CASE REPORT

Prolonged paralysis in a child with organophosphate pesticide poisoning

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A 17-month-old boy presented to a local community health centre in Cape Town, South Africa, with severe organophosphate pesticide poisoning (OPP), necessitating the use of intravenous atropine to control cholinergic symptoms, as well as emergency intubation for ongoing respiratory distress. He required prolonged ventilatory support in the intensive care unit at his referral hospital and had subsequent delayed neurological recovery, spending 8 days in hospital. We present this case to emphasise the importance of adequate atropinisation in the management of severe OPP and to highlight the dangers of inappropriate use of suxamethonium for intubation in patients with OPP.

Organophosphates are registered for use as pesticides in the agricultural sector in South Africa (SA). Unfortunately, many products are sold illegally for use as domestic rodenticides, where young children may be at risk of accidental exposure.[1] In SA, data on organophosphate pesticide poisoning (OPP) in children are scarce.[2-5] A review of cases (2003 - 2008) seen at Red Cross War Memorial Children's Hospital, Cape Town, SA, showed that of 311 pesticide incidents, 203 were caused by cholinergic pesticides (organophosphates and carbamates), leading to a median hospital stay of 3 days for symptomatic patients (*n*=195/203).[2] Of these cholinergic incidents, 120 (59%) patients required admission to a high-care or intensive care unit (ICU); 5 of them died. The severity of presentation of this cohort shows that more than half of paediatric patients may require respiratory support, including assisted ventilation, in addition to the administration of atropine for control of muscarinic symptoms. Adequate knowledge of appropriate ventilatory resuscitation and early medical management for patients with OPP is essential for medical practitioners providing emergency care. We describe a case of severe OPP with prolonged apnoea and paralysis, most likely due to suboptimal atropinisation and the use of suxamethonium for airway intubation.

Case report

A 17-month-old well-grown boy was found acutely ill at home. He was vomiting, sweating, drowsy and breathing with difficulty. In the morning, his mother had put out rat poison mixed with rice and left the boy in the care of his 12-year-old sibling.

The child was rushed to the local community health centre. On arrival, he had a respiratory rate (RR) of 30 breaths per minute, oxygen saturation levels of 100%, heart rate (HR) of 137 bpm, and was drowsy with pinpoint pupils and bronchorrhoea. A diagnosis of presumed OPP was made. He was given an intravenous (IV) atropine test dose of 0.01 mg/kg. At 5 - 10-minute intervals further bolus doses of 0.2 mg, 0.2 mg, 0.2 mg and 0.3 mg were administered intravenously. The child showed some response to atropine with tachycardia and clearing of secretions, but still had pinpoint pupils. While awaiting the ambulance for transfer to the referral hospital, his oxygen saturation decreased to 85% and the decision was taken to

intubate and ventilate him. Rapid sequence induction was performed using IV midazolam 0.2 mg (0.02 mg/kg) and suxamethonium 20 mg (1.7 mg/kg); he improved with manual ventilation with a self-inflating bag and 40% oxygen.

The patient was tranferred by ambulance on a transport ventilator and with an atropine infusion (0.017 mg/kg/h). He remained sweaty, had pinpoint pupils and was noted to have sudden reductions in HR – from 186 to 95 bpm. Although he had bilateral crepitations on chest auscultation, he maintained oxygen saturation levels of 98% throughout his transfer. No further atropine bolus doses were given *en route* to the referral hospital.

On arrival at the receiving hospital, 2 hours after initiating medical resuscitation, he was assessed as being severely ill, with an HR of 97 bpm, blood pressure of 153/70 mmHg, pinpoint pupils, some oral secretions, severe bilateral crepitations and an oxygen saturation level of 62%, despite an ongoing atropine infusion. Arterial blood gas showed: pH 6.9, pCO_2 11.1 kPa, pO_2 8.0 kPa, bicarbonate 12.6 mmol/L and base excess –13.9 mmol/L. His oxygen saturation improved to 100% after manual ventilation with a self-inflating bag and 40% oxygen. He was given IV Ringer's lactate solution 120 mL and further IV atropine bolus doses of 0.2 mg and 0.4 mg. The clinical notes indicated an inadequate response to atropine, as his pupils remained pinpoint, but did not report on the clearing of secretions in the lungs. Additional medical treatment included IV ceftriaxone 1.2 g and acy-clovir 240 mg for management of possible sepsis.

The patient was taken to the ICU for a continued atropine infusion of 0.017 mg/kg/h and intermittent positive pressure ventilation (IPPV). On arrival in the ICU, he had crepitations in the left lung, but good air entry bilaterally. His body was washed and gastric lavage was performed.

