



## Oxime and atropine failure to prevent intermediate syndrome development in acute organophosphate poisoning

Neuspeh sprečavanja razvoja intermedijernog sindroma kod akutnog trovanja organofosforinim insekticidima primenom oksima i atropina

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### Abstract

**Introduction.** Intermediate syndrome (IMS) was described a few decades ago, however, there is still a controversy regarding its exact etiology, risk factors, diagnostic parameters and required therapy. Considering that acute poisonings are treated in different types of medical institutions this serious complication of organophosphate insecticide (OPI) poisoning is frequently overlooked. The aim of this paper was to present a case of IMS in organophosphate poisoning, which, we believe, provides additional data on the use of oxime or atropine. **Case report.** After a well-resolved cholinergic crisis, the patient developed clinical presentation of IMS within the first 72 h from deliberate malathion ingestion. The signs of IMS were weakness of proximal limb muscles and muscles innervated by motor cranial nerves, followed by the weakness of respiratory muscles and serious respiratory insufficiency. Malathion and its active metabolite were confirmed by analytical procedure (liquid chromatography-mass spectrometry). Pralidoxime methylsulphate, administered as a continuous infusion until day 8 (total dose 38.4 g), and atropine until the day 10 (total dose 922 mg) did not prevent the development of IMS, hence the mechanical ventilation that was stopped after 27 h had to be continued until the day 10. **Conclusion.** Continuous pralidoxime methylsulphate infusion with atropine did not prevent the development of IMS, most likely due to the delayed treatment and insufficient oxime dose but also because of chemical structure and lipophilicity of ingested OPI. A prolonged intensive care monitoring and respiratory care are the key management for the intermediate syndrome.

### Key words:

poisoning; phosphoric acid esters; neurotoxicity syndromes; atropine; oksimes; respiration, artificial; treatment outcome.

### Apstrakt

**Uvod.** Intermedijerni sindrom (IMS) opisan je pre nekoliko decenija, međutim i dalje postoje kontroverze u vezi sa njegovom etiologijom, faktorima rizika, dijagnostičkim parametrima i potrebnom terapijom. S obzirom na to da se akutna trovanja leče u medicinskim ustanovama različitog tipa, ova teška komplikacija akutnih trovanja organofosforinim insekticidima (OFI) često se ne prepoznaje. Cilj rada bio je da se prikaže slučaj akutnog trovanja organofosforinim insekticidom koji će dati dodatne podatke o upotrebi oksima i atropina. **Prikaz bolesnika.** Nakon kupirane holinergetske krize kod bolesnika, 72 h od namerne ingestije malationa, došlo je do razvoja kliničke slike IMS. Znači IMS su uključivali slabost mišića gornjih ekstremiteta i mišića inervisanih motornim kranijalnim nervima, što je bilo praćeno slabošću respiratorne muskulature i teškom respiratornom insuficijencijom. Malation i njegov aktivni metabolit potvrđeni su analitičkom procedurom (tečna hromatografijamašena spektrometrija). Kontinuiranom infuzijom pralidoksim metilsulfata do osmog dana (ukupno 38,4 g) i atropina do desetog dana (ukupna doza 922 mg), nije sprečen razvoj IMS, te je mehanička ventilacija, koja je prekinuta nakon 27 h, morala biti nastavljena do desetog dana. **Zaključak.** Kontinuiranom infuzijom pralidoksim-metilsulfata i atropina nije sprečen razvoj IMS, najverovatnije zbog odloženog početka lečenja i nedovoljne doze primenjenog oksima, ali i hemijske strukture i lipofilnosti ingestiranog OFI. Istaknut je značaj produžene opservacije u jedinici intenzivne nege i respiratorne podrške u lečenju intermedijernog sindroma.

### Ključne reči:

trovanje; estri fosforne kiseline; neurotoksičnost, sindromi; atropin; oksimi; disanje, veštačko; lečenje, ishod.

