Neuromuscular weakness and Type II respiratory failure as a result of chronic and intermediate organophsophate poisoning

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ABSTRACT

We report 3 cases with generalized neuromuscular weakness and Type II hypercapnoeic respiratory failue as a result of respiratory muscle weakness. This proved to be due to intoxication with organophosphate insecticides.

Keywords: Organophosphate acute, chronic and intermediate intoxication, neuromuscular and psychiatric disturbances, respiratory failure.

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Organophosphate compounds are widely used in Saudi Arabia as pesticides in domestic and agricultural setups. Poisoning with these compounds, which could happen accidentally or intentionally, may present as acute, chronic or intermediate syndromes. Permanent neural damage may result from chronic repeated exposure to these compounds and irreversible neuropathy has been particularly associated with the intermediate and chronic form of intoxication.[1-4] The intermediate syndrome usually arises as a late complication of acute poisoning.

Case Reports.

Patient 1. A 28-year old woman was brought to the emergency room after she had a grand mal seizure at home. She was intellectually subnormal and she dropped from school at an early age. She also had a rapid tremor of both hands since early childhood, otherwise she was physically fit.

For a period of four months prior to this current presentation, she had been feeling depressed. She also had great difficulty with speech and eating. She was noted to be generally very weak. She was unable to even use the door handle and she experienced difficulty in breathing, especially at nighttime. She had difficulty standing up and walking and when she walked she always fell to her right side. She was seen by a psychiatrist two days prior to her attendance at the emergency room. He diagnosed endogenous depression and prescribed her amitriptyline and fluoxetine. She was given the medications by her parents and they persistently denied that she overdosed herself. She was also given multiple herbal medications by faith healer.

Physical examination revealed a well-nourished woman. No sign of physical trauma were noted. She was unconscious but responsive to painful stimuli. Her level of consciousness was noted to fluctuate

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during the observation period. She was pyrexial. Pulse was also fluctuating between 70/minute to 120/minute and sinus rhythm was noted on the ECG monitor. Blood pressure was recorded initially as 120/80 but later records of 250/140 were noted. Heart sounds were normal. Chest was clear initially, but after a few hours basal crepitations were recorded by the same observer. She was noted to hypoventilate and a respiratory rate of down to 8/minute was recorded.

She had generalized tics and myoclonic jerks all over the body, but more noticeably in the upper. All the four limbs were flaccid with absent reflexes. She had pinpoint pupils bilaterally and fundoscopy after mydriatic installation was normal. The patient was also noted to be dribbling large amounts of saliva from her mouth, and later on after she was intubated she had large amounts of secretions from her endotracheal tube. The soft palate was noted to be paralyzed in midline. Examination of her abdomen revealed relatively sparse bowel sounds, but she was noted to be incontinent of urine and faeces. Full blood counts, urea, creatinine and electrolytes, liver function tests, blood sugar, calcium and urine analyses were all normal. Computerized tomography scans of brain and lumbar puncture were normal. Red blood cell cholinesterase was 2.1 U/ml (normal 4.7 - 14.7).

The patient was intubated and ventilated, commenced on intravenous atropine infusion but no pralidoxime was given due to the long history of symptoms. The dose of atropine was titrated according to the cholinergic response. Within a matter of hours she was noted to be much calmer and nyoclonic jerks were reduced. Her peripheral limb weakness had persisted however, as well as respiratory muscle and muscles of swallowing weakness. While in intensive care she developed multi-drug resistant pseudonomas septicaemia and she died five weeks after admission. Her RBC cholinesterase level, estimated two days prior to her death, rose to 6.0 U/ml. Toxicological analysis of serum, urine and the herbal medications she ingested was negative for organophosphates.

Patient 2. A 63-year old lady had been bed-ridden for four years due to generalized weakness. She was seen frequently at home due to attacks of dyspnoea, and on a few occasions a high blood pressure was recorded. She was maintained on frusemide and nifedipine for treatment of pulmonary oedema and hypertension. The family also reported intermittent periods of confusion.

