Intermediate Syndrome Following Organophosphate Insecticide Poisoning

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Acute organophosphate insecticide poisoning can manifest 3 different phases of toxic effects, namely, acute cholinergic crisis, intermediate syndrome (IMS), and delayed neuropathy. Among them, IMS has been considered as a major contributing factor of organophosphate-related morbidity and mortality because of its frequent occurrence and probable consequence of respiratory failure. Despite a high incidence, the pathophysiology that underlies IMS remains unclear. Previously proposed mechanisms of IMS include different susceptibility of various cholinergic receptors, muscle necrosis, prolonged acetylcholinesterase inhibition, inadequate oxime therapy, downregulation or desensitization of postsynaptic acetylcholine receptors, failure of postsynaptic acetylcholine release, and oxidative stress-related myopathy. The clinical manifestations of IMS typically occur within 24 to 96 hours, affecting conscious patients without cholinergic signs, and involve the muscles of respiration, proximal limb muscles, neck flexors, and muscles innervated by motor cranial nerves. With appropriate therapy that commonly includes artificial respiration, complete recovery develops 5–18 days later. Patients with atypical manifestations of IMS, especially a relapse or a continuum of acute cholinergic crisis, however, were frequently reported in clinical studies of IMS. The treatment of IMS is mainly supportive. Nevertheless, because IMS generally concurs with severe organophosphate toxicity and persistent inhibition of acetylcholinesterase, early aggressive decontamination, appropriate antidotal therapy, and prompt institution of ventilatory support should be helpful in ameliorating the magnitude and/or the incidence of IMS. Although IMS is well recognized as a disorder of neuromuscular junctions, its exact etiology, incidence, and risk factors are not clearly defined because existing studies are largely small-scale case series and do not employ a consistent and rigorous definition of IMS. Without a clear understanding of the pathophysiology of IMS, specific therapy is not available. The prognosis of IMS, however, is likely to be favorable if respiratory failure can be promptly recognized and treated accordingly. [*J Chin Med Assoc* 2007;70(11):467–472]

Key Words: acetylcholine, cholinergic crisis, intermediate syndrome, organophosphate insecticide poisoning

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Introduction

Pesticide poisonings remain a serious public health problem worldwide. According to the World Health Organization's estimate, 3 million cases of pesticide poisoning occur every year, resulting in more than 250,000 deaths.[1] This number also accounts for a substantial fraction of the almost 900,000 people worldwide who die by suicide every year. Among the numerous pesticides that can result in death, organophosphate insecticides are the most common culprit agents because of their high toxicity.

Acute organophosphate insecticide poisoning can manifest 3 different phases of toxic effects, namely, acute cholinergic crisis, intermediate syndrome (IMS), and delayed polyneuropathy.[2–5] Acute cholinergic crisis develops within a few minutes to several hours after exposure, and affects peripheral muscarinic and nicotinic

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receptors, as well as the central nervous system, through the inhibition of carboxylic esterase enzymes, of which acetylcholinesterase is the most clinically important. Typical manifestations of cholinergic crisis include, but are not limited to, nausea, vomiting, diarrhea, abdominal cramp, urinary incontinence, miosis, salivation, lacrimation, bronchorrhea, bradycardia, hypotension, fasciculation, muscle paralysis, dizziness, confusion, seizures, coma, and respiratory failure. Death can occur within a very short space of time if life-threatening conditions, such as respiratory failure, are not treated promptly and appropriately.

Organophosphate-related delayed neurotoxic effect, which is commonly referred to as organophosphate-induced delayed neurotoxicity (OPIDN), occurs 2–3 weeks after acute exposure to certain organophosphate insecticides.[2] The clinical features are predominantly motor neuropathy and primarily manifest as numbness and weakness of the lower extremities, followed by progressive ascending weakness of limb muscles.[2,5] The disease entity is believed to be due to the inhibition of a poorly characterized esterase called the neuropathy target esterase.[5]

In addition to acute cholinergic crisis and delayed neurotoxicity, organophosphate insecticides can cause IMS as well. The term IMS was first described by Senanayake and Karalliedde in 1987 because it arose in the interval between the end of the acute cholinergic crisis and the onset of OPIDN.[2] According to that report, IMS was characterized by weakness of proximal limb muscles, neck flexors, respiratory muscles, and motor cranial nerves, and was attributed to muscle fiber necrosis following acute cholinergic crisis. Numerous studies have been published following Senanayake and Karalliedde's report, and the incidence of IMS has been reported to be as high as 80%.[6–14] Although the incidence of IMS may be high and the syndrome has been considered a major contributing factor of organophosphate-related morbidity and mortality, the pathophysiology that underlies IMS remains unclear.

