

# Predicting the intermediate syndrome in organophosphorus poisoning

James Coulson

Intentional organophosphorus (OP) poisoning is estimated to kill between 230,000 and 350,000 people a year worldwide, with a further 20,000 dying following accidental exposure.<sup>[1]</sup> The occurrence of a “type II paralysis,” usually proximal muscle paralysis, in survivors after the resolution of cholinergic features was recognized as complicating up to 18% of OP related admissions during an early case-series.<sup>[2]</sup>

Senanayake and Karalliedde<sup>[3]</sup> classified this paralysis as the “intermediate syndrome” and described it as a distinct clinical entity on the basis of electromyographic (EMG) evidence of postsynaptic neuromuscular junction (NMJ) failure that occurred between 24 and 96 h after the resolution of the cholinergic crisis and prior to the onset expected for delayed neuropathy. The respiratory muscles are often affected and a prolonged period of ventilator support is required with all the associated risks of clinical complications and healthcare costs that such treatment entails.

The pathophysiological mechanism of the syndrome remains obscure and empirical data are limited, although oxidative stress and changes in receptor-ligand binding kinetics have been reported. Muscle biopsies taken during the Bleecker *et al.* case series reported a limited degree of fiber necrosis that was considered to be insufficient to account for the clinical features observed during the study.<sup>[4]</sup> Biomarkers of oxidative stress, at least in erythrocytes, have been identified in patients with the intermediate syndrome.<sup>[5]</sup> A rat model of dimethoate poisoning described changes in skeletal muscle and lymphocyte, but not the central nervous system, nicotinic receptor binding function 48 h postexposure.<sup>[6]</sup>

**From:**

Department of Pharmacology, Therapeutics and Toxicology, Cardiff University School of Medicine, UHW Main Building, Heath Park, Cardiff, UK

**Correspondence:**

Dr. James Coulson, Clinical Pharmacology, Cardiff University, Heath Park Campus, Cardiff, Wales, UK. Email: coulsonJM@cardiff.ac.uk

**Access this article online**

**Website:** [www.ijccm.org](http://www.ijccm.org)

**DOI:** 10.4103/0972-5229.160268

**Quick Response Code:**



Several risk factors have been proposed for the development of intermediate syndrome. The type of OP and the severity of poisoning may be important. In a small prospective case series ( $n = 19$ , eight of which developed intermediate syndrome), Bleecker *et al.*,<sup>[4]</sup> noted that dimethyl OP agents were more commonly implicated in comparison with diethyl OP compounds. An observation later confirmed by Indira *et al.*,<sup>[7]</sup> Bleecker *et al.*,<sup>[4]</sup> also observed that the clinical features and recovery correlated closely with EMG features and hypothesized that the NMJ dysfunction related to both pre- and post-synaptic changes.

The degree of acetylcholinesterase inhibition has also found to be greater in individuals who went on to develop the syndrome.<sup>[4]</sup> The 1<sup>st</sup> day serum acetylcholinesterase activity does not, however, appear to predict the onset of the intermediate syndrome but may predict survival.<sup>[8]</sup> A finding not inconsistent with the observations reporting by Indira *et al.*,<sup>[7]</sup> of an increased relative risk of the intermediate syndrome in

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**For reprints contact:** [reprints@medknow.com](mailto:reprints@medknow.com)

**How to cite this article:** Coulson J. Predicting the intermediate syndrome in organophosphorus poisoning. *Indian J Crit Care Med* 2015;19:377-8.

patients with a higher poisons severity score or reduced Glasgow Coma Scale.