She was obese and tachypnoeic at rest with shallow breathing. She was recently cyanosed but well perfused. She also had twitching in small muscles of the hands. Pulse rate was 110/min bounding in character, and blood pressure initially recorded as 180/00. There was a soft ejection systolic murmur at lower left parasternal area. Jugular venous pressure was elevated and mild pitting ankle and sacral oedema was observed. There were bilateral soft inspiratory and expiratory repetitions despite the poor inspiratory effort and faint widespread rhonchi. Examination of the abdomen was unrevealing. Neurologically she was oriented and rational. She was noted to be drowsy but easily rousable. Both pupils were small but equal in size and reactive to light. Eye movements and fundoscopy were normal. Rest of cranial nerve examination was unrevealing. She was flaccid in all four limbs with grade 2/5 power in all four limbs. Sensation was intact and all reflexes were present.

Chest radiography showed poor inspiratory effort with possibly enlarged heart, congested pulmonary hillae with upper lobe venous congestion. Her serum creatinine kinase was normal and serum pseudocholinestrase was markedly reduced to 0.9 (4.7 - 14.4 U/ml). Tensilon test was negative. Nerve conduction studies done at a later stage showed severe axonal degeneration. Reviewing the history, she told of definite exposure to insecticide fumes in closed rooms of her apartment on multiple occasions over the past few years prior to presentation.

Arterial blood gases showed hypoxia with mild hypercapnoes. She was managed with diuretics and vasodilator plus controlled oxygen via nasal canula, but initially this caused elevation of PCO_2. She could not tolerate ? liter/minute of oxygen, which was effective kin alleviating the hypoxia without worsening of hypercapnoea. Physical rehabilitation programme was initiated to improve her muscle power but with little success. Patient was discharged on controlled domiciliary oxygen plus frusemide and nifedipine. A few weeks later she was readmitted with deterioration in her general status. She was found to be in respiratory failure to gain and ventilation in intensive care was instituted. She developed septicemia with multiple organ failure a few days after admission and finally succumbed to death. Her repeat serum cholinesterase remained persistently low at 0.9 U/ml on her second admission.

Patient 3. A 70-year old retired non-smoker, telephone operator presented with one year history of increasing weakness in both upper and lower limbs and intermittent dysphagia more marked for solid food. He was treated previously on two occasions for aspiration and since then he has complained of dyspnoea at rest. He also had difficulty in controlling his bowel and bladder emptying, despite him being fully aware of his incontinence. Over the same period his speech became more laboured and he had difficulty trying to make his voice audible. There was no past medical history of significance and he was on no regular medications.

Physical examination revealed a distressed man with tachypnoea, respiratory rate of 26/minute but breathing was shallow. He was centrally cyanosed. He had a large body build with no evidence of wasting. His pulse rate was d76/minute initially but variable rate ranging between 40-200/minute was noted. Blood pressure was recorded as 130/70 with considerable fluctuation seen later on. The rest of his cardiovascular examination was normal. His chest examination revealed shallow breathing with inspiratory and expiratory crepitations marked at both bases. He was not capable of making a strong cough. Examination of the abdomen was unremarkable. His higher cerebral functions were normal. He had marked dysphonia, but no dysphasia nor dysarthria. There was mild, bilateral ptosis but eye movements were all normal although they were slow. Both pupils were small but reactive to light and accommodation. Fundoscopy was normal. Rest of cranial nerve examination was normal except for centrally paralyzed soft palate and reduced gag reflex. All limbs had flaccid paresis with absent tendon jerks. Sensorium was intact.

