

Perspective

Organophosphate Poisoning–Induced Intermediate Syndrome: Can Electrophysiological Changes Help Predict Outcome?

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Organophosphate (OP) pesticides contribute to a substantial burden of mortality and morbidity from self-poisoning, particularly in developing countries. Such poisonings are associated with several syndromes, including acute cholinergic crises, the intermediate syndrome (IMS), and organophosphate-induced delayed neuropathy. In a study published in *PLoS Medicine*, Jayawardane and colleagues begin to scientifically characterize a specific constellation of signs and symptoms seen after poisoning with organophosphates [1]. Specifically, they aim to define the pathophysiology of IMS, which was initially described in 1987 as an illness occurring after the resolution of acute cholinergic crises and associated with proximal muscle weakness [2]. Since this seminal article was published, there has been tremendous controversy in the toxicology world concerning the true definition and existence of IMS as an isolated entity [3,4]. Here, Jayawardane and colleagues further elucidate the nature of IMS by systematically recording repetitive nerve stimulation (RNS) patterns at the neuromuscular junction in patients poisoned with OPs.

The Initial Definition of IMS

In 1987, Senanayake and Karalliedde reported on ten patients who presented 24–96 hours after acute cholinergic crises from exposure to methamidophos, fenthion, dimethoate, and monocrotophos.

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Linked Research Article

This Perspective discusses the following new study published in *PLoS Medicine*:

Jayawardane P, Dawson AH, Weerasinghe V, Karalliedde L, Buckley NA, et al. (2008) The spectrum of intermediate syndrome following acute organophosphate poisoning: A prospective cohort study from Sri Lanka. *PLoS Med* 5(7): e147. doi:10.1371/journal.pmed.0050147

Jayawardane and colleagues evaluate a cohort of 78 patients with organophosphate poisoning from Sri Lanka, and identify changes in repetitive nerve stimulation that precede, and may help predict, the onset of intermediate syndrome.

These patients had acute muscle paralysis in the proximal limb muscles, neck flexors, motor cranial nerves, and respiratory muscles, and some required ventilatory support [2]. This particular constellation of signs was designated the intermediate syndrome. Over the ensuing years, other patients have presented with similar findings within 24–96 hours after exposure to organophosphates, and there has been substantial debate as to whether IMS, the syndrome defined on the basis of this group of patients, is a true syndrome or represents subtherapeutic oxime therapy. Although the clinical picture is well-defined, changes in the neurophysiology at the neuromuscular junction in IMS are poorly delineated. Jayawardane and colleagues have clearly described a large cohort of OP-poisoned patients and delineated the electrophysiological abnormalities that occur at the neuromuscular junction in conjunction with the clinical entity of IMS [1].

Electrophysiological Recordings in Organophosphate Poisoning: The New Study

In the paper published in *PLoS Medicine* [1], the researchers describe results of a prospective observational study of 78 patients with symptomatic OP poisoning presenting to two hospitals in the Central Province of Sri Lanka between May 2005 and December 2006. All patients were treated under the same protocol, receiving a 10–15 mg bolus of atropine intravenously followed by 10–15 mg atropine infusion over 12 hours. Additional atropine was used to control signs and symptoms of muscarinic excess. Pralidoxime was given as a 1 g infusion every 6 hours for 48 hours. All patients were assessed daily with a focused neurological exam. RNS of the right and left median and ulnar nerves was done at the bedside within

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Abbreviations: IMS, intermediate syndrome; OP, organophosphate; RNS, repetitive nerve stimulation

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24 hours of presentation in 69 of 78 patients and then repeated daily until all abnormalities resolved.

The Main Findings

Ten of 78 patients were diagnosed with IMS by the authors' diagnostic criteria. An additional 30 of 78 patients showed varying degrees of weakness from electrophysiological changes and were designated as having an incomplete, or *forme fruste* variant of IMS. From these data, the researchers identified a series of stereotypic electrophysiological changes associated with IMS, and were able to correlate the progression of muscle weakness with the electrophysiological changes, including an alteration in the pattern when patients developed respiratory muscle failure. During the recovery phase, electrophysiological improvement preceded patient recovery on the basis of clinical findings. Motor nerve conduction velocity was normal in 60 patients regardless of clinical weakness. The researchers were able to document no difference in treatment regimens between those who developed IMS or the *forme fruste* variant, and those who did not. Since one of ten patients with IMS and six of 30 patients with the spectrum disorder did not receive pralidoxime, and the remainder of patients did receive the standard dose of 1 g intravenously every 6 hours for 48 hours, these data may suggest that pralidoxime dosing has less impact on the development of IMS than previously suggested.

What Do These Findings Mean?

In this study, a large cohort of OP-poisoned patients were studied with electrophysiological tracings of sequential RNS in the proximal muscle groups. The data show that there is clear progression of electrophysiological changes that parallel the development of IMS, followed by a resolution of electrophysiological changes that may

precede clinical improvement. These data help to document the existence of IMS as a clinical entity. If these distinctive electrophysiological changes are subsequently validated in further studies, they should lead to improved diagnostic and prognostic tools for clinical use in OP-poisoned patients.

Limitations of the Study

Although this study shows that the IMS spectrum disorder is associated with a continuum of stereotypic RNS changes and is distinct from acute muscarinic cholinergic crises, it still does not clearly define the underlying cause of the disorder. There is a large contingent of clinicians who feel that oximes are not necessary to treat ill OP-poisoned patients, and these physicians tend to use high-dose atropine and supportive care [5]. In this study, all patients received atropine, and seven of 78 patients received only atropine without pralidoxime. It is not clear whether the specific RNS findings in the atropine-only group differed from other individuals in the atropine plus oxime group. The electrophysiological findings suggest that IMS represents a complex series of interactions and cannot be classified as a simple receptor block on one side of the synaptic cleft. Although beyond the scope of the study, sequential RNS tracings of patients before and after administration of high-dose oximes might delineate acetylcholine's effect on the neuromuscular junction during IMS.

What Research Remains To Be Done?

The authors provide limited data to help establish the existence of IMS as a clinical entity distinct from the muscarinic cholinergic crises. One individual enrolled in the study was clearly cholinergic during development of clinical IMS findings, and several other patients developed transient muscarinic findings during

development of IMS. The RNS tracings in these patients were no different from other patients without overt muscarinic findings.

The study did not address the issue of oxime treatment on the development of IMS. There is at least one other study that has shown improved neck flexor function, morbidity, and mortality in patients receiving high-dose pralidoxime infusions [6]. All of the patients included were treated either without oximes or with low-dose intermittent oximes. A large randomized trial of OP-poisoned patients receiving no oximes, low-dose oximes, or high-dose oximes would be useful in establishing appropriate treatment in relation to reducing muscle weakness and mortality. In such a trial, studying additional outcomes such as RNS and nerve conduction, particularly phrenic nerve conduction velocity, would go a long way towards answering the question of whether IMS is a clearly defined entity, and whether oximes truly make a difference to patient outcome. ■

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