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Case Report

Intermediate Syndrome After Organophosphate Ingestion

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Abstract

Organophosphate poisoning is not uncommon in Taiwan. However, no case of intermediate syndrome (IMS) has been published. We report a case of delayed-onset IMS presenting with abrupt respiratory failure following the acute cholinergic crisis of phenthoate poisoning. Based on electrophysiological studies from the literature, IMS results from an excess amount of acetylcholine at neuromuscular junction nicotinic acetylcholine receptors due to prolonged inhibition of acetylcholinesterase. This phenomenon leads to downregulation of the acetylcholine receptor and promotes muscle weakness. There are still no appropriate parameters to predict the development of IMS. Perhaps electrophysiological studies can be applied in the future. Ventilatory support is the most important treatment; the benefits of pralidoxime treatment are still controversial. IMS is still a challenging complication of organophosphate poisoning. Physicians should not overlook IMS. [*Tzu Chi Med J* 2007;19(3):159–163]

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1. Introduction

Organophosphate (OP) pesticides are widely used in agriculture. OP poisoning is not uncommon in suicidal patients in Taiwan because these pesticides are readily available from the market [1,2]. OP pesticides are inhibitors of acetylcholinesterase (AChE). Emergency department (ED) physicians can recognize a patient with possible OP poisoning by the typical cholinergic signs, including increased secretions (bronchorrhea, salivation, tearing or sweating), bradycardia, vomiting and increased gastrointestinal motility (diarrhea or cramping), miosis, muscle fasciculation and even coma resulting from severe exposure [3]. The ratio of death to total OP intoxication cases during 1985–1997 in Taiwan was 11.5% [4]. Relatively low incidences of mortality were found in both the USA and Taiwan in recent reports, and only low percentages of chronic sequelae developed in survivors [1,5]. Consequently, occasional life-threatening complications, e.g., abrupt respiratory failure due to intermediate syndrome (IMS), are sometimes overlooked. Here, we report a case of IMS in Taiwan.

2. Case report

A 56-year-old man suffering from unconsciousness with incontinence and vomiting was found by his family and immediately brought to the ED. Bilateral pin-point pupils, profuse salivation, muscle fasciculation, and bilateral crackles on examination of breathing sounds were observed by ED physicians. OP poisoning was implicated by the clinical presentation. Atropine 1 mg and pralidoxime 500 mg were quickly administered. Intubation was performed due to dyspnea and airway protection. Subsequently, his family found half a bottle of phenthoate, an OP pesticide, and an empty bottle of rice wine in his room. Hence, OP poisoning was impressed. After primary management in the ED, the patient was transferred to the intensive care unit (ICU) for further management.

Initial levels of serum and red blood cell (RBC) AChE were 2 and 15 μM/sec/L, respectively (normal ranges, 20–61 and 20–46 μM/sec/L, respectively, at Tzu Chi General Hospital). In the ICU, the continuous infusion dosages of atropine (Atropair®) and pralidoxime (2-PAM®) were titrated according to the amount of secretion, muscle fasciculation and pupil size. An antimicrobial agent, ampicillin/sulbactam (Unasyn®), was administered for aspiration pneumonia based on pyrexia, leukocytosis (white blood cells (WBCs), 29,200 cells/μL), left shifting (15% and 76% of band-form and segment-form WBCs, respectively) and bilateral lower lung field infiltrations on chest X-ray. Pralidoxime was discontinued on the 3rd day of hospitalization after recovery of consciousness and muscle power. The endotracheal tube was also removed on the same day, and the patient was then supported by noninvasive positive pressure ventilation with bilevel positive airway pressure (BiPAP). Later, sputum culture revealed *Klebsiella pneumonia* and *Pseudomonas aeruginosa*. The antibiotic was then changed to ciprofloxacin. Only a few infiltrations over bilateral lung fields were observed in the following chest X-rays and no further fever was noted.

Unfortunately, sudden-onset irritability, dyspnea and carbon dioxide retention ($_PCO_2$ 116.3 mmHg in arterial gas) developed on the 7th day of hospitalization. The patient was re-intubated and pralidoxime was reinstated under suspicion of IMS. Follow-up RBC AChE had decreased to 2 μM/sec/L on the 8th day of hospitalization. Unexpected removal of the endotracheal tube by the patient occurred on the 9th day of hospitalization. Intubation was reinstated 1 day later due to respiratory muscle fatigue. Administration of pralidoxime was continued until the 10th day of hospitalization. Subsequent RBC AChE activity was 23 μM/sec/L on the 14th day of hospitalization. Ventilatory support was continued until the 15th day of hospitalization and weaning was successful this time. The patient was transferred to an ordinary ward on the 16th day of hospitalization due to his stable condition. Atropine infusion was stopped on the 21st day of hospitalization and the patient was discharged on the 22nd day of hospitalization. The relationship between the level of RBC AChE and the clinical course is shown in Fig. 1.

