Late and Interrupted Oxime Therapy In An Intermediate Syndrome Following Chlorpyrifos Poisoning: Case Report

Klorprifos Zehirlenmesini Takiben Gelişen Intermediate Sendromda Geç ve Aralıklı Oksim Tedavisi: Olgu Sunumu

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Geliş tarihi / Received: 23.06.2015 **Kabul tarihi / Accepted:** 07.07.2015

Abstract

Intermediate syndrome (IMS) is characterized by weakness of proximal limb and respiratory muscles, neck flexors, and cranial nerves. Several hypothesis have been developed to explain its etiology (neuromuscular junction disfunction, inadequate or late oxime therapy, prolonged and severe inhibition of acetylcholinesterase). Chlorpyrifos is a organophosphate with relatively low toxicity. IMS secondary to chlorpyrifos is very rare. We report a case of 56-year-old man who developed an IMS after chlorpyrifos ingestion. Although he presented with cholinergic symptoms initially, his mental and respiratory status deteriorated and profound motor paralysis consistent with IMS occurred on the second day. The patient required ventilatory support. Pralidoxime could only be administered late (52 hours post-ingestion), and intermittently for 23 days. The course of the patient was complicated with ventilator-associated pneumonia and septic shock, but after 32 days he was discharged. This case suggests that patients suffering from chlorpyrifos intoxication can be under the risk of IMS.

Key Words: Poisoning; Chlorpyrifos; Oximes

Öz

İntermediate sendrom (İMS) proksimal ekstremite ve solunum kaslarında, boyun fleksorlarında ve kranial sinirlerde zayıflıkla karakterizedir. Etyolojiyi açıklamak için birkaç hipotez geliştirilmiştir (nöromusküler bileşke disfonksiyonu, yetersiz veya geç oksim tedavisi, asetilkolinesterazın uzamış ve ciddi inhibisyonu). Klorprifos düşük toksisiteyle ilişkili organofosfattır. Klorprifosa sekonder İMS çok nadirdir. 56 yaşında erkek hastada klorprifos oral alımından sonra gelişen İMS'u sunuyoruz. Başlangıçta kolinerjik sendrom belirtileri gösteren hastada ikinci günde mental ve respiratuar durumu kötüleşip İMS'u düşündüren derin motor paralizi gelişti. Hastaya ventilatör desteği gerekti. Pralidoksim geç (oral alımdan 52 saat sonra) ve 23

günde aralıklı olarak verilebildi. Hastanın takiplerinde ventilatör ilişkili pnömoni ve septik şok gelişmesine rağmen 32. gününde taburcu edildi. Bu olgu klorprifos intoksikasyonlarıyla gelen hastalarda İMS riski olduğunu göstermektedir.

Anahatar Kelimeler: Zehirlenmeler; Klorprifos; Oksimler

Introduction

Organophosphate compounds (OP) are frequently used insecticides and may poison human beings in a suicide attempt or via accidental exposure. The manifestations are due to an over activity of the cholinergic systems as a result of inhibition of acetylcholinesterase (1,2). Diagnosis is based on the history, clinical presentation and measurement of cholinesterase levels in plasma (3)

Acute OP poisoning can be developed in three phases, namely, acute cholinergic crisis, intermediate syndrome (IMS), and delayed neuropathy (4). 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. The clinical manifestations of IMS typically occur within 24 to 96 hours, affecting conscious patients without cholinergic signs, and involve the muscles of respiration and proximal limbs, neck flexors, and muscles innervated by motor cranial nerves (5-8). Symptoms often include weakness of muscles innervated by some cranial nerves. Even though the clinical picture is well-defined, the true etiology and pathophysiology of IMS remains controversial. Several hypothesis have been developed. Although some of them blame inadequate oxime therapy others state late initiation of oxime therapy. However, in some reports it is stated that early and continuous oxime therapy could not prevent the onset of IMS, and in others succesfull outcomes of IMS could not be achieved without oxime therapy (9-11). Therefore, the usefulness of oximes in OP poisoning and during IMS remains questionable (12). The prognosis of IMS is likely to be favorable if respiratory failure can promptly be recognized and treated accordingly (4).

Among OPs, chlorpyrifos is considered to be moderatly toxic. Until now, there are only three reports of IMS induced by chlorpyrifos intoxication (11,13,14).

We describe a case of IMS to whom pralidoxime was administred late, long-term, intermittently and, at insufficient doses.

Case Report

A 56-year-old man with a history of depression was admitted to a state hospital afte auto-intoxication with chlorpyrifos. Five hours before the admission, the patient was told to be ingested an unknown quantity of 25% chlorpyrifos with a suicidal intent. On admission, he was confused and the vital signs were stable. Gastric lavage was performed. He was then transferred to the emergengy department of our university with the request of the family.

