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INTERMEDIATE SYNDROME IN ORGANOPHOSPHATE POISONING: CASE SERIES
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SUMMARY

Acute organophosphate insecticide poisoning is very common in developing countries and the mortality is high because of lack of adequate hospitalization, inadequate atropinization and undiagnosed intermediate syndrome which occur within 24-96 hour after the ingestion of poison. Acute organophosphate 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. 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. The treatment of IMS is mainly supportive. Nevertheless, because IMS generally concurs with severe organophosphate toxicity and persistent inhibition of acetylcholinesterase, early aggressive decontamination, appropriate antidotal therapy, and prompt institution of ventilatory support should be helpful in ameliorating the magnitude and/or the incidence of IMS. The prognosis of IMS, however, is likely to be favorable if respiratory failure can be promptly recognized and treated accordingly.

INTRODUCTION

Organophosphorous insecticides are used extensively in horticulture and agriculture. Because of its easy availability organophosphorous poisoning is a significant cause of morbidity and mortality in developing countries including East Africa.

In organophosphorous poisoning, three well defined clinical phases are seen:

1. Initial acute cholinergic crisis characterized by muscarinic manifestations.
2. Intermediate syndrome
3. Delayed neuropathy

Acute Cholinergic Crisis: -Typical manifestations of cholinergic crisis include, 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 short space of time if life-threatening conditions, such as respiratory failure, are not treated promptly and appropriately. It is also called Type I Paralysis.

Intermediate syndrome: - 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 DN (1). The syndrome occurs after the acute cholinergic crisis is over and patient is clinically improved. 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%(2-10)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. 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. It is also called Type II Paralysis.

Delayed Neuropathy:- Organophosphate-related delayed neurotoxic effect, which is commonly referred to as organophosphate-induced delayed neurotoxicity (OPIDN), occurs 2–3 weeks after acute exposure to certain organophosphate insecticides (2).The clinical features are predominantly motor neuropathy and primarily manifest as numbness and weakness of the lower extremities, followed by progressive ascending weakness of limb muscles (2,5). The disease entity is believed to be due to the inhibition of a poorly characterized esterase called the neuropathy target esterase (5). It is also called Type III Paralysis.

CASE 1

A 58 year male was admitted at midnight with complaints of profuse diarrhea ,vomiting ,excessive sweating and cough with lots of secretion for 1 day, *he was a known alcoholic ,with history of accidental ingestion of Diaxinon (an organophosphate, thought it was whisky, but later on it was confirmed a suicidal attempt).The day before he was admitted our hospital ,he was admitted in a small hospital, after few hour of ingestion, where he was given Atropine 1 mg, Ceftriaxone 1 gm and Diazepam and was discharged on same day.*

On admission he was conscious and oriented to time, place and person, pupils bilateral 3 mm and were reactive to light, he was coughing, tachypnoeic, HR-78/min, BP-144/78, Temp-36.8, on auscultation there were bilateral crackles in lungs, heart sound were normal. He was admitted in general ward with diagnosis of chemical pneumonitis and was put on IV antibiotics, nebulization, mucolytics, IV fluids, antimotility drug (Loperamide), antispasmodic (cyclopam) .His baseline lab investigation were within normal range apart from moderate neutrophila . After 2 hrs of admission he developed respiratory distress with altered sensorium, so he was moved to HDU. In HDU, he was drowsy but was responding to call, BP-108/64, HR-112/min, RR-36/min, SPo2 -82% on room air, chest was wet bilaterally. He was put on Nonrebreather oxygen mask and atropine infusion@0.3mg/hrs . We didn't use Pralidoxim. His neurological status was improving and SPO2 was 98%. He remained stable over night. He remained stable for next 6 days. On day 7th of the admission atropine infusion was stopped but after few hours he became drowsy, developed lots of pulmonary secretion and shallow breathing ABG revealed respiratory acidosis (Ph 7.21, PaCO2 86mmhg), he was intubated and was put on mechanical ventilator support. After few hours of intubation he was conscious and was following command on ventilator, chest was clear, hemodynamics were stable so he was extubated. He remained stable on atropine infusion for next 36 hours .On day 9th, his breathing was easy and hemodynamics were stable, the atropine infusion stopped but within 2 hours he became drowsy again and was having shallow breathing @5-6 bpm, SPO 2 was 92%on oxygen mask, ABG revealed respiratory acidosis (Ph 7.18, PaCO2 87.2 mmhg). He was intubated and was put on mechanical ventilator support. Atropine infusion was restarted @1mg/hr. After 3 hrs of intubation he was fully awake and self extubated. He remained stable on oxygen mask up to next 24 hours. On day 10th, he became drowsy again, ABG revealed severe respiratory acidosis (Ph-7.24. PaCO2 106 mmhg), he was re-intubated and was put mechanical ventilator support. On mechanical ventilator, it was noted that he had developed proximal muscles weakness in limbs and respiratory muscle weakness. He was taken for NCCT Brain to R/O any stroke, but it was normal study. He had developed Quadriparesis associated with respiratory muscle weakness. Multiple attempts to extubate the patient failed due to persistent respiratory muscle weakness. On 16th day, the Tracheostomy was planned, but after review the studies on Intermediate Syndrome in Organophosphate poisoning, he was given one more day and finally he was extubated on day 18th. The atropine infusion was stopped on day 19th. He was transferred to ward on day 20th and he walked out to home on day 21st. Now a day he owned a vehicle service workshop and drives car up to 140km/hrs.