## Introduction

The intermediate syndrome (IMS) is a delayed onset of muscular weakness and paralysis that occurs 1–4 days after the resolution of acute cholinergic syndrome in acute organophosphate (OP) poisoning<sup>1</sup>. It was first reported by Wadia et al.<sup>2</sup> in 1974 as the “type II paralysis after organophosphate poisoning”. In 1987 Senanayake and Karalliede in 1987 termed this pattern of weakness as “intermediate syndrome” as the symptoms and signs occur before OP induce delayed polyneuropathy. Clinically, IMS is characterized by acute paralysis and weakness in the territories of several cranial motor nerves, neck flexors, facial, extraocular, palatal, nuchal, proximal limb, and respiratory muscles. Although this syndrome has been described for decades, due to sometimes diverse clinical picture, it often remains undiagnosed, at least until the occurrence of significant respiratory weakness. The controversy exists regarding not only the question of whether IMS is a clearly defined entity, but also its exact etiology, risk factors, diagnostic parameters and required therapy<sup>1–3</sup>.

## Case report

A farmer, at the age of 54, was brought to the Emergency Department of a regional medical center in a coma, with miosis, muscle fasciculations, hypersalivation and rales on auscultation. His wife stated that he drank malathion 2 h earlier and explained that during the last month he had been depressed and refused to eat. After intubation, gastric lavage was done. Atropine 3 mg *iv* and infusions were administered. At admission to the National Poison Control Center (NPCC), 5 h after deliberate ingestion of malathion, the patient was in a coma, unresponsive to noxious stimuli. His vital signs were as follows: blood pressure 120/80 mmHg, pulse 40/min, and respiratory rate 26/min. Physical examination showed copious bronchial secretion and pinpoint pupils. Soon after admission, myoclonic leg jerks and respiratory insufficiency developed. During the first 30 min the patient received 12 mg of atropine and activated charcoal was administered. The patient was transferred to Intensive Care Unit (ICU) in NPCC where intermittent positive pressure ventilation (IPPV) was started and atropine continued as intravenous infusion. Pralidoxime methylsulphate (200 mg/h as a continuous infusion) and supportive treatment were administered. Routine laboratory tests were within normal limits, except for white blood cell count  $18.9 \times 10^9/L$  (reference range,  $4.00\text{--}10.80 \times 10^9/L$ ). Blood gases showed acidosis (pH 7.212, pO<sub>2</sub> 123 mmHg, Sat O<sub>2</sub> 97.2%, pCO<sub>2</sub> 35.5 mmHg, ABE – 12.6 mmol/L, and lactate 1.1 mmol/L).

First measurement of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) showed activity of 1,806 U/L and 1,586 U/L. A significant reduction of activity of AChE 1198 U/L and BChE to 277 U/L occurred after 6 hours. Organophosphate and metabolites were confirmed in serum and urine by liquid chromatography-mass spectrometry, based on solid-phase extraction procedure, a chromatographic separation using an ACQUITY UPLC<sup>®</sup> HSST3 column and mass

spectrometric detection in the positive ion mode. A mobile phase consisted of Solvent A (5 mM ammonium formate pH 3.0) and Solvent B (0.1% acetic formate in methanol), in a linear gradient (constant flow-rate 0.3 mL/min). Malathion was confirmed in blood in concentration of 1.21 mg/L on the day 1, and 0.22 mg/L on the day 2. In urine it was confirmed in concentration of 0.54 mg/L the day 1, and 0.34 mg/L the day 2, and malaoxon was detected in concentration of 0.12 mg/L and 0.13 mg/L respectively. After the first 27 h the patient was recovering and MV was no longer needed.

Two cholinesterase assays, monitored daily, showed that AChE did not correlate well with the severity of poisoning, whereas BChE was more sensitive index of OP poisoning (AChE 1806–1198–1273 U/L–1384 U/L–1295 U/L–1447 and BChE 1586–277–391 U/L–476 U/L–585 U/L–670 U/L).

After a well-resolved cholinergic crisis during the first 27 h, the generalized flaccid weakness of upper extremities and neck muscles, worsening of ophthalmoplegia, with progressive respiratory insufficiency was registered on the day 3, which was explained as intermediate syndrome. The repetitive nerve stimulation test (hypothener – *n. ulnaris* system at 3 Hz), at admission showed insignificant compound muscle action amplitude (CMAP) decrement, that progressed to 30% of CMAP amplitude decrement on the day 5, related to post-synaptic failure of neuromuscular transmission. Pralidoxime methylsulphate therapy was administered until the day 8 with the total dose of 38.4 g, and atropine until the day 10 (total dose 922 mg). The mechanical ventilation was continued from the day 3 until the day 10. After that the of the patient condition improved steadily and on the day 21 he was discharged from the hospital.