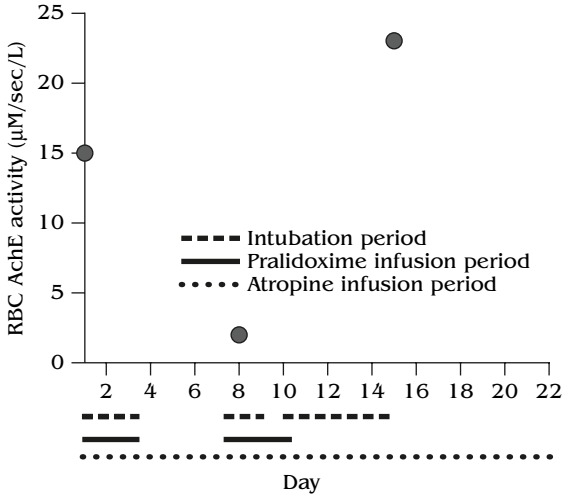

Fig. 1 — Red blood cell acetylcholinesterase (RBC AChE) activity and clinical course.

3. Discussion

Neuromuscular weakness resulting from OP poisoning is divided into three types: (a) type I paralysis—muscle weakness occurring within the first admission day associated with cholinergic signs; (b) type II paralysis or IMS—delayed muscle weakness occurring after the acute cholinergic phase of OP poisoning; (c) type III paralysis—polyneuropathy occurring 2–3 weeks after OP poisoning (6).

OP poison-induced IMS was first described in 1987 (7). IMS occurred after recovery from the acute cholinergic crisis but before OP-induced delayed polyneuropathy (8). It is usually observed 12–72 hours after OP poisoning and may last up to 5–6 days (7). This syndrome is characterized by sudden-onset muscle weakness, including the respiratory muscles (particularly the diaphragm), as well as paralysis of the neck muscles (inability to raise the head from the pillow) and weakness of proximal limb muscles (7). Occasionally, certain cranial nerve palsies, such as the external ocular, jaw, facial and palatal muscles, may be observed (7). Patients usually become anxious due to rapidly progressive difficulty in breathing. Consciousness is not lost unless hypoxia or carbon dioxide retention exists (8). Intubation and mechanical ventilation is needed if respiratory failure occurs, and the duration of ventilatory care varies between

7 and 21 days (8). In our case, IMS developed on the 7th day after OP poisoning. It seemed to be delayed more than the usual manifestation. However, no other conditions such as deterioration of pneumonia or sputum impaction could explain the sudden onset of respiratory failure. This delayed-onset IMS might result from the large amount of OP ingested and the OP being stored for longer in the patient's body.

Leon et al (9) reviewed published insecticide intoxications between 1965 and 1995, and they found that IMS occurred in 20–68% of affected patients. However, no IMS cases from Taiwan have been reported on MEDLINE, and not even in a 633-case collection of OP poisoning by the National Taiwan Poison Control Center from 1985 to 1999 (10). From our observations, we suppose that delayed extubation is usually chosen by Taiwan physicians if respiratory failure develops after OP poisoning. So, onset of IMS might overlap with the period of ventilator support. However, the mean duration of mechanical ventilation has not been recorded in previous studies in Taiwan (1). Statistically, parathion was the causative agent of IMS in up to 75% of cases in previous studies (9). Fenthion, dimethoate, monocrotophos, methamidophos and malathion were also reported to cause IMS (11,12) but no reported case developed IMS after phenthoate ingestion. In the World Health Organization (WHO) classification of OP pesticides, phenthoate and parathion are classified as class II-moderately hazardous and class Ia-extremely hazardous, respectively. The oral LD_{50} (LD: lethal dosage) in rats for phenthoate and parathion mentioned on the online material safety data sheet (MSDS) is >600 mg/kg and 20–30 mg/kg, respectively. This information shows that the fewer phenthoate IMS cases might be due to its lower toxicity. This IMS case, caused by less hazardous phenthoate, might be due to the large amount of this OP that was ingested.