Illustrative Cases

Case 1

A 26-year-old male attempted to commit suicide by ingesting an unknown amount of an unnamed pesticide. He was found lying next to a farm field with clear consciousness and marked weakness. He was sent to a local hospital, where gastric lavage, activated charcoal, and Fuller's earth were given because the patient stated that he probably had taken paraquat. He was then referred to our toxicological service.

On arrival, his vital signs were as follows: blood pressure 138/82 mmHg, pulse 90/min, respiratory rate 18/min, and temperature 36.4°C. Physical examination revealed the presence of coma, pinpoint pupil, salivation and bronchorrhea. Urine sodium dithionite test for paraquat was negative. Laboratory data were remarkable for potassium 3.1 mmol/L (reference range, 3.4–4.7 mmol/L), amylase 309 U/L (reference range, 0–190 U/L), and white blood cell count 18,500/mm^3 (reference range, 4,500–11,000/mm^3). Because organophosphate intoxication with impending respiratory failure was highly suspected, he was intubated with assisted ventilation. Moreover, he was treated with atropine and pralidoxime, and was admitted to the intensive care unit. Initial red blood cell (RBC) cholinesterase level was 14 UKAT/L (reference range, 20–46 UKAT/L), and plasma cholinesterase level was 1 UKAT/L (reference range, 20–61 UKAT/L).

On day 2, the patient was clear without respiratory distress, bronchial secretion, or muscle weakness, although the creatinine phosphokinase level had increased to 1,956 U/L (reference range, 27–168 U/L). The culprit pesticide was later identified to be methamidophos rather than parathion or paraquat. The doses of atropine and pralidoxime were gradually tapered and finally discontinued on the morning of day 3. Weaning from the ventilator was successfully performed, and he was transferred to the general ward. He remained symptomless and did not manifest obvious muscle weakness until the night of that day, when he was noted to develop confusion, followed by deep coma. Physical examination was remarkable for unresponsiveness, flaccid extremities, decreased deep tendon reflexes, shallow respiration, and dilated pupils. His breathing sound was clear and pulse oximetry monitoring showed normal oxygen saturation with 2 L/min oxygen supplement. Arterial blood gas analysis nevertheless revealed hypercapnia with PCO_2 of 96 mmHg. IMS was diagnosed and he was reintubated. After ventilatory support for another 6 days, he was smoothly extubated and was discharged uneventfully on day 12. Both atropine and pralidoxime were not administered during the second course of artificial ventilation.

Case 2

A 33-year-old previously healthy policeman attempted suicide by ingesting 4–5 mouthfuls of methamidophos. He was found comatose in his bedroom and was sent to a local hospital, where asystole was noted on arrival. Cardiopulmonary resuscitation was immediately instituted, and he regained his vital signs. He was treated with atropine 1 mg and pralidoxime 2 g, and was referred to our toxicological service.

On arrival, the patient was in a deep coma, with a Glasgow Coma Score of $E_1V_TM_1$. Physical examination revealed the presence of pinpoint pupil, hypotension, tachycardia, chemical conjunctivitis, cold sweating, and garlic-like odor. Laboratory data were remarkable for white blood cell count 22,100/mm^3, creatinine 1.5 mg/dL (reference range, 0.7–1.5 mg/dL), glucose 182 mg/dL (reference range, 65–115 mg/dL), arterial pH 7.23, PCO_2 36 mmHg, PO_2 214 mmHg, HCO_3 14.6 mmol/L, RBC cholinesterase 3 UKAT/L, and plasma cholinesterase 1 UKAT/L. Routine toxicological screen was negative for other drugs or toxins. Electrocardiography showed sinus tachycardia and left anterior hemiblock. Computed tomography of the brain was unyielding for hypoxic or traumatic insult. The patient was treated with vigorous fluid replacement as well as continuous infusion of atropine 10 mg/day and pralidoxime 12 g/day, and was then admitted to the intensive care unit.