On arrival, his vital signs were as follows: blood pressure was 75/45 mmHg, heart rate was 45 beats/min, respiratory rate was 18/min, temperature was 36.50C. His Glascow Coma Scale (GCS) was 14/15. His pupils were pin-point. He had bronchorrhoea and hypersalivation. Fasciculations were noted. Further physical examination revealed no abnormalties. Laboratory studies were unremarkable except white blood cell count 12,200 /mm3 (reference range, 4,500-11,000/mm3), and neutrophil count 90.2%. Salin infusion and supplemental oxygen were started. Atropine, 2mg was given intravenously, and dopamin,

10mcg/kg/min was started. Additionally, he was given activated charcoal (1g/kg) by gastric tube, and was transferred to our intensive care unit.

In the intensive care unit, atropin was repeated in boluses of 0.5-1 mg as needed to treat muscarinic effects. General supportive measures were continued. His initial plasma cholinesterase level was 211 U/l (normal range of our lab is 3714-11513 U/l), indicating severe intoxication. Pralidoxime could only be given late (aproximately 52 hours after chlorpyrifos ingestion; 42 hours after ICU admission), because the drug was out-of stock. On the second day in intensive care unit (53 hours after ingestion; 43 hours after ICU admission), the patient's mental and respiratory status rapidly deteriorated and wheezing and cracles were heard in his lung fields. Physical examination was remarkable for shallow respiration, fasciculation in his eyelids and tongue, tremor, unresponsiveness, and weakness of neck flexors (1/5) and the proximal muscles of the extremities (2/5). Arterial blood gas analysis showed severe hipoxemia and mild hypercapnia. His body temperature was 38.7oC. The patient was intubated and mechanically ventilated. On the fourth day, the patient GCS was 3/15. After the first dose of pralidoxime (1g/day) the plasma cholinesterase level was 539 U/l and parlidoxime therapy was continued with interruption due to supply problems (first 3 doses were 1g/day followed by 2g/day). The pralidoxime was continued for 23 days (cumulative dose of 28 g) (Figure 1).

His course was first complicated by IMS, and community-acquired pneumonia. Then, ventilator-associated pneumonia, bacteremia and a septic shock episode developed during the patient's stay in the ICU. On the 23rd day, due to the gradual improvement in patient's clinical status and ameliorated muscle strength (neck 3/5; proximal extremity 4/5) he was extubated. Plasma cholinesterase level which was measured on the 27th day was still suppressed to 550 U/l as seen in Figure 2. The patient was then transferred to ward with psychiatric follow up after 32 days and was discharged from hospital several days later. There were no important neurological deficits at the time of discharge. Unfortunately the needle electromyography could not obtained for this patient.

Discussion

Intermediate syndrome after an acute cholinergic crisis is considered to be related to the severity of OP poisoning, and it has been reported to be particularly linked with very potent organophosphates or with highly lipophilic organophosphates that have longer half-lives (4-10). Previously proposed mechanisms of IMS include different susceptibility of various cholinergic receptors, muscle necrosis, prolonged acetylcholinesterase inhibition, inadequate or late oxime therapy, downregulation or desensitization of postsynaptic acetylcholine receptors, failure of postsynaptic acetylcholine release, and oxidative stress-related myopathy (4-8,15-17)

When the clinical course of our case is evaluated, it should be regarded as an IMS, because cholinergic syndrome was occured first, and then, 53 hours after chlorpyrifos ingestion, shallow respiration, fasciculation in his eyelids and tongue, tremor, unresponsiveness, weakness of neck flexors (1/5) and the proximal muscles of the extremities (2/5), and respiratory insufficiency evolved.

In our case, it can be speculated that IMS is related to late and inadequate oxime therapy. However, there are some reports where early and continuous oxime therapy did not prevent the onset of IMS, or succesfull outcomes of IMS was obtained without oxime therapy (9-11,14).

Moreover, the use, the dose and timing of oxime administration is controversial. Oximes, as a part of antidotal therapy, ensure the recovery of phosphorylated enzymes via a process refered as reactivation of inhibited acetylcholinesterase. Recently, in a randomised trial by Kirti Pawar and colleagues it has been reported that patients who received early high-dose pralidoxime regimen (after 2 g loading dose over 30 min, 1 g/hr for 48 h) had lower mortality, less intubation and ventilator support, observed muscle weakness and incidence of pneumonia were less and required less atropin during the first day than a lower dose regimen (after 2 g loading dose over 30 min, 1g/hr every 4 hours) (18). This therapy has not only clinical relevance in terms of potential benefits but also economical relevance and stocking pralidoxime in every hospital is not convenient (1). Some authors support that pralidoxime therapy should be given as soon as possible in suspected OP poisoning and ideally before aging occurs (19). Others reveal that pralidoxime + atropine does not have any benefit over atropine alone in OP poisoning (20). Benthur et al. recommend oxime therapy even late in the course of untreated or partially treated OP poisoning, especially when the etiologic agent is a lipid-soluble compound that can cause a protracted and severe course of poisoning (12).

It has been also shown in various systematic reviews and meta-analyses that oxime was associated with either null effect or possible harm (21-23). The lack of current prospective randomized trials, with appropriate patient strafication, necessiate ongoing assessment of the role of oximes in OP poisoning.