CASE 2

A 48 year old police man was brought in emergency department at 8.00 pm, in semiconscious condition by his neighbor, with history of found semiconscious at his house at 7.00 pm with vomitus, urine and feces around the patient. As per history given by neighbor last time the patient was seen at 2.00 pm entering to his house.

On admission the patient was very drowsy with shallow breathing, all limbs were flaccid, Pupils were bilateral pin point, drooling saliva from his mouth and very pungent smell was felt from his mouth. On auscultation the chest was wet bilaterally; Heart rate was 46/min, BP -196/11o , SpO2 was 90 on room air, Abdomen was soft on palpation , urinary bladder was not palpable , undergarments were soiled with urine and feces. Atropine 2 mg injected IV. He was taken to CT scan brain department to for CT brain to rule out any Cerbrovascular Accident, the CT brain was normal and the patient was shifted to Intensive Care Unit. The patient was intubated with Endotracheal Tube and was put on Mechanical Ventilator. Atropine infusion started @1 mg/hr. Nasogastric tube was inserted and Gastric content aspirated with very strong and pungent odour, whitish colour mixed with food. Sample kept for toxicological screen. Gastric lavage started with clean water .The patient was put on sedation and analgesia infusion on ventilator, Inj Pralidoxim 2000 mg given iv over 30 min infusion and continuous infusion of Pralidoxim @250mg/hrs started for next 12 hrs. The patient had a good recovery

and the following day during morning hours during sedation break in ICU, he was awake, pupils were 3 mm bilaterally, and he was responding on call and was having active movements in all limbs. Chest was clear and hemodynamically he was stable. The Pralidoxim infusion was stopped and continues with Atropine infusion @0.5 mg/hrs. ***On day 2nd*** by the evening he was doing very well, fully awake, was following verbal commands, tolerated Spontaneous Breathing Trial for 1 hrs so he was extubated successfully, IV fluid was stopped and allowed oral liquid diet, Atropine infusion was stopped. ***On day 3rd*** the whole day he remained stable. ***On day 4th*** during morning hrs his clinical condition had changed again, he became drowsy, HR-60/min, drooling saliva tachypnoeic, profuse sweating, flaccidity in all four limbs and chest was wet on auscultation. Inj Atropine 2mg given IV state and a continuous infusion @1 mg/hrs was started. Inj Pralidoxim 2 gm IV bolus given and continuous infusion @250mg/hr was started. ***The patients was not re-intubated,*** he kept under close observation. The NG tube inserted for feeding. After few hrs the patient responded very well, sensorium improving, secretions reduced, breathing was easy on oxygen mask. ***On day 5th*** the whole day the patient remained stable, he was conscious but slightly confused, power was improved in all four limbs (4/5) and he was kept on Atropine and Pralidoxim infusion. ***On day 6th*** he remained stable; Atropine and Pralidoxim infusion were stopped and moved to High Dependency Unit, he was able to swallow oral liquid so NG tube was removed. ***On day 7th*** remained stable, no new issues. ***On day 8th*** at 4.00.pm, he was complaining severe abdominal pain at epigastric region was sweating profusely, Bradycardia -HR 47/min with sinus rhythm without any ST changes, but neurologically he was still conscious and was following verbal commands. IV antispasmodic given and Inj Atropine 1mg IV bolus given and was put on infusion @1mg/hrs. Sudden epigastric pain was evaluated – Cardiac Enzymes were normal nut mildly elevated Amylase level. The patient improved after few hrs, was feeling thirsty, hemodynamically stable. Atropine infusion was stopped. ***On day 9th*** he remained stable up to 4.00 pm and then again developed excessive sweating but there were no other complaints ,he fully awake and answering very well ,HR -71/min . Inj Atropine 1 mg IV bolus given and infusion @0.5 mg/hrs was started for 5-6 hrs and after that it was stopped. His Thyroid function test was normal, repeated twice, and other lab abnormality was found apart from mild leukocytosis with neutrophila. ***On day 11th*** he was transferred to the general ward, he recovered very well and finally he was discharged home ***on day 19th***.

