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ORGANOPHOSPHORUS COMPOUND INDUCED 'INTERMEDIATE SYNDROME'

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ABSTRACT

Acute organophosphate insecticide poisoning can manifest 3 different phases of toxic effects, namely, acute cholinergic crisis, intermediate syndrome (IMS), and delayed neuropathy. 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. Despite a high incidence, the pathophysiology that underlies IMS remains unclear. Previously proposed mechanisms of IMS include different susceptibility of various cholinergic receptors, muscle necrosis, prolonged acetylcholinesterase inhibition, inadequate oxime therapy, downregulation or desensitization of postsynaptic acetylcholine receptors, failure of postsynaptic acetylcholine release, and oxidative stress-related myopathy. The clinical manifestations of IMS typically occur within 24 to 96 hours, affecting conscious patients without cholinergic signs, and involve the muscles of respiration, proximal limb muscles, neck flexors, and muscles innervated by motor cranial nerves. With appropriate therapy that commonly includes artificial respiration, complete recovery develops 5–18 days later. Patients with atypical manifestations of IMS, especially a relapse or a continuum of acute cholinergic crisis, however, were frequently reported in clinical studies of IMS. The prognosis of IMS, however, is likely to be favorable if respiratory failure can be promptly recognized and treated accordingly.

INTRODUCTION

Poisoning is the most common mode of unnatural death in South East Asia causing hundreds of thousand deaths per year. Among them Organophosphorus (OP) compound, a pesticide poisoning is the major clinical problem. Organophosphorus pesticide poisoning is a main clinical and public health problem across much of rural Asia.[1] Of the estimated 500,000 deaths from self-harm in the region each year, about 60% are due to pesticide poisoning. Many studies conclude that organophosphorus pesticides are responsible for around two-thirds of these deaths, a total of 200,000 a year.[2] The suicidal intent is the most common mode of poisoning whereas others are an impulsive act, homicidal, accidental and various other triggering factors.Acute organophosphate insecticide poisoning can manifest 3 different phases of toxic effects, namely, acute cholinergic crisis, intermediate syndrome (IMS), and delayed polyneuropathy.[2–5] Acute cholinergic crisis develops within a few minutes to several hours after exposure, and affects peripheral muscarinic and nicotinic receptors, as well as the, but are not limited to, nausea, vomiting, diarrhea, abdominal cramp, urinary incontinence, miosis, salivation, lacrimation, bronchorrhea, bradycardia, hypotension, fasciculation, muscle paralysis, dizziness, confusion, seizures, coma, and respiratory failure. Death can occur within a very central nervous system, through the inhibition of carboxylic esterase enzymes, of which acetylcholinesterase is the most clinically important. Typical manifestations of cholinergic crisis include short space of time if lifethreatening conditions, such as respiratory failure, are not treated promptly and appropriately.

In addition to acute cholinergic crisis and delayed neurotoxicity, organophosphate insecticides can cause IMS as well. The term IMS was first described by Senanayake and Karalliedde in 1987 because it arose in the interval between the end of the acute cholinergic crisis and the onset of OPIDN.[2] According to that report, IMS was characterized by weakness of proximal limb muscles, neck flexors, respiratory muscles, and motor cranial nerves, and was attributed to muscle fiber necrosis following acute cholinergic crisis. Numerous studies have been published following Senanayake and Karalliedde's report, and the incidence of IMS has been reported to be as high as 80%.[6–14] Although the incidence of IMS may be high and the syndrome has been considered a major contributing factor of organophosphate-related morbidity and mortality, the pathophysiology that underlies IMS remains unclear.