Electrophysiological studies may offer some hints regarding the development of IMS. Three phenomena of electrophysiological studies were observed in IMS: (a) repetitive firing following a single stimulus; (b) gradual reduction in twitch height or compound muscle action potential followed by an increase, with repetitive stimulation of ≥20 Hz (decrement-increment response); and (c) continued reduction in twitch height or compound muscle action potential with repetitive simulation (decrementing response) (13). The decrementing response is the most frequent finding during IMS resulting from a marked downregulation of acetylcholine receptors (AChRs) at the post-junctional membrane, along with a failure of the pre-junctional ACh mobilization receptor. Downregulation of AChRs is due to a compensatory response after prolonged exposure to ACh followed by decrease of AChRs resulting from endocytosis (14). A pure decrementing response has been observed at the highest levels of AChE inhibition (15). Further, very weak AChE staining in skeletal muscle by immunohistochemistry was observed in a case of IMS (16). In summary, IMS results from excess ACh at the neuromuscular junction nicotinic AChRs following prolonged inhibition of AChE. Although some clinical studies reported a positive correlation between IMS and electrophysiological findings (17,18), more evidence from large numbers of clinical cases is required for verification.

Many physicians use serum or RBC AChE activity to monitor OP poisoning. Serum AChE, also called pseudocholinesterase or butyrylcholinesterase (BuChE), is found in the serum, liver, pancreas, heart and brain. It is subject to a high degree of variation influenced by many conditions, such as liver dysfunction, decompensated heart disease, malnutrition, allergic disease and malignant neoplasm (3). Further, no discernible difference in the serum AChE between day 1 and day 3 after OP poisoning has been observed in IMS patients (19). Hence, there is no predictive value of serum AChE for IMS. In contrast, RBC AChE is more reliable, with better correlation in terms of clinical presentations (20,21). In this case, the nadir of RBC AChE was observed while IMS was developing. Increased RBC AChE was noted when the patient recovered from IMS and was successfully weaned off mechanical ventilation. This observation fits in with the previous report that stated that clinical recovery correlates well with RBC AChE recovery to 30% of normal (22). However, studies regarding RBC AChE level as a predictor of IMS should be conducted in the future.

The OP-AChE bond is not spontaneously reversible without pharmacological intervention (23). AChE can be reactivated by oximes (e.g. pralidoxime) *in vitro* and *in vivo* (24,25), although the rate of reactivation may be affected by the dose of oxime administered and persistence of active OP in the body (26). The dose and route of exposure, the chemical structure of the OP, the time to initiation of therapy, and possibly efforts to decrease absorption or enhance elimination of the OP are factors leading to prolonged cholinesterase inhibition (27). A prospective study demonstrated the persistence of detectable OP in gastric juice several days after oral ingestion despite repeated lavage (28). In addition, the structure of the OP may modify the efficacy of pralidoxime and influence the risk of prolonged cholinesterase inhibition (29). Oxime was believed to be effective and necessary in treating OP poisoning. A bolus of 30 mg/kg of pralidoxime followed by infusions of >8 mg/kg/hr was suggested by WHO-sponsored recommendations (30). However, there has been a paucity of controlled trials in humans. One meta-analysis demonstrated no statistically significant association between oxime therapy and mortality, ventilatory requirements or the incidence of IMS (31). Sudakin et al (27) also reported a case of IMS after malathion ingestion despite continuous infusion

of pralidoxime. Therefore, the appropriate strategy for OP poisoning, especially when IMS occurs, should be further investigated. We still believe that oxime is a good candidate for IMS therapy but more prospective randomized controlled trials with appropriate patient stratification should be conducted. In addition, fresh frozen plasma (FFP), which contains BuChE, was thought to be an alternative strategy for IMS treatment (32). In this study, IMS developed in 28.6% of patients receiving pralidoxime treatment but no IMS case occurred with FFP transfusion. No cases of mortality were reported in the FFP + atropine + pralidoxime group compared with 14.3% in the pralidoxime group. However, only 24 cases were enrolled in the study. Further randomized controlled research is required.

In summary, IMS might not be such an uncommon complication of OP poisoning. The few cases reported in Taiwan might be the result of physicians' unawareness. All physicians should keep in mind that IMS may occur following acute cholinergic crisis despite aggressive treatment. Ventilatory support is adequate but the use of pralidoxime is still controversial in the treatment of IMS. FFP may be considered as an alternative or adjuvant therapy. Prevention, prediction and treatment of IMS after OP poisoning is still a challenge, and further investigations should be carried out.

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