CASE -3

A 52 year male was brought in emergency department by his family members at 08.00pm. On examination, he was awake, restless and agitated. HR-141/min (ST) with good pulse, RR-30/min with clear chest, pupils were pin point, and abdomen was soft and non-tender. As per history given by his wife that he has ingested insecticide and rat poison at around 11.OO am, they came with the empty container written TERMETICIDE (Organophosphate) and a sachet (LANIRAT).He was a known patient of major depressive illness on treatment under Psychiatrist with history of multiple suicidal with ingestion of Organophosphate within 2 years. The wife said that he has done several time like this and was admitted in hospital several times. He was not having excessive salivation, Lacrimation, Bronchorrhoea, Diarrhea and Urinary incontinence, he was asking for urination. There was no classical pungent smell in his breathing. He was admitted in HDU. The Gastric lavage was done and there was mild abnormal smell in lavage fluid. We didn't start Atropine infusion on admission and order was given to start atropine infusion in case he develop secretion. We started him on Pralidoxim, 2000 mg state infusion over 30 min and then continuous infusion with 250 mg/hrs for 24 hrs. ***Lab-ABG-mild metabolic acidosis with good respiratory compensation, Urea-8.0, Creatine-124, Na-138.0, K-3.7, Uric acid-6.24, Ca-2.21, Phosphate-1.1, Mg-0.99, Hb-13.8, Wbc-11.6, Platelets-175.0, ESR-20, CRP-19.9, INR-1.27, Lactate-2.21***.He remained stable overnight. ***On day 2nd*** his HR-90/min, RR-16/min and he was communicating well and was tolerating oral feed. ***On day 3rd*** he developed excessive secretion-Rhinorhea, salivation, coughing and transmitted sound on chest auscultation. Atropine 1mg/hrs and Pralidoxim infusion@250mg/hrs was started for 12 hrs, secretions reduced within next 24 hrs. ***On day 4th*** he remained stable and atropine infusion was stopped at evening. ***On day 5th*** in morning hours he developed Bradycardia HR-56/min (SR), he was having profuse sweating and excessive secretion from oral cavity but he was having good cough reflex, In Atropine 1 mg IV bolus given and infusion started @1mg/hr which was increased up to 2mg/hrs because of persistent secretion. He remained stable on atropine infusion@2 mg/hr ***up to day 8th*** and then it was tapered off on the same day. ***On day 9th*** he was transferred to the general ward in stable condition. ***On day 10th*** in afternoon, in general ward, he developed lots of secretion and had breathing difficulty with poor cough reflex. Pupils were constricted bilaterally but he was arousable, aggressive chest physiotherapy was done, Inj Atropine 3 mg IV given state and he was transferred back to ICU. In ICU, we started atropine infusion @4 mg/hr and the secretion were reduced within 2-3 hrs; ***we didn't use Pralidoxim this time and the patient was not intubated*** but he was kept under close observation ,and the emergency trolley was kept near the patient's bed. The atropine was reduced to 2mg/hr after 6 hrs and ***on day 11th*** it was reduced

to 1mg@hrs .***On day 12th,*** he was stable on atropine 1@mg/hrs. ***On day 13th,*** the atropine infusion was stopped. ***On day 15th*** he was transferred to ward in stable condition. Finally he was discharged to home ***on day 22nd*** in stable and ambulatory condition.

DISCUSSION

Mechanism: - The mechanism of intermediate syndrome is not clear. It was felt by some authors that it may be due to the nicotinic signs of acetyl cholinesterase inhibition (**11**).