His arterial blood gases showed respiratory acidosis with pH=7.1, PO_2=5.4 Kpask, PCO_2=8.9 Kpask. Full blood count, urea, creatinine, electrolytes, calcium, random blood sugar were all normal. Chest radiogram showed poor inspiratory effort otherwise normal. An attempt to treat him conservatively with supplementary oxygen and breathing exercises were not successful, and within a few hours he needed ventilatory support. His serum cholinesterase was reported later on as 0.1 U/ml (4.7-14.7) and after further questioning to patient and family they gave positive history of using domestic insecticide spray in large amounts and in closed room while the patient was exposed to the insecticide fume inside the room. Lung function testing confirmed severe restrictive defect. Nerve conduction studies revealed severe axonal degeneration of peripheral nerves involving both large and small axons. The patient could not be weaned of ventilatory support and eventually he was discharged home on long term domestic ventilation plus nasogastric feeding. Patient and his family were clearly instructed to avoid further exposure to insecticides.

Discussion. Respiratory failure due to intoxication with cholinesterase inhibitors, such as organophosphate compounds can result from airway obstruction, non-cardiac pulmonary oedema and hypoventilation as a result of neuromuscular weakness. Airway obstruction can result from bronchospasm and excessive bronchial secretions. The latter can also result in plugging of airways and collapse of related segment or lobe.[5,6] Other mechanisms have been proposed and suggested by recent reports such as vocal cord paralysis[7] and anaphylactoid reaction as a result of organophosphate compounds acting as secretagogues inducing mast cell degranulation and release of humoral mediators of anaphylaxis.[8]

Neuromuscular dysfunction without signs of cholinergic excess is seen in intermediate and chronic (or delayed) syndromes of organophosphate intoxication. The intermediate syndrome occurs 7 to 75 hours after the acute cholinergic crisis of intoxication and it occurs mainly in patients who recovered from the acute cholinergic crisis after severe organophosphate poisoning. The muscular weakness is seen particularly in neck flexors, proximal limb muscles, muscles innervated by motor cranial nerves and respiratory muscles. The syndrome may not be as uncommon as it was thought. In a recent report from China, it had a prevalence rate of 7.7% after acute poisoning, while Indian literature has reported an incidence of the syndrome up to 47% post acute poisoning.[3,9,10] The first case in this paper demonstrates the well described neural dysfunction and resultant respiratory failure seen in intermediate syndrome.

Development of respiratory failure can be predicted from severity of the acute poisoning[3,5,9,10] as assessed from the dose ingested as well as severity of cholinergic crisis. Some authors reported serum amylase to be a useful marker to predict development of respiratory failure after acute poisoning.[11] The last two patients reported in this paper have presented with chronic syndrome of organophosphate intoxication, which could be very puzzling to treating physicians if they are not aware of the chronic manifestations of organophosphate intoxication.[4,6] Diagnosis is achieved from history of exposure to organophosphate compounds, clinical picture and evidence of lowering of acetylcholinesterase level. Toxicological analysis of body fluids such as serum, urine or saliva may be used although not routinely available service in many clinical laboratories, but it is useful where medico-legal issues have arisen.

The normal range for serum acetycholinesterase is wide in the population and this may mask lowering of the enzyme level if one single reading is examined. This can be overcome by examining serial readings of the enzyme at intervals and looking for a rise in enzyme level after removal of subjects from site of exposure.[1,2] This approach is particularly helpful in following up agricultural workers at risk of exposure to organophosphate insecticides.[12,13] Causes of low level of acetycholinesterase include genetic deficiencies of enzyme synthesis or synthesis of abnormal variants, both of which are usually familial.[13-16] Exposure to cholinesterase inhibitors such as organophosphate, carbamate and pyrethroid compounds is an important group of causes which can be confirmed from history of exposure or if needed by toxicological analysis.[17] As the serum

enzyme is synthesized in the liver, it can also be reduced in chronic liver disease.[13,15] Raised level of the enzyme is seen in Alzheimer's disease by lowering the enzyme has been reported to be of benefit.[18,19]

Although there is no specific therapy to reverse the neural damage after chronic repeated exposure to organophosphate compounds, it is of vital importance to identify this toxic cause of neuropathy and avoid further damage by removal from site of exposure.

