed, he was reintubated and mechanically ventilated. He was sedated by haloperidol and diazepam. Then, atropine psychosis was suspected and the drug was discontinued. The psychotic feature then subsided.

On the following days, patient's secretion became less and hemodynamics was stable. Several weaning attempts were tried without success.

Mechanical ventilation support was continued until the 11th day when weaken neck flexors and limb muscles improved to grade 4/5. Ventilator weaning was then reinitiated and patient could be weaned off the ventilator easily. He was finally extubated on the 12th day and fully recovered on the 20th day.

His gastric content and urine specimen, analyzed by gas chromatography/mass spectroscopy, were positive for monocrotophos. The serum cholinesterase was 0 unit/mL. He admitted that he purposely took the insecticide for suicide.

Case 2

A twenty-two-year-old woman was referred to the hospital because of severe organophosphate poisoning. She intended suicide by ingesting dicrotophos insecticide 1 day ago. She was found unconscious with pinpoint pupils, hypersecretion, hypersalivation, bradycardia (heart rate of 46/min) and fasciculation. She was intubated with assisted ventilation. During the first 2 days, 337.2 mg (562 ampoules) of atropine, but no 2-PAM, was administered to the patient. She was referred to the hospital for further treatment late of the second day. On physical examination, she was in drowsiness, having the vital signs: heart rate 85-96/min, BP 107/69 mmHg, RR 16/min (on volume respirator). Pupils were pinpoint. Muscle fasciculation was found. Atropine 14.4 mg (24 ampoules)/hour and 2-PAM 1 gram every 6 hours were administered intravenously.

On the 3rd day of the poisoning (the 2nd day of admission) she was more alert and able to follow verbal commands. Heart rate was 90-100/min. Pupils were 2 mm in diameter and reacted to light. Salivation was increased, but secretion was decreased. She had bilateral ptosis. Impairment of conjugated eye movement, bilateral medial gaze and upward gaze palsy were observed (Fig. 1, 2). Weakness of proximal muscles as



Fig. 1 A picture of the second patient during the development of intermediate syndrome. She had ptosis of both eyes and was not able to spontaneously open her eyes fully. The picture shows impairment of medial gaze of the left eye when gazed at the right. The right eye also had impaired medial gaze when gazed at the left



Fig. 2 This picture shows weakness of both arms, especially the proximal parts. She was not able to raise her arms. Muscle strength of handgrips was nearly normal. Ptosis of both eyes was noted

well as neck muscles was detected as shown in Table 2. The intermediate syndrome was diagnosed. Atropine was gradually decreased to the rate of 2.4 mg/hour. 2-PAM was administered only on day 2 to day 4; then no fasciculation and generalized muscle weakness were found.

On the following days, she was alert but could not breathe spontaneously. Continuous mandatory ventilation (CMV) mode was needed. The muscarinic signs were detected, but only a lower dose of atropine was needed to control the cholinergic effects.

The extra-ocular muscle weakness recovered on the 6th day after the intoxication. Ptosis recovered on the 7th day. The secretion was dry and lungs were clear. However, weaning from the respirator was not successful. Arterial blood gas, immediately after weaning with T-piece, FiO₂ 0.4, showed respiratory acidosis (pH 7.39, pCO₂ 53, pO₂ 168 mmHg, HCO₃ 31.9 mEq/L). Synchronized intermittent mandatory ventilation mode (SIMV) was applied to the patient until the 11th day. Atropine in the decrement rate of 0.6 mg/hour was needed for drying the secretion.

On the 13th day, she was able to breathe spontaneously in continuous positive airway pressure (CPAP) mode, but showed a tendency to breathe at a slower rate while sleeping.

Proximal muscle weakness improved to grade 4/5 and she was able to be extubated on the 14th day. The patient was discharged from the hospital on the 20th day after the intoxication. When she returned for follow up on the 30th day, all muscle weakness had disappeared.