According to the views of Gadoth and Fisher (**12**) the manifestations are due to nicotinic paralysis. They felt that the organophosphorous poison stored in the adipose tissue after absorption got liberated from there and act on the nicotinic receptors. In these patients there is a rapid regeneration of enzyme acetyl cholinesterase resulting in recovery from neuromuscular blockade. Later, the release of a previously inactivated cholinesterase inhibitor results in the paralysis. Sedgwick and Senanayake (**11**) gave a hypothesis that the down regulation of acetyl choline receptors could explain the syndrome and neurophysiological findings of Intermediate syndrome. These receptors have a half life of 10 days before undergoing inactivation within the muscle fibres. Down regulation of acetyl choline receptors in the presence of acetyl cholinesterase inhibition would be expected to cause a different syndrome from myasthenia gravis. Any liberated acetyl choline is likely to have time to activate one or more receptors once or even several times before it diffuses away. Even though the half life of acetyl choline receptors is 10 days, the reason why intermediate syndrome appears within 24-96 hours following the consumption of poison may be that the heavily activated receptors become desensitized rendering them more readily endocytosed. The events following acute OPP provide a conducive setting for free radical generation. Free radicals mediate muscle damage and inflammation after strenuous exercise as well as the cellular injury of ischemia reperfusion (**13**).

Our cases highlighted occurrence an intermediate syndrome following acute cholinergic crisis in organophosphorous poisoning requiring ICU and ventilator support. According to Gold frank's toxicological emergencies (**16**), the muscle weakness, in general, resolves in 5 to 18 days. Some time it can be longer than 18 days. The maximum reported time of resolution in the literature is 30 days (**15**). This is a huge burden on already scarce medical resources in the developing country. OP poisoning is common in developing world and regulation of pesticide control is not adequate in our country (**14**).

We also highlight through these case report that although organophosphate poisoning is common in East African countries but we could not find a single case report or case series on this important entity from our country. Studies published on organophosphate poisoning from developing countries has described clinical presentation of cholinergic excess, investigation, management and outcome of patient but no description of intermediate syndrome. Although hazardous pesticide is easily available in the market, the entity might be going unrecognized or unpublished. Therefore the risk as well as incidence in our setting is unknown. Recognition of the Intermediate syndrome will help us identify the risk existing in our community and thus will help plan intervention accordingly.

Recognition of signs of muscle weakness before full blown respiratory failure happens is also important. To keep the patient in close observation for at least two weeks and assessment of muscle weakness at the time of complain of difficulty breathing and initiation of prompt treatment would help to avoid life threatening complication in OPP.

We generally treat these patients based on clinical finding of cholinergic excess in our setting. Banning of product associated with intermediate syndrome would be another desirable intervention.

The incidence of intermediate syndrome varies from 5.4% to 47% in various reported works (**2, 18, 19**). It is observed that this syndrome predominated in male and in the third decade of life (**1,18**). Agents commonly causing Intermediate Syndrome are fenthion, monocrotophos, dimethoate, methyl parathion, diazinon, Ethylparathion, Malathion, and sumithion (**2, 17-19**). The high incidence of intermediate syndrome in organophosphorous poisoning emphasis the need for careful monitoring of these patients. They should be kept under strict observation for a period of 7-10 days in the hospital to detect the development of intermediate syndrome. Mortality can be reduced by early recognition of the syndrome and prompt ventilatory support.

Management: IMS carries a high risk of death among patients with respiratory failure. Therefore, prompt recognition of the syndrome is the cornerstone of IMS management. Treatment of IMS *per se* is mainly supportive (**1,3,4,10,20**) and there are no specific antidotes available for this devastating Syndrome. Nevertheless, because IMS generally concurs with severe organophosphate toxicity and persistent inhibition of acetylcholinesterase, early aggressive gastrointestinal decontamination, followed by appropriate therapy of atropine and oximes, and prompt institution of ventilatory support, should be helpful in ameliorating the magnitude and/or the incidence of IMS. For example, Chen, in a study of 286 patients with organophosphate poisoning, demonstrated that therapy with obidoxime, a more potent oxime compared to pralidoxime, significantly

decreased the incidence of respiratory failure, the length of hospitalization, and mortality (**9**).

In conclusion, intermediate syndrome contributes to morbidity and mortality. Early recognition will help in prompt ventilator support. We recommend that patient with acute organophosphate poisoning should be assessed for muscle weakness after cholinergic crisis is over to anticipate impending respiratory arrest due to intermediate syndrome. 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. The prognosis of IMS, however, is likely to be favorable if respiratory failure can be promptly recognized and treated accordingly. Future studies on IMS should focus on delineating the pathophysiology of IMS and the identification of clinical and/or laboratory predictors of IMS by employing well-defined definitions of IMS.

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