Some patients with IMS may require mechanical ventilation due to the weakness of respiratory muscle. However, aspiration of gastric contents, excessive secretions, pneumonia, and sepsis induced acute respiratory distress syndrome developing during clinical courses may also necessiate ventilatory support (3). In several studies the morbidity and mortality from acute OP poisoning is attributed to respiratory failure. Therefore endotracheal intubation and mechanical ventilation are life-saving measures when respiratory failure occurs (24,25). The duration of ventilatory care in IMS may differ considerably and it is usual for patients to need ventilatory support for 7-15 days and even up to 21 days. Therefore ventilator-associated pneumonia and sepsis are frequently encountered complications in these patients. Recovery from the intermediate syndrome is normally complete. But sequelea related to the therapy or miopathy are important problems that may occur.

Suprisingly, in spite of very low plasma cholinesterase level, our patient was weaned from ventilator on the 23rd day. Plasma cholinesterase activity usually recovers within weeks after exposure. Interpretation of very low plasma concentration aproximately 3 week after intoxication is very diffucult, but it may result from ineffective, interrupted and insufficient doses of pralidoxime, high levels of OP in the blood initially, unresponsiveness to oxime, the patient's genetic deficiency, or some other unknown causes.

In conclusion, this case suggests that patients suffering chlorpyrifos intoxication are also at risk for developing IMS. Therefore, we recommend close observation and careful monitoring of respiratory function in a intensive care setting for at least 96 hours in chlorpyrifos intoxcications. The prognosis of IMS is likely to be favorable if respiratory failure can be recognized and treated accordingly.

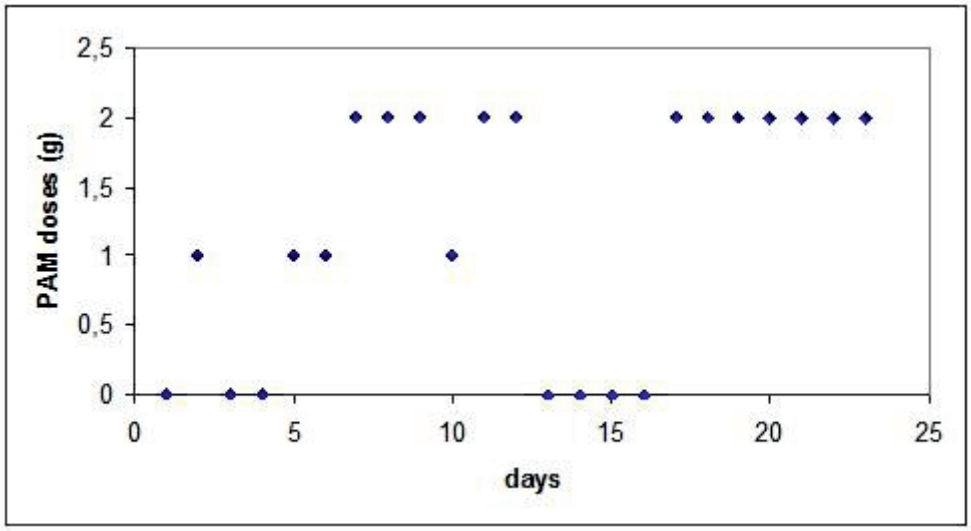

Figure 1.Interrupted PAM therapy (PAM: pralidoxime).

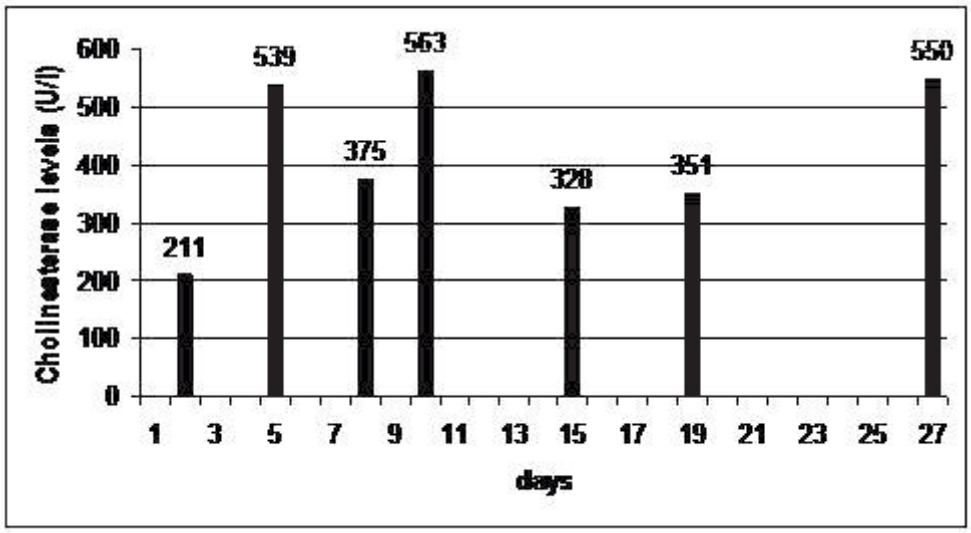

Figure 2. Cholinesterase levels during ICU stay

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