Despite receiving no ongoing sedation, the child was noted to be completely paralysed with gasping respirations on the ventilator >20 hours after receiving medical attention. He had good air entry bilaterally, his pupils remained pinpoint, with no reaction to light, and he had no spontaneous movements. His atropine infusion was increased to 0.02 mg/kg/h. Later that day, he started making spontaneous movements with flexion of the upper extremities and

withdrawal to painful stimuli, but there was minimal movement of the lower limbs and no spontaneous eye opening. At this point, his atropine infusion was decreased to 0.004 mg/kg/h. Overnight, he was given diazepam and clonidine for marked restlessness and the following morning his atropine infusion was again increased to 0.017 mg/kg/h. Almost 3 days after presenting to hospital, the patient became more responsive, his pupils were 3 - 4 mm and sluggishly reactive, and he was therefore electively extubated. He subsequently had mild respiratory distress with a RR of 55 breaths per minute, subcostal recessions, alar flaring and stridor, but good air entry bilaterally. The patient was given dexamethasone, nebulised with adrenaline, placed on continuous positive airway pressure (CPAP) for 1 day, with ongoing clonidine and diazepam for sedation, and atropine was weaned to 0.004 mg/kg/h. The following day his level of consciousness was assessed as 10/15 on the Glasgow Coma Scale (GCS), his pupils were 4 - 5 mm and reactive, and he had good air entry bilaterally. His atropine infusion was discontinued and he was transferred to the general medical ward on nasal-prong oxygen.

On reception in the ward, he was restless and drowsy, with tachypnoea, bilateral crepitations and an HR of 90 bpm. No further doses of atropine were administered. His sedation was stopped and after 2 days on nasal-prong oxygen he could breathe adequately in room air.

The suspicion of OPP was confirmed by a pseudocholinesterase level of <1 000 U/L (laboratory reference range 4 620 - 11 500 U/L) on two occasions 48 hours apart. Although the rodenticide active ingredient was not identified by laboratory analysis, the severity of presentation, low pseudocholinesterase level and duration of symptoms suggest it was an organophosphate and not a carbamate pesticide; treatment would, however, have been identical for both. No electromyographic studies were performed. Serum salicylate levels were negative. His blood gas steadily improved and renal function was normal. His clotting parameters and liver enzymes were slightly deranged initially; neither required active management. The patient's procalcitonin was 6.36 µg/L and a chest radiograph showed perihilar infiltrates more marked on the left. He developed a low-grade fever and *Klebsiella pneumonia* was cultured on a tracheal aspirate. He completed 7 days of IV cefotaxime and acyclovir.

Of particular mention is the patient's protracted neurological recovery. In the ICU, there had been concern of a hypoxic brain injury due to his longer than anticipated ventilatory requirements and reduced movements. A computed axial tomography (CAT) brain scan showed subtle effacement of the superior surface sulci and basal cisterns only, but no cerebral oedema and no intracranial pathology. No abnormalities were detected in his lumbar puncture aspirate. Once all sedation was discontinued in the general ward, only spontaneous eye opening and some purposeful movements were evident, as he remained hypotonic with marked head lag, a weak cry and unable to push up or sit unsupported. He progressed slowly over a few days and was able to walk, albeit with an unsteady gait, on discharge. He was not attended to by a physiotherapist during his hospital admission. There is no comment on his gag reflex, but continuous nasogastric feeds were started when he was in the ICU; these progressed to bolus feeds and finally to normal eating before discharge.

His case was reported to the City of Cape Town Health Department. A social worker assessed the home circumstances and his parents were given home safety counselling before discharge of the patient.

Subsequent telephonic contact with the family confirmed that the child was 'doing well', but no formal neurological follow-up examination has been undertaken.

Discussion

Organophosphates bind irreversibly to acetylcholinesterase and plasma cholinesterase, rendering them unable to cleave acetylcholine at pre- and postsynaptic junctions and at skeletal muscle and central nervous system receptors. This results in a clinical syndrome of cholinergic overstimulation. During the acute cholinergic crisis, respiratory embarrassment is due to bronchorrhoea, bronchospasm, respiratory muscle weakness and central nervous system depression with loss of central respiratory drive.[6,7] Any ongoing respiratory difficulty and neurological weakness may be due to delayed neurotoxic effects, such as intermediate syndrome,[6,8] or complications secondary to the acute crisis, e.g. hypoxic brain injury or aspiration.[8]

Treatment of OPP requires particular attention to supportive care of the respiratory, neurological and cardiovascular systems. Antidotes may be used; atropine provides relief of muscarinic and central nervous system symptoms,[8] and the clinical efficacy of oximes is contested as current evidence is insufficient.[9] With appropriate treatment, clinical reversal of symptoms in the acute cholinergic phase should occur within hours, but the response to and duration of treatment are also dependent on the route of exposure, amount and type of organophosphate.[10] Although thorough topical decontamination is required, gut decontamination (activated charcoal and gastric lavage) should only be done if the patient presents within 1 - 2 hours of ingestion of a potentially life-threatening amount of organophosphate.[6,11]

The case described had an atypical clinical course, as the child showed prolonged neuromuscular blockade and apnoea beyond what would be expected of the acute cholinergic crisis after decontamination and atropinisation. It is likely that a variety of mechanisms contributed to his slower than usual recovery.