The study was conducted at Department of Medicine, Indira Gandhi Medical College (IGMC) Shimla, which is a tertiary care centre of Northern India. Patients admitted

with history of organophosphorous poisoning during the period of 1/7/2018 to 30/7/2019.It was a hospital based prospective observational study. Immediately after the arrival of the patients at the emergency, history was taken to confirm the type of OP compound taken and the interval between the consumption of poison and arrival at the emergency room. Apart from the routine and detailed clinical examination, assessment was also done based on the POP scoring system, which included pupil size, respiratory rate, pulse rate, level of consciousness of the patient and the presence or absence of convulsion and fasciculation. Based on this assessment, a score was given to the patients. Information was collected through pre-tested proforma. Clinical score (POP scale) was noted on admission and accordingly patients were grouped into mild (POP score 0-3), moderate (POP score 4-7) and severe poisoning (POP score 8-11 According to cholinesterase activity (pseudocholinesterase) the OP poisoning was graded as normal (>50%), mild (20-50%), moderate (10-20%) and severe (<10%). Patients were evaluated at time of admission and were followed up during treatment. Patients were followed up to death/discharge. The patients were routinely managed in the wards or ICU according to the severity, with pralidoxime and intravenous (IV) atropine bolus and drip, maintaining the adequate level of atropinization. For clinical outcome, the total duration of hospital stay or death were considered. Complete recovery or death was used as the end point.

RESULTS

A total of 60 patients of organophosphorus poisoning who were admitted in medicine department in IGMC SHIMLA with history of organophosphorous poisoning during the period of 1/7/2018 to 30/7/2019 were studied in this prospective observational study, based on the inclusion and exclusion criteria. Among them 68% were male and 32% were female. In this study there was male predominance, and male to female ratio was 2:1. The age of patients ranged from 18 to 68 years. Most of the patients were aged between 21 to 40 years and median age was 31.5 years. Out of 60 patients 10 were classified under the category of IMS, on the basis of clinical examination and laboratory investigations. These patient presented with history of ingestion of large quantity of poison.

Clinical Features

Among the admitted patients, clinical manifestations of IMS typically occured within 24 to 96 hours. Marked weakness of neck flexion and varying degree of proximal limb muscle weakness, and weakness of shoulder abduction and hip flexion, were the constant clinical features. Respiratory insufficiency was also common at the onset of the syndrome. Other manifestations were involvement of muscles innervated by motor cranial nerves and decreased deep tendon reflexes. Sensory impairment is not a clinical manifestation of IMS. Noted investigations among these were markedly decreased level of serum pseudocholine esterase levels, raised CPK and serum amylase levels.

MECHANISMS

IMS is well recognized as a disorder of the neuromuscular junction; however, its exact underlying mechanisms are not clearly defined. Senanayake and Karalliedde in their first report of IMS suggested that the syndrome might be caused by pathologic changes in the postsynaptic end-plate region of striated muscles because such lesions were described in experimental animal 2 Eyer, proposed that myonecrosis was mediated by calcium mobilization in the muscle fibers.[3] Several researchers stated that oxidative cellular damage to muscle membranes could be another possible mechanism of muscle necrosis.[9,11] Clinically, John et al demonstrated an association between increased blood muscle enzymes (i.e. creatinine phosphokinase and lactate dehydrogenase) and the development of IMS, which also supported the role of muscle injury in IMS.[10] On the contrary, it was found in a prospective study of 19 patients with organophosphate poisoning that muscle fiber necrosis was unlikely to be the etiology of IMS because muscle biopsy specimens in patients with IMS showed a few necrotic fibers only.[5,6] This led to the proposition that IMS was a combined pre- and postsynaptic impairment of neuromuscular transmission as evidenced by electromyographic observations, and that IMS occurred after prolonged and severe acetylcholinesterase inhibition.[6,15]

SUMMARY

IMS is a major cause of morbidity and mortality in patients with acute organophosphate insecticide poisoning. Although IMS is well recognized as a disorder of neuromuscular junctions, its exact etiology, incidence, and risk factors are not clearly defined. Without a clear understanding of the pathophysiology of IMS, specific therapy is not available and supportive measures remain the cornerstone in the management of IMS. Tht prognosis was poor among patient presenting late to the hospital. However the prognosis of IMS, is likely to be favourable if respiratory failure can be promptly recognized and treated accordingly.

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