Discussion

In organophosphate poisoning, muscle weakness, which is found during cholinergic crisis, is caused by over-stimulation of nicotinic cholinergic receptor at neuromuscular junction which causes depolarization blockade. The clinical features are muscle fasciculation and then generalized muscle weakness. There is another specific pattern of muscle weakness which is described as having weakness of proximal muscles,

Table 2. The power of each limb muscle group at the time when intermediate syndrome was diagnosed in case2

Muscle category		Right	Left
Shoulder	F/Abd	3/3	3/3
Elbow	F/E	3/3	3/3
Wrist	F/E	3/3	3/3
Handgrip		5/5	5/5
Hip	F/Abd	0/0	0/0
Knee	F/E	2/2	2/2
Ankle	DF/PF	3/3	3/3
Toe	EHL/FHL	5/5	5/5
Neck	flexion	not able to be against gravity	

Abbreviations:

F/Abd	flexion/abduction
F/E	flexion/extension
DF/PF	dorsiflexion/plantar flexion
EHL/FHL	extensor hallucis longus/flexor hallucis longus

neck muscles, cranial nerve palsies, accessory respiratory muscles, and diaphragm. It was first reported by Wadia et al in 1974 as the type II paralysis after organophosphate poisoning⁽¹⁾. Senanayake and Karalliede termed this pattern of weakness as "intermediate syndrome" (IMS) in 1987⁽²⁾. The syndrome usually develops after acute cholinergic crisis phase, but may be superimposed with the cholinergic phase. Intermediate syndrome usually develops in cases of severe organophosphate poisoning. The onset is within 1-4 days after ingestion and it lasts for 7-21 days. The presented patients had severe organophosphate poisoning and required a high dose of atropine to control the muscarinic cholinergic effects. They developed the typical features of IMS as well as the onset of the syndrome. Because it generally occurs after or during the cholinergic crisis, if the clinical finding is not closely observed, it may be easily disregarded. The syndrome caused the presented patients to be not able to wean the respirator for a week since they had the IMS, even though the cholinergic effects were well controlled⁽³⁾.

Severity of cholinergic crisis during poisoning is more significant than the specific organophosphate in determining the development of IMS⁽⁴⁾. However, not every organophosphate insecticide is reported to be associated with the intermediate syndrome. List of the organophosphate insecticides which cause IMS includes chlorpiriphos, diazinon, dimethoate, ethylparathion, fenthion, malathion, methamidophos, methylparathion, monocrotophos, omethoate, and parathion⁽⁵⁻⁸⁾. Dicrotophos has not been reported. Therefore, the second case in the present report is the first case of dicrotophos that caused the IMS.

The exact mechanism underlying the intermediate syndrome has not been well elucidated. A hypothesis of muscle injury or necrotizing myopathy causing IMS fails to explain the whole clinical feature^(4,5,9,10). Many electrophysiologic studies by electromyography and repetitive nerve stimulation have suggested that IMS might be due to the combination of pre and post synaptic impairment of neuromuscular transmission at the junction^(4,5,11).

Oximes are acetylcholinesterase enzyme reactivators which are theoretically helpful for organophosphate poisoning. There are many oximes including pralidoxime (2-PAM), obidoxime, trimedoxime and pyridine aldoxime methiodide⁽¹²⁾. Another controversy with regard to oximes is the effect of oxime therapy and development of IMS. In the present report, the 2-PAM therapy was delayed for 1 day in the second case, and she developed IMS. The delay was once considered