A possible cause for this patient's prolonged morbidity is suboptimal treatment with atropine. There was a delay in optimising atropinisation; static rather than incremental bolus atropine doses were given and once an infusion was started, only two further bolus doses were administered despite ongoing muscarinic symptoms. In moderate-to-severe OPP, the current recommendation is to double the dose of atropine every 5 - 10 minutes until clinical improvement occurs, particularly the drying of respiratory secretions, reversal of bronchospasm and improvement in HR and blood pressure.[6,12] Pupils may take a little longer to dilate. Once stabilised, an atropine infusion is started, calculated at an hourly rate of 10 - 20% of the total amount required to stabilise the patient, and titrated according to clinical response. Any breakthrough of muscarinic symptoms requires bolus doses in addition to, or even with an increase in, the atropine infusion.[12] Regular review of patients is critical to assess response to atropine. It has been shown that rapid atropinisation results in reduced mortality, shorter time to atropinisation, less atropine toxicity and less intermediate syndrome.[8,13] In severely poisoned patients, large quantities of atropine may be required with the potential to deplete the available hospital stock. Fortunately, atropine is inexpensive and has an 18-month expiry period. This more aggressive approach to atropinisation would possibly have contributed to a speedier recovery and even obviated the need for emergency intubation and ventilation in this patient. Furthermore, the timeous use of oximes may have aided in reversing any nicotinic effects such as respiratory muscle weakness, but because of the ongoing controversy surrounding their role in acute OPP[8,9] and their expense, they are rarely available or used in our setting.

Prolonged paralysis can be associated with the use of suxamethonium, a depolarising muscle relaxant, which is commonly used for patient intubation owing to its short duration of action.

Both suxamethonium and the non-depolarising muscle relaxant mivacurium are metabolised by plasma cholinesterases;[7,14] therefore, their metabolism is reduced in the presence of OPP, resulting in an exaggerated iatrogenic paralysis. This phenomenon has been reported in adults[15,16] and children[17-19] with OPP and suxamethonium use, and may have been a contributing factor to this child's prolonged apnoea. Where muscle relaxants are required for airway intubation in patients with OPP, depolarising agents not metabolised by plasma cholinesterases are preferable.

Other causes of reduced cholinesterase activity, which can contribute to increased OPP severity but were not present in this patient, are malnutrition, liver and renal disease, malignancy, burns, heart disease, oral contraceptive use, pregnancy, hypothyroidism, use of cholinesterase inhibitors (e.g. pyridostigmine) and plasmapheresis.[7,14]

Our patient's clinical course was not typical of an intermediate syndrome sometimes seen in OPP, as his respiratory function did not regress after initial recovery, he had generalised muscle weakness rather than predominantly proximal weakness, and he did not develop any cranial nerve palsies. It is however possible that any recovery period between the acute cholinergic crisis and the development of intermediate syndrome was masked by the prolonged suxamethonium-induced paralysis. Intermediate syndrome usually presents 1 - 4 days after apparent recovery from severe, acute OPP. Patients develop muscle weakness, especially of the muscles of respiration (including neck flexors and bulbar muscles) and proximal muscles, as well as cranial nerve palsies. It is thought to be owing to neuromuscular junction dysfunction and perhaps inadequate oxime therapy. Patients present with worsening respiratory function, but recover fully with ventilatory support.[6,7]

A central cause for our patient's respiratory depression may have been due to hypoxic brain injury. Although the CAT scan did not completely exclude this possibility, it is less likely, as at last contact the child had fully recovered with no crude cognitive impairment.

Other options for his unusual clinical course include that he was homozygous for atypical plasma cholinesterase and therefore presented with a more severe clinical picture,[7,14] or that the unidentified organophosphate agent was highly lipophilic, resulting in ongoing toxicity.

Conclusion

Optimising resuscitation efforts is vital in ensuring improved outcomes for patients with OPP. Early aggressive atropinisation with incremental atropine bolus doses followed by infusion improves outcomes and may even reduce the need for intubation and ventilation in patients with severe OPP.

Where emergency airway protection is required, the weakness caused by OPP may obviate the need for any muscle relaxant. However, if a muscle relaxant is clinically needed, suxamethonium and mivacurium should be avoided and alternative agents be made available as emergency stock for such patients. Alternative muscle relaxants, as determined by local availability and cost, include rocuronium (rapid speed of onset), cisatracurium (non-organ-dependent elimination) and vecuronium.

Teaching points

- In patients with severe OPP, rapid atropinisation with initial doubling of bolus doses, followed by an atropine infusion, improves outcomes. Regular assessment of treatment response is required.
- Acute respiratory failure in OPP is due to bronchorrhoea, bronchospasm, respiratory muscle weakness and central nervous system depression.
- Suxamethonium and mivacurium for intubation should not be used in patients with OPP, and alternative muscle relaxants should be considered. Where suxamethonium has been used for airway management, prolonged paralysis must be anticipated.

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