On day 2, he was clear and his breathing sound was clear. His pupils were 2 mm in diameter with prompt light reflex. However, he appeared weak and was unable to flex his neck or abduct his shoulders, although the muscle power of his distal limbs was within normal limits. Treatment with atropine and pralidoxime was continued and his muscle power gradually improved to full strength. He was successfully weaned on day 4 and was transferred to the general ward on day 5. The RBC and plasma cholinesterase level improved to 35 UKAT/L and 5 UKAT/L, respectively, on that day. The patient's remaining hospitalization course was fairly uneventful except for transient mild atelectasis of the left lower lung. On day 9, he was discharged with normal levels of RBC and plasma cholinesterase (45 UKAT/L and 23 UKAT/L, respectively). He developed OPIDN 3 weeks after the toxic exposure and continued to manifest mild weakness of all extremities 1 year later.

Mechanisms

IMS is well recognized as a disorder of the neuromuscular junction; however, its exact underlying mechanisms are not clearly defined. Senanayake and Karalliedde in their first report of IMS suggested that the syndrome might be caused by pathologic changes in the postsynaptic end-plate region of striated muscles because such lesions were described in experimental animals (hens and rats) that developed a similar pattern of paralysis after organophosphate insecticide poisoning.[2] Eyer, in a review paper, supported the aforementioned hypothesis and proposed that myonecrosis was mediated by calcium mobilization in the muscle fibers.[3] Several researchers stated that oxidative cellular damage to muscle membranes could be another possible mechanism of muscle necrosis.[9,11] Clinically, John et al demonstrated an association between increased blood muscle enzymes (i.e. creatinine phosphokinase and lactate dehydrogenase) and the development of IMS, which also supported the role of muscle injury in IMS.[10]

On the contrary, it was found in a prospective study of 19 patients with organophosphate poisoning that muscle fiber necrosis was unlikely to be the etiology of IMS because muscle biopsy specimens in patients with IMS showed a few necrotic fibers only.[5,6,16] This led to the proposition that IMS was a combined pre- and postsynaptic impairment of neuromuscular transmission as evidenced by electromyographic observations, and that IMS occurred after prolonged and severe acetylcholinesterase inhibition.[6,15] Benson and McIntire, however, did not agree and suggested that either different susceptibility of various cholinergic receptors or inadequate oxime therapy played a role in the development of IMS if IMS did exist.[17] Baker and Sedgwick, in a single fiber electromyographic study of patients voluntarily exposed to sarin, found reversible subclinical changes compatible with the development of nondepolarizing neuromuscular block.[18] They stated that IMS could be explained by the above findings, which were due to a reduction in the number of functioning acetylcholinesterase receptors at the postjunctional membrane or a failure of acetylcholine release. In 1997, Sedgwick and Senanayake further proposed that downregulation or desensitization of postsynaptic acetylcholine receptors after prolonged acetylcholine stimulation could explain the occurrence of IMS.[19]

Clinical Features

Following exposure to various organophosphate insecticides, clinical manifestations of IMS typically occur within 24 to 96 hours, and affect conscious patients without fasciculation or other cholinergic signs.[2] Marked weakness of neck flexion and varying degree of proximal limb muscle weakness, manifesting as weakness of shoulder abduction and hip flexion, are the constant clinical features. Respiratory insufficiency is also common and frequently draws medical attention to the onset of the syndrome. Other possible manifestations are involvement of muscles innervated by motor cranial nerves and decreased deep tendon reflexes. Sensory impairment is not a clinical manifestation of IMS. With appropriate therapy, recovery from IMS occurs 5–18 days after the onset of weakness. According

to the report by Senanayake and Karalliedde, the regression of toxic signs among patients who survived IMS followed a distinct pattern.[2] Muscle power first resumed in cranial nerve-innervated muscles, followed by respiratory muscles, proximal muscles, and neck flexors.

