

Severe Organophosphate Poisoning with Acute Cholinergic Crisis, Intermediate Syndrome and Organophosphate Induced Long Term Ptosis

Deepankar Chaurasia¹, Somvanshi Vaibhav Kumar Ramavtar², Shinde Pravin Suresh³

Abstract

Organophosphate compounds are the organic derivatives of Phosphorous containing acids and their clinical effects are due to action on neuromuscular junction and Autonomic Synapses. After exposure these agents cause acute and sub-acute manifestations depending on the type, severity of the agents and duration of presentation, like Acute Cholinergic Manifestations, Intermediate Syndrome (transient palsy) with Nicotinic features and Delayed Central Nervous System Complications. The patient reported here had severe Organophosphate Poisoning complicated by Intermediate Syndrome and Organophosphate Induced long term Ptosis. Highlighting such cases helps increase awareness of health care workers about these rare complications of a common problem.

Introduction

Organophosphate compounds are the organic derivatives of Phosphorous containing acids and their effect on Neuromuscular Junction and Autonomic synapses is clinically important. In the Neuromuscular Junction Acetylcholine is released when a nerve impulse reaches terminal axonal end and it diffuses across the Synaptic Cleft and binds to Cholinergic Nicotinic receptors on the muscle fibers, causing them to contract. Cholinesterase enzyme splits Acetylcholine into Acetic Acid and Choline, thus stopping its action (Figure 1). The end products of the metabolism of Acetylcholine are taken up by nerve fibers and resynthesized into Acetylcholine (Figure 2).¹ Cholinesterase is critical for nerve function, so the irreversible blockage of this enzyme, which causes acetylcholine accumulation, results in muscle overstimulation. Following classical Organophosphates poisoning, three well defined clinical phases are seen: Initial Acute Cholinergic Crisis, the Intermediate Syndrome and Delayed Central nervous side effects. Here severe and prolonged cholinergic crisis with unusual complications,

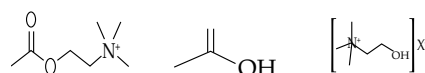


Fig. 1: Acetylcholine, acetic acid and choline¹

notably Intermediate Syndrome and Delayed ptosis are described in the same patient in different course of time.

Case Report

The patient was admitted to Lalit Narayan Mishra Railway Hospital North Eastern Railway Gorakhpur (LNMRH) for three weeks and discharged with improved status and followed up for next 3 months.

Immediate features and management

A seventeen years old right handed female patient from Railway colony Gorakhpur who ingested unquantified

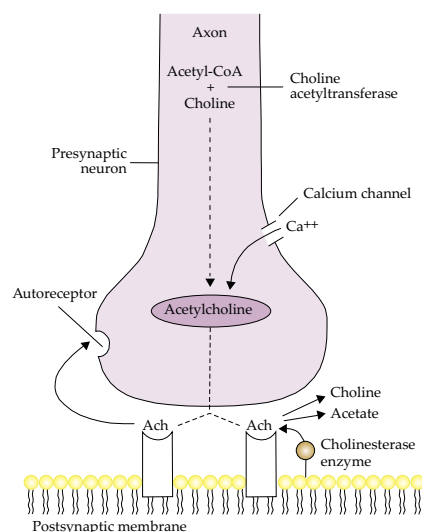


Fig. 2: Neuromuscular junction (NMJ): Metabolism and resynthesis of acetylcholine¹

amount of Chlorpyrifos 50% and Cypermethrin 5% E.C. combination comes with trade name Carbine insecticide, which was purchased by the girl, in an attempt to commit suicide on march 11, 2016. She ingested the poison the previous night mixed with milk and was found on the ground, throwing seizures with vomiting and urinary incontinence by the family members next morning. Subsequently she lost consciousness and was taken to Emergency room of LNMRH on the same date where atropine 5mg IV every 15 minutes was administered but charcoal administration could not be performed as family members refused for the ryle's tube insertion at first place in the emergency room and were rejecting our clinical suspicion of any poisonous substance intake by the girl but as the clinical suspicion was so high that on the clinical ground management was started and family members were asked to search the room of the girl for any unidentified substance which they later discovered there after 24 hours.