References

1. Ellehorn M, Barceloux DG. Insecticides: in medical toxicology: Diagnosis and treatment of human poisoning. Elsevier Publication 1980: 1070-9.
2. Hayes WJ. Toxicology of pesticides. Baltimore: Williams and Willkins 1975: 410-517.
3. Senanyake N, Karalliedde L. Neurotoxic effects of organophosphorous insecticides: an intermediate syndrome. N Eng J 1987; 316: 761-3.
4. Namba T, Nolte CT, Jacknel J, Grob D. Poisoning due to organophosphate insecticides: acute and chronic manifestations. Am J Med 1971; 50: 745-92.
5. Goswamy R, Chaudhuri A, Mahashour A. Study of respiratory failure in organophosphate and carbamate poisoning. Heart and Lung 1994; 23: 466-72.
6. Bardin PG, Van Eden SF, Moolman JA, Foden AP, Joubert JR. Organophosphate and carbamate poisoning. Arch. Int. Medicine 1994, 154: 1433-41.
7. Thompson JW, Stocks RM. Brief bilateral vocal cord paralysis after insecticide poisoning. A new variant of toxicity syndrome. Arch Otolaryngol Head Neck Surgery 1997; 123(1): 93-6.
8. Cowen FM, Shis TM, Lenz DE, Madsen JM, Broomfield CA. Hypothesis for syndergisitic toxicity of organophosphorous poisoning - induced cholinergic crisis and anaphylactoid reactions. J Appl Toxicol 1996; 16: 25-33.
9. He F, Xu H, Qin F, Xu L, Huang J, He X. Intermediate myasthenia syndrome following acute organophosphate poisoning: an analysis of 21 cases. Hum Exp Toxicol 1998; 17: 40-5.
10. Samuel J, Thomas K, Jeyaseelan L, Peter JV, Cherian AM. Incidence of intermediate syndrome in organophosphate poisoning. J Assoc Physicians India 1995; 43: 32-3.
11. Matsumiya N, Tanaka M, Iwai M, Kondo T, Takahashi S, Sato S. Elevated amylase is related to the development of respiratory failure in organophosphate poisoning. Hum Exp Toxicol 1996, 15: 250-3.
12. Al Shatti AK, El Desouky M, Zaki R, Abu Al Azem M, Al Lagani M. Health care for pesticide applicators in a locust eradication campaign in Kuwait. Environ Res 1997; 73: 219-26.
13. McQueen MJ. Clinical and analytical consideration in the utilisation of cholinesterase measurements. Clin Chem Acta 1995; 237: 91-105.
14. Santoro P, Lucci A, Tardi C. Silent cholinesterase genes: three homozygotes in a small Caucasian population. Boll. Soc Ital Biol Sper 1992; 68: 187-94.
15. Hada T, Murantani K, Ohue T, Imanishi H, Moriwaki Y, Ioh M et al. A variant serum cholinesterase and a confirmed point mutation at Gly-365 to Arg found in a patient with liver cirrhosis. Internal Medicine (Japan) 1992; 31: 357-62.
16. Hirasaki S, Koide N, Ujike K, Yamamoto H, Fujita Y, Tanigama T. A family with heriditary serum cholinesterase deficiency. Intern Medicine 1995; 34: 632-5.
17. Bardin PG, Van Eeden SF, Moolman JA, Foden AP, Joubert JR. Organophosphate and carbamate poisoning. Arch Int Med 1994; 154: 1433-44.
18. Flicker L. Acetylcholinesterase inhibitors for Alzheimerís disease. Br Med J 1999; 318: 615-6.
19. Bosler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Biance P et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international, randomized, controlled trial. Br Med J 1999; 318: 633-40.