Patients with atypical manifestations of IMS, especially a relapse or a continuum of acute cholinergic crisis, however, were frequently reported in the literature and were included in many clinical studies of IMS.[6,7,15] For example, De Bleecker et al, in a prospective study of 19 patients with organophosphate poisoning, identified 8 patients with IMS, 6 of them had relapsing cholinergic signs, such as lacrimation, increased bronchial and salivary secretion, diarrhea, sweating, bradycardia, and fasciculation, that superimposed on IMS.[6] He et al studied 21 IMS cases, 3 of whom actually showed rebounding of acute cholinergic crisis prior to the development of IMS.[7] Moreover, the onset of IMS in that study ranged between 7 and 75 hours post-exposure, and lasted between 6 and 30 days.

Because the definition of IMS differed across studies, reports on its incidence varied accordingly. In the first report of IMS, 10 out of 92 patients with organophosphate poisoning developed IMS, which yielded an incidence of 11%.[2] The reported incidence of IMS ranges from 7.7% to as high as 84% (Table 1).[6–14] Findings on the risk factors of IMS also differed among studies. Although IMS generally occurred among patients with prolonged and severe inhibition of acetylcholinesterase,[6,15] not every patient with severe inhibition of the enzyme developed IMS.[10,11] There were other risk factors of IMS as well, including delayed metabolism of organophosphates due to toxicokinetic factors of the insecticides or impaired organ function, severity of poisoning, elevated muscle enzymes, and inadequate or late oxime therapy (Table 1).[6,9–11,13,16,17]

IMS has also been linked preferentially to patients' exposure to specific organophosphates, namely fenthion, dimethoate and monocrotophos, all of which are dimethoxy compounds.[2] However, IMS was not limited to patients with exposure to these organophosphates. Parathion, combined ethylparathion and methylparathion, methamidophos, dichlorvos, and various other organophosphate insecticides have all been implicated in the development of IMS.[4,6,7,11–15,20]

Electrophysiologic Findings

Electrophysiologic study has been proposed as a specific diagnostic tool for patients with IMS.[2] Nevertheless, findings of electrophysiologic studies in patients

Table 1. Summary of selected published studies of intermediate syndrome following organophosphate insecticide poisoning

	Incidence, *n* (%)*	Time of onset (hr)	Neck flexor	Proximal muscle	Respiratory failure	Cranial nerve palsy	Clinical risk factors	Mortality, *n* (%)*
Senanayake & Karalliedde (1987)[2]	10/92 (11)	24–96	10/10	10/10	7/10	8/10	Dimethoxy compounds†	2 (20)
De Bleecker et al (1993)[6]	8/19 (42)	N/A	N/A	N/A	N/A	N/A	Combined ethylparathion and methylparathion poisoning, severe/prolonged inhibition of AChE	1 (13)
He et al (1998)[7]	21/272 (8)	7–75	21/21	21/21	17/21	17/21	Severity of poisoning, persistent inhibition of AChE	4 (19)
Lee & Tai (2001)[8]	5/23 (22)	72–90	N/A	N/A	N/A	N/A	Severity of poisoning	0 (0)
Khan et al (2001)[9]	18/25 (72)	72	18/18	18/18	18/18	18/18	Severity of poisoning, persistent inhibition of BuChE	4 (22)
Dandapani et al (2003)[11]	16/19 (84)	72	16/16	N/A	N/A	N/A	Severity of poisoning, reduced AChE and BuChE levels, markers of oxidative stress	2 (13)
Guven et al (2004)[12]	8/33 (24)	24–96	8/8	8/8	8/8	8/8	Severity of poisoning, persistent inhibition of BuChE	4 (50)
Chen (2004)[13]	126/286 (44)	N/A	N/A	N/A	N/A	N/A	Inadequate oxime therapy	N/A
Liu et al (2006)[14]	41/291 (14)	24–120	26/41	26/41	27/41	N/A	Severity of poisoning	8 (20)