On physical examination at the emergency room her blood pressure was 80/60mmHG, pulse rate 88/min, respiratory rate 24/min and temperature was 37.90C. She had rhonchi all over the chest, pupils were pinpointed and Glasgow Coma Scale (GCS) was 4/15. She also had paradoxical abdominal muscle movement and tentative suicidal cut marks over flexor surface of left forearm (Figure 3). On investigation white blood cell count 13,500/dl, hematocrit 44.1%, platelet count 134,000/dl, erythrocyte sedimentation rate 22/hr and random blood sugar was 114mg/dl. However, serum transaminases, alkaline phosphatases, serum electrolytes, liver

¹Consultant physician, ²Resident Internal Medicine, ³Resident Internal Medicine, Lalit Narayan Mishra Railway Hospital, Northeastern Railway, Gorakhpur, Uttar Pradesh

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Table 1: Dose of atropine at LNMRH

Time from day of OP ingestion	Range of atropin dosage in 24 hours
Day 1	5mg iv every 15-20 min
Day 2-3	2mg iv every 15-20 min
Day 3-6	2mg iv every 2-4 hours
Day 7-10	1mg iv every 4-6 hours
Day 10-16	1mg iv every 12-24 hours
Day 16-20	0.6 mg iv 24 hourly
Day 21 (Discharged)	Discontinued

and renal function tests were in normal range. Furthermore, chest X-ray was normal and ECG showed normal sinus rhythm. Oxygen saturation was 74% with 8L/min flow of oxygen through nasal prongs but subsequently with face mask it was consistently above 88%.

She was admitted to the Medical Intensive Care Unit (MICU) with presumptive Diagnosis of an assessment of severe Organophosphate poisoning with acute cholinergic crisis and intermediate syndrome leading to type II respiratory failure. She was atropinized with atropine 2mg IV stat and then 2 mg every 15 minutes, and Ceftriaxone 1 gm IV every 12 hours after sensitivity testing were administered. She had intensive monitoring of vital signs and organ functions. She was continued on large dose of atropine (upto 80 mg/24 hrs) and oxygen administration of 6L/min by face mask and started ryles tube feeding after opting consent by family members 36 hours onwards the admission (Table 1).

Her GCS was 4/15 in the first 48hrs in the MICU after that she started to make incomprehensible sounds followed by some meaningful words but subsequently the level of consciousness was waxing and waning. Therefore, she was continued with large dose of atropine with administration of 2 mg every 15 minutes and on the third day of MICU admission she was intubated and put on assisted ventilation. In the meanwhile she again developed tonic clonic seizure and was started on Diazepam 5 mg IV stat and it was maintained with dose of 30mg in 500cc of IV fluids every 12 hours for 8 days and then tapered down gradually after improvement of seizure. On sixth day she became conscious but unable open her eyelids, vision was normal checked after assistive opening of the eyelids. Her menstrual cycle started earlier than usual (Last menstruation period date was 29th Feb 2016) which was painful for

**Fig. 3: Tentative suicidal cut marks on the forearm**

which tab mefenamic acid 250mg once a day was given for 3 days. On eighth day she developed numbness of both feet which was followed by weakness of both lower extremities which progressed to involve upper extremity and urinary and fecal incontinence with loose stools (12 episodes/day for 2 days). On physical examination she was conscious and oriented. Power in both lower extremities was 0/5, while in upper extremities it was 3/5. Deep tendon reflexes were depressed at both extremities while tone was reduced on the lower extremity and all modalities of sensory examinations were normal. She was negative for HIV and had normal myelography and spine x-rays. Then physiotherapy was started and subsequently her sphincter function recovered within 2 days. She showed improvement of both the upper as well as lower extremities which she started feeling himself on 13th day. On complete neurological examination 14th day power of both upper extremities was 5/5, while lower extremities was 4/5 and ptosis was still persisting.

