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How Organophosphate Pesticides Affect the Peripheral Nervous System: Insights into the Pathophysiology of Intermediate Syndrome

WHO class I and II organophosphate (OP) compounds contribute to the majority of pesticide related deaths in rural Asia and the world. Amongst the 3 million exposed, 200,000 eventually die as a result of the exposure. Organophosphate associated intermediate syndrome (IMS) is a major cause of morbidity and mortality in these patients. Despite its clinical description more than half a century ago by Wadia et al and Senanayake et al, the pathophysiology of IMS remains unclear. There exist no specific treatment options and most patients require prolonged ventilatory support which further contributes to morbidity and mortality. A clearer understanding of IMS pathophysiology may lead to improved and specific treatment options. We aim to describe the incidence, clinical profile and predictors of intermediate syndrome in acute OP poisoning patients and explore its pathophysiological mechanisms.

Of 40 acute OP poisoning patients enrolled prospectively, 15 (38%) developed IMS. While all IMS patients had preceding severe Type I paralysis at onset, only 80% presented with a muscarinic toxidrome. Additional clinical risk factors predicting IMS onset included neck muscle weakness at admission [OR -7.87; CI-1.86-33.4), sensorium assessed by Glasgow coma scale [GCS] (OR -1.38; CI -0.36-5.43) and poisoning severity assessed by Namba scale (OR-1.78; CI -0.3-12.8). Patients with a dimethyl WHO class 1 compound poisoning had a higher risk of developing intermediate syndrome (45%) compared to patients with diethyl compound consumption (16.7%; p=0.06). While plasma butyrylcholinesterase levels did not reveal any correlation with IMS incidence, profound suppression of acetyl cholinesterase (RBC cholinesterase) (<5mU/µmol Hb) at admission predicted IMS. 75% of patients with AchE <5mU/µmol Hb developed IMS compared to 25% of patients with AchE values > 17 mU/µmol Hb (p=0.009). Based on risk factor analysis we propose a predictive scoring system for IMS with sensorium assessed by GCS (maximum score-2), poisoning severity assessed by Namba scale (maximum score-3), type of compound (maximum score 2), WHO class (maximum score-2) and neck muscle weakness (maximum score-4). A score of <8 was associated with a low IMS risk (area under the curve 0.784; sensitivity 79%; specificity 72%; positive predictive value 56%; negative predictive value 92%).

No statistically significant difference between serum creatinine kinase (CK) levels amongst OP patients with IMS compared with OP patients without IMS was noted. Day 5 leukocyte oxidative stress levels were greater in IMS patients than in those without IMS. 75%(3/4) IMS patients who underwent electrophysiological studies within 48 hours of admission, displayed severe or progressive decrement patterns on repetitive nerve stimulation at intermediate and fast frequency stimulation rates. These findings correlated with the need for prolonged ventilation. 75% (3/4) had normal nerve conduction studies while one patient had repetitive compound muscle action potentials (CMAPs). There was no synchronized CMAP dispersion. Muscle excitability studies were normal in all patients.

In conclusion, the lack of significantly higher serum CK levels in IMS patients; normal muscle excitability and abnormal RNS findings together suggest that weakness is primarily due to a neuromuscular transmission defect rather than structural muscle change. The absence of synchronized CMAP dispersion suggests against the possibility of channel defects as an underlying pathogenic mechanism. Failure to adequately respond to oxidative stress may be an additional contributive factor.