as a cause for developing the syndrome. However, occurrence of IMS in the first case opposed this belief. The patient developed IMS even though he was given 2-PAM therapy very early on right after the ingestion of monocrotophos. Previously, it has been proposed that early and adequate oxime therapy may prevent the development of IMS^(13,14). However, subsequent studies in many countries oppose this view and have reported the opposite finding⁽¹⁵⁻¹⁷⁾. There is a randomized control trial study of 2-PAM therapy in organophosphate poisoning⁽¹⁶⁾. It was found that 2-PAM not only fails to have efficacy to prevent the syndrome, but also increases the risk to develop IMS⁽¹⁶⁾. Moreover, subsequent reports also show IMS in organophosphate poisoning, even with pralidoxime therapy⁽⁵⁻⁷⁾. The presented cases had IMS regardless of 2-PAM therapy. It neither showed its efficacy to prevent IMS nor an effect to induce IMS. However, each oxime might have unequal efficacy or react differently with varying affinity to organophosphates. The various studies so far reported included different oximes as well as different organophosphates^(6,16-20). It might be too heterogeneous to yield the same outcome. Therefore, the effect of oxime therapy on IMS has to be further explored. So, the present results are consistent with the Cochrane review of oxime therapy for acute organophosphate pesticide poisoning. It concludes that there is insufficient evidence to indicate whether oxime therapy is beneficial or harmful in the management of organophosphate insecticide poisoning⁽²¹⁾.

Recognition of intermediate syndrome will help physicians to predict that the patient might be dependent on the assisting ventilator longer than cases that do not have, although signs and symptoms of cholinergic crisis are controlled. Extubation of endotracheal tube in the early phase should be considered with precaution. Close observation of their respiration after cholinergic crisis should be performed. Adequate and appropriate respiratory care is the key point of the treatment.

The incidence of IMS is 7-60% worldwide^(5,10,17,22). Although organophosphate poisoning is common in Thailand, the incidence of IMS is not yet known⁽²³⁻²⁵⁾. The authors believe that the cases reported herein are the first 2 cases of IMS and may be examples of cases that may have been overlooked. The present report therefore aims at alerting physicians to clearly recognize the syndrome and to be aware that the syndrome could still develop in patients receiving prior 2-PAM since the initial phase. It will help clinicians more with regard to the understanding of the clinical

course of organophosphate poisoning in their patients.

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“การเป็นพิษระยะกลาง” ภาวะแทรกซ้อนจากภาวะเป็นพิษจากสารเคมีกำจัดแมลงกลุ่มฟอสเฟตอินทรีย์

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ผู้เขียนได้รายงานผู้ป่วยเป็นพิษจากการกินสารเคมีกำจัดแมลงกลุ่มฟอสเฟตอินทรีย์ 2 รายที่เกิดการเป็นพิษระยะกลางระหว่างที่ผู้ป่วยมีภาวะเป็นพิษจากสารกลุ่มฟอสเฟตอินทรีย์ ผู้ป่วยทั้ง 2 รายมีภาวะเป็นพิษจากฟอสเฟตอินทรีย์ที่รุนแรง ต้องได้รับยาอะโทรปีนขนาดสูง รายแรกได้ยาต้านพิษพราลิดอกซิมร่วมด้วยตั้งแต่แรก ส่วนรายที่ 2 ไม่ได้รับยาพราลิดอกซิม ใน 2 วันแรก ทั้ง 2 รายเกิดมีอาการอ่อนแรงของกล้ามเนื้อต้นแขน ต้นขา กล้ามเนื้อการหายใจ รายแรกมีกล้ามเนื้อคอร่วมด้วย ส่วนรายที่ 2 มีอาการอ่อนแรงของกล้ามเนื้อตา มีหนังตาตก และกรอกตาไม่ได้ ทั้ง 2 รายต้องใช้เครื่องช่วยหายใจประมาณ 2 สัปดาห์ จึงสามารถหย่าเครื่องช่วยหายใจได้ รายงานนี้มีวัตถุประสงค์เพื่อให้แพทย์ได้ตระหนักถึงการเป็นพิษระยะกลางจากภาวะเป็นพิษจากสารเคมีกำจัดแมลงกลุ่มฟอสเฟตอินทรีย์ ซึ่งมักถูกมองข้าม หากแพทย์ได้เข้าใจการดำเนินโรคนี้อย่างดีแล้ว ก็สามารถวางแผนการรักษาผู้ป่วยได้เหมาะสมมากขึ้น