Cholinergic and central nervous system symptoms with pupillary constriction, respiratory hypersecretions and fluctuating consciousness were peculiar features with in the first week ; mental status was deteriorating when the dosage of atropine was titrated down. By the end of two weeks mental status, pupillary signs, hypersecretion, numbness, weakness improved but ptosis was sustained; edrophonium test could not be performed due to family economical

constrain; she was extubated; subsequently Atropine and Diazepam were spaced and discontinued. Finally, at the end of third week she was discharged after psychiatric evaluation and counseling was provided and was able to walk without support but ptosis was persisting for which masterly inactivity plan of action was adopted. She was asked to come for follow up again after 15 days then 1 month then 2 months. Ptosis started to improve by the end of 2nd month and full recovery by the end of 3rd month and she started to open her eyes fully without any weakness.

Discussion

Organophosphate poisoning is one of the commonest types of poisoning in India for suicidal intent and is one of the commonest causes of intensive care unit admissions for poisoning and mortality. Estimates from World Health Organization (WHO) indicate that global incidence of OP poisoning each year is about 1 million via accidental ingestion and 2 million via intentional ingestion.² The incidence of intermediate syndrome varied from 5.4% to 47% in various reported works.³ In the case reported here it was severe poisoning and majority of complications described in literature were observed in succession in this patient⁴ although confirmatory tests like RBC cholinesterase level were not done due to family economical constrain. One of the challenging situations in our case was intractably prolonged cholinergic features and central nervous system manifestations like seizure and ptosis. These manifestations were recurring and the patient was kept on high dose Atropine for three weeks. Such delayed manifestations are reported to occur because of Acetylcholinesterase Enzyme (AChE) aging, poor rephosphorylation and decreased synthesis of new enzymes.

Our patient developed respiratory failure at the second day of poisoning which is earlier than typical duration for Intermediate Syndrome. Intermediate Syndrome occurs between the initial acute Cholinergic manifestations and the late Organophosphate Induced Delayed central Nervous system symptoms and was first described by wadia etal.⁵ The basis for Intermediate Syndrome (the Nicotinic Syndrome) is that nicotinic transmission requires inhibition of at

least 80% of the synaptic AChE unlike the muscarinic synapses and nerve endings where AChE can be easily inhibited and the Nicotinic Syndrome occurs only in severe poisoning. The end result is hyperstimulation of the Neuromuscular Junction by excessive Acetylcholine, initially resulting in fasciculation, which later is followed by Neuromuscular Paralysis which happened in sequential manner in our case; the effect of intermediate syndrome may last for 2-18 days.^{4,5} In our patient respiratory muscle groups, skeletal muscles of limbs were affected causing respiratory failure and transient weakness in the limbs. In Organophosphate Poisoning respiratory failure is very important complication which can lead to significant morbidity and mortality.

The late feature which occurred in our patient was sub- acutely developed weakness of lower and upper extremities and drooping of eyelids. Myelography and spine x-rays were ordered which turned out to be normal. Organophosphate associated Myelopathy may be the cause of fecal and urinary incontinence in our patient although MRI was not

done. The management in severe Organophosphates poisoning is supportive care of homeostasis, administration of high dose of atropine and rephosphorylation attempts by Oximes. Airway control and adequate Oxygenation are paramount in Organophosphate poisonings and Intubation may be necessary in cases of respiratory distress. Adequate atropinization is demonstrated by assessing signs including pupils, pulse rate, pulmonary secretions and mental state. Once atropinized, a maintenance type dose at 1-3 mg 1/2 hourly is usually sufficient.⁶ 2-PAM is generally given in most intensive care units at a dose of 1 gm 4 to 6 hourly. Oximes displace the Organophosphates from the Acetylcholine Esterases and bind to the enzyme itself. Although these agents appear useful theoretically, in practice their effect is not confirmed in human studies to be useful. Management of intermediate syndrome is by early detection and supportive care like the case of respiratory failure management. There is no specific therapy for the late-onset neuropathy and ptosis due to Organophosphate compounds.

In conclusion, patients with severe

Organophosphate Poisoning present with Acute Cholinergic manifestations which would need large dosage of Atropine administration and thorough evaluation of clinical features is needed to titrate the dose down and discontinue it. Moreover, careful follow-up is needed for the rare complications of Organophosphate Poisoning like Intermediate Syndrome, Palsy and Ptosis. Therefore, I recommend health care workers should be aware of these complications, their manifestations and how to manage them.

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