## Discussion

The pathophysiology of IMS, despite a high incidence (10%–68%), remains unclear<sup>1</sup>. Some clinicians suggest that IMS may result from inadequate oxime therapy (subdosage, shorter duration of therapy, modality of administration), albeit there are others who feel that oximes are not necessary or even deny the existence of IMS explaining delayed deterioration among OP-poisoned patients by hypotatropinisation<sup>3–5</sup>.

The case presented in this paper refer to the patients with severe malathion poisonings, admitted to hospital more than 5 h after ingestion, implying possible risk for poor response to the therapy. Gastric lavage was made in the local hospital, 2 h after the ingestion. The American Academy of Clinical Toxicology and the European Association of Poison Centers and Clinical Toxicologists position paper suggests that “gastric lavage should not be performed routinely, but it should be considered only if a patient has ingested a potentially life-threatening amount of a poison, and the procedure can be undertaken within 60 minutes of ingestion”<sup>6</sup>. Administration of activated charcoal in conventional doses, is generally recommended for reducing further absorption of OP pesticides, and all of our patients received it in single doses. During the last few years much has changed in toxicology

and some new data from a randomized controlled trial (RCT), aimed to assess efficacy of routine treatment with multiple-dose activated charcoal, showed no benefit compared to a treatment with the single use of charcoal<sup>7</sup>.

Pralidoxime methylsulphate was applied as a continuous infusion (200 mg/h), but it could not prevent the development of IMS. The explanation for that might be a delayed treatment and insufficient pralidoxime dose (200 mg/h) but also the chemical structure and lipophilicity of ingested OP. The clinical usefulness of oximes has been challenged for decades by toxicologists throughout the world<sup>8-9</sup>. The paucity of data from RCT, disparate results with oxime treatment ranging from benefit to harm, could be explained by substantial delay to the treatment, type and dose of OP, and different therapeutic protocols that included pralidoxime in doses from 1g every 6 h to 1g per h. Only one RCT so far compared the World Health Organization (WHO) recommended doses (30 mg/kg/h followed by 8 mg/kg/h continuously) with placebo. This trial showed no clinical benefits and a trend towards harm, despite a clear evidence that reactivation of acetylcholinesterase was achieved<sup>9</sup>.

There are other proposed mechanisms of IMS which include different susceptibility of various cholinergic receptors, muscle necrosis, downregulation or desensitization of postsynaptic acetylcholine receptors, failure of postsynaptic acetylcholine release, and oxidative stress-related myopathy<sup>10-14</sup>. In our patient, who had nicotinic signs of OP poisoning, the level of creatine phosphokinase was normal as well as the level of aspartate aminotransferase normal, so this could not have been the cause of IMS.

The presented patient developed the clinical picture of IMS within the first 72 h after the ingestion of OP formulation in a suicide attempt. Though other signs of IMS poisoning were present, it was the respiratory insufficiency that drew medical attention to the onset of the syndrome. At that time, no significant decrease of AChE and BChE compared to the initial values was registered.

Repetitive stimulation test in the patient with malathion poisoning showed post-synaptic failure of neuromuscular

transmission, implying the development of IMS, in accordance with the study of Jayawardane et al<sup>15</sup>. In a prospective study of 70 patients with OP poisoning, the authors identified a series of stereotypic electrophysiological changes associated with IMS.

The risk of death in IMS is as high as it is in the cholinergic crisis. A prolonged clinical medical supervision after recovery from the cholinergic crisis is necessary because of the risk of IMS appearance. Based on this presentation, that the cornerstone of IMS management is supportive therapy, essentially directed towards the treatment of rapidly developing respiratory distress and respiratory failure. Any delay in instituting mechanical ventilation will result in death<sup>1-3,15</sup>. However, whilst it is not expected that atropine therapy would merit in the IMS, as the symptoms and signs are clearly not muscarinic, oxime given during the cholinergic crisis might be effective if it reactivates AChE. However, the optimal oxime dose is yet to be determined<sup>16-17</sup>.

### Conclusion

IMS is a major contributing factor of morbidity and mortality related to organophosphate poisoning. In our patient, continuous pralidoxime methylsulphate infusion did not prevent the development of IMS, most likely due to the delayed treatment and insufficient oxime dose, but also the chemical structure and lipophilicity of ingested OP. Although the efficiency of atropine and oxime in IMS is limited, the administration of these drugs, after early aggressive gastrointestinal decontamination, is recommended to be continued for a longer period. However, prolonged clinical medical supervision and respiratory care are specifically emphasized as the key of management for the intermediate syndrome.

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