In this edition of the Journal, a prospective observational study by Kumar *et al.*<sup>[9]</sup> reported a significant rise in serum creatine phosphokinase (CPK) on admission and again, 48 h postadmission in three individuals with OP poisoning who subsequently developed intermediate syndrome compared to 72 h with OP poisoning who did not. Serum CPK concentrations were also noted to correlate with markers of poisoning severity such as the Peradeniya organophosphorus poisoning score, and the total dose of atropine administered, and inversely correlated with the degree of butyrylcholinesterase activity. These findings are consistent with those of Bhattacharyya *et al.*<sup>[10]</sup> who also described a correlation between admission CPK; the severity of poisoning and the risk of developing the intermediate syndrome.

The study by Kumar *et al.*<sup>[9]</sup> has several strengths: The diagnosis of OP exposure was confirmed by cholinesterase activity measurement in each case; a standard treatment protocol was adhered to and the investigators excluded for the potential confounders that may cause an elevated serum CPK concentration, like seizures. The sample size of 75 makes this one of the larger studies focusing on the intermediate syndrome. The actual number of individuals who developed the syndrome was small. The authors acknowledge this limitation and note that this was due to the exclusion of those with severe poisoning.

It remains unclear, therefore, if CPK is truly an independent risk factor for the intermediate syndrome or, instead, reflects disease severity; which in turn may be the principle risk factor for the onset of the syndrome. Determining the relative contributions of these and other potential risk factors for intermediate syndrome will require more research.

A predictive test to risk-stratify those most likely to develop the syndrome is, however, a goal worth pursuing. If a successful test can be validated, using

a resource that is readily available in the majority of healthcare settings then it should considerably aid the early identification of patients who are likely to require transfer to a center that can provide ventilator support over several days duration and also may facilitate further research into preventative therapies. The authors are to be commended for undertaking research into this problem, which is highly prevalent and disproportionately affects the more socioeconomically disadvantaged in our community.

#### **Financial support and sponsorship**

Nil.

#### **Conflicts of interest**

There are no conflicts of interest.

#### **References**

1. Gunnell D, Eddleston M, Phillips MR, Konradsen F. The global distribution of fatal pesticide self-poisoning: systematic review. *BMC Public Health* 2007;7:357.
2. Wadia RS, Sadagopan C, Amin RB, Sardesai HV. Neurological manifestations of organophosphorous insecticide poisoning. *J Neurol Neurosurg Psychiatry* 1974;37:841-7.
3. Senanayake N, Karalliedde L. Neurotoxic effects of organophosphorus insecticides. An intermediate syndrome. *N Engl J Med* 1987;316:761-3.
4. De Bleecker J, Van den Neucker K, Colardyn F. Intermediate syndrome in organophosphorus poisoning: a prospective study. *Crit Care Med* 1993;21:1706-11.
5. Dandapani M, Zachariah A, Kavitha MR, Jeyaseelan L, Oommen A. Oxidative damage in intermediate syndrome of acute organophosphorous poisoning. *Indian J Med Res* 2003;117:253-9.
6. Yang D, Niu Y, He F. Functional changes of nicotinic acetylcholine receptor in muscle and lymphocyte of myasthenic rats following acute dimethoate poisoning. *Toxicology* 2005;211:149-55.
7. Indira M, Andrews MA, Rakesh TP. Incidence, predictors, and outcome of intermediate syndrome in cholinergic insecticide poisoning: a prospective observational cohort study. *Clin Toxicol (Phila)* 2013;51:838-45.
8. Aygun D, Doganay Z, Altintop L, Guven H, Onar M, Deniz T, et al. Serum acetylcholinesterase and prognosis of acute organophosphate poisoning. *J Toxicol Clin Toxicol* 2002;40:903-10.
9. Kumar GC, Bhuvana K, Venkatarathnamma PN, Sarala N. Serum creatine phosphokinase as predictor of intermediate syndrome in organophosphorus poisoning. *Ind. J. Crit. Care Med* 2015; 19:384-7.
10. Bhattacharyya K, Phaujdar S, Sarkar R, Mullick OS. Serum creatine phosphokinase: a probable marker of severity in organophosphorus poisoning. *Toxicol Int* 2011;18:117-23.