**All numbers in the parentheses are rounded to the nearest integer; †including fenthion, dimethoate and monocrotophos. AChE = acetylcholinesterase; BuChE = butyrylcholinesterase.*

with IMS did not yield consistent results.[2,6,7,19,21] In the paper reported by Senanayake and Karalliedde, tetanic stimulation of the abductor pollicis brevis muscle showed a marked fade at 20 Hz and 50 Hz, and there was no post-tetanic facilitation.[2] In contrast, De Bleecker et al demonstrated early decrements at low frequencies of stimulation (1–3 Hz) with normal series at 10, 20 and 50 Hz, or decrements at intermediate frequencies (10–20 Hz) with normal findings at both low and 50 Hz frequencies.[6] A few days after poisoning, either mild decrement–increment phenomenon at high frequencies (20 or 50 Hz) or isolated increments (up to 220%) at 10 or 20 Hz were recorded. Neither increment nor decrement after repetitive stimulation was shown in a case reported by Sedgwick and Senanayake.[19] In the study reported by He et al, some patients had amplitude decrements at frequencies of 10, 20 or 30 Hz, while 2 patients did not show any decrements.[7] Jayawardane et al recently conducted a prospective serial repetitive nerve stimulation study of 70 patients with organophosphate insecticide poisoning.[21] They found that serial repetitive nerve stimulation findings correlated with muscle power in 9 patients who developed classical IMS. In the early phase of IMS, decrement–increment pattern at 10–30 Hz was detected. With clinical progression, decrement–increment pattern was noted at low frequencies (1–3 Hz), which then changed to severe decrements, mostly at high frequencies, among patients with severe IMS. Because decrement–increment phenomenon at intermediate and high frequencies were found among patients manifesting muscle weakness who did not develop classical IMS, the authors concluded that IMS was probably a spectrum disorder and neurophysiologic examinations might be useful in predicting the development of IMS.

Management

IMS carries a high risk of death among patients with respiratory failure. Therefore, prompt recognition of the syndrome is the cornerstone of IMS management. Treatment of IMS *per se* is mainly supportive,[2,7,8,14,17] and there are no specific antidotes available for this devastating syndrome. Nevertheless, because IMS generally concurs with severe organophosphate toxicity and persistent inhibition of acetylcholinesterase, early aggressive gastrointestinal decontamination, followed by appropriate therapy of atropine and oximes, and prompt institution of ventilatory support, should be helpful in ameliorating the magnitude and/or the incidence of IMS. For example, Chen, in a study of 286 patients with organophosphate poisoning, demonstrated that therapy with obidoxime, a more potent oxime compared to pralidoxime, significantly decreased the incidence of respiratory failure, the length of hospitalization, and mortality.[13]

Repeated dose of fresh frozen plasma therapy has been proposed in the treatment of IMS. Guven et al found that frozen plasma therapy could prevent the development of IMS and related mortality through the restoration of plasma acetylcholinesterase.[12] The authors, however, did not explain how the change in plasma acetylcholinesterase concentration could be relevant to the function of the neuromuscular junctions. Moreover, the study was not a randomized trial, and the authors did not provide enough information to determine whether the treatment effect was confounded or not. Similar results were found in a study of 36 Chinese patients with IMS.[22] Among 13 patients who received whole blood transfusion of 400–800 mL/day for up to 5 days, only 1 patient died, while 7 out of 23 patients without blood transfusion died.

Summary

IMS is a major cause of morbidity and mortality in patients with acute organophosphate insecticide poisoning. Although IMS is well recognized as a disorder of neuromuscular junctions, its exact etiology, incidence, and risk factors are not clearly defined because existing studies are largely small-scale case series and do not employ a consistent and rigorous definition of IMS. Without a clear understanding of the pathophysiology of IMS, specific therapy is not available and supportive measures remain the cornerstone in the management of IMS. The prognosis of IMS, however, is likely to be favorable if respiratory failure can be promptly recognized and treated accordingly. Future studies on IMS should focus on delineating the pathophysiology of IMS and the identification of clinical and/or laboratory predictors of IMS by employing well-defined definitions of IMS.

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