CASE REPORT

Reversal of Cardiovascular Toxicity in Severe Organophosphate Poisoning with 20% Intralipid Emulsion Therapy: Case Report and Review of Literature

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Abstract

Background: Cardiac toxicity is one of the life-threatening effects of severe organophosphate (OP) poisoning. We presented a patient with severe OP poisoning, in cardiovascular shock poorly responsive to conventional treatments, who could be resuscitated successfully with intravenous lipid emulsion (ILE) therapy.
Case report: A 26-year-old female was admitted to our emergency department who had ingested unquantifiable amount of parathion. On admission, she was tachycardic, tachypneic and hypotensive with pin-point pupils. Neurological examination revealed Glasgow coma scale (GCS) of 6. Immediately, she was admitted to intensive care unit, and was intubated and put under mechanical ventilation. Standard treatments including atropine and pralidoxime (according to WHO protocol) were given to the patient. However, the patient did not show favorable response to antidotes and supportive treatments and her condition continued to deteriorate. Because of bradycardia and hypotension, she was given noradrenaline vasopressor support. Due to failure of treatments in improvement of the patient's condition, a single 100 mL bolus (1.5 mL/kg) of 20% intralipid was administered intravenously and the same dose repeated 2 minutes later. Over 15 minutes, cardiovascular condition of the patient noticeably improved. ILE was continued up to a total dose of 300 mL when extrasystoles disappeared. The patient could be extubated from ventilator with GCS score of 15 on the 5th day of admission.
Discussion: OPs are lipid soluble and ILE can move these kinds of compounds away from the site of toxicity and dissolve them in the plasma which will alleviate their toxic effects.
Conclusion: This is the first human case report of OP poisoning which showed efficacy of intralipids as antidotal therapy outside the accepted setting of local anesthetic toxicity.

Keywords: Cardiotoxicity; Intravenous Fat Emulsions; Organophosphorus compounds; Parathion; Poisoning

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INTRODUCTION

Organophosphorus (OP) poisoning is one of the commonest types of deliberate self-poisoning in developing countries which entails in great number of intensive care unit (ICU) admissions and mortality (1,2). Severely OP poisoned patients should receive immediate resuscitation including circulatory support and mechanical ventilation when indicated. In patients with severe OP poisoning, treatment with anticholinergics is still the mainstay of treatment and should be initiated as soon as the airway has been secured (3). There are reports of successful use of intralipids or intravenous lipid emulsion (ILE) therapy in resuscitation of patients with cardiac arrest and hemodynamic instability due to toxicity of lipid soluble drugs(4,5).

We hereby report a severely OP poisoned patient with poor response to conventional treatment with anticholinergics, who developed ventricular tachycardia within 8 hours of ingestion, which could be reversed successfully with ILE therapy.

CASE REPORT

A 26-year-old woman was admitted to the emergency department of Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India after suicidal ingestion of unquantifiable amount of parathion. Prior to admission, she had developed altered sensorium following an episode of seizure. On admission, she was restless in postictal state. Her vital signs showed pulse rate of 48 beats/minute, blood pressure of 86/54 mmHg and respiratory rate of 10 breaths/minute. Neurological examination revealed Glasgow coma scale (GCS) of 6 with reduced movements of all four limbs. Pupils were pin-point bilaterally with absent doll's eye movement. Plantar reflex was extensor bilaterally. Deep tendon reflexes were sluggish. She had plenty of oral

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secretions, generalized fasciculation and typical pungent smell of OP compounds. Examination of chest showed bilateral crepitation. Bowel sounds were increased but there was no diarrhea. Examination of other systems was normal.

The patient was immediately admitted to ICU, and was intubated and put under mechanical ventilation on pressure-regulated volume control mode of ventilation with FiO2 of 1, Respiratory rate of 12, positive end expiratory pressure of 6 and tidal volume of 450 mL. Ryle's tube aspiration was done which revealed large quantity of bluish aspirate smelling of OP compounds. Fluid resuscitation was started with 1 liter of crystalloid (Lactated Ringer's) fluid and 500 mL of colloid fluid. Decontamination was performed as per our protocol which includes removing all clothing from and gently cleansing patients suspected of OP exposure with soap and water. The patient was treated with atropine and pralidoxime (PAM) along with broad spectrum antibiotics (piperacillin/tazobactam and metronidazole). Atropine was given 5 mg bolus dose with two more doses at 5 to 10 minute intervals, followed by infusion at the rate of 2 mg/h. Then the dose of atropine was titrated as per her clinical response and signs of atropinization. Pralidoxime was started according to World Health Organization (WHO) protocol. Phenytoin sodium was given for the treatment of seizures.

Baseline (on admission) laboratory investigations of the patients revealed normal renal and liver functions, and normal serum levels of sodium, potassium, calcium and magnesium. Arterial blood gas (ABG) analysis showed severe acidosis, hypercapnia and hypoxia (Table 1). Plasma cholinesterase (PChE) level was 1234 (IU/L) (reference range: 4000-11000 IU/L). Chest X-ray showed bilateral haziness suggesting acute respiratory distress syndrome.

Table 1. Laboratory findings of the patient at presentation

Investigation	Result
Arterial blood gas analysis	
pH	7.22
pCO2 (mmHg)	45
pO2 (mmHg)	50
HCO3 (mEq/L)	12.24
Oxygen saturation (percent)	78%
Creatine phosphokinase (U/L)	110
Creatinine (mg/dL)	0.9
Sodium (meq/L)	142
Potassium(meq/L)	3.7
Magnesium(meq/L)	1.5
Aspartate aminotransferase (U/L)	25
Alanine aminotransferase (U/L)	50
Alkaline phosphatase (U/L)	90
Total bilirubin (mg/dl)	0.8
International normalized ratio (IU)	1.12
Prothrombin time (sec)	12.4

In ICU, the patient was put under close monitoring by serial checking of central venous pressure, ABG and electrocardiogram. However, the patient did not show favorable response to antidotes and supportive treatments and her condition continued to deteriorate. Subsequently, due to bradycardia and hypotension she was given noradrenaline vasopressor support (10 µg/min). Nevertheless, her heart rate continued to be around 50 to 54 even after 6 hours. Eight hours after ingestion of OP agent, the patient developed arrhythmias with fast ventricular rate, QT prolongation which progressed to ventricular tachycardia (VT) and ventricular fibrillation. Standard cardiopulmonary resuscitation in addition to repeated DC cardioversion, administration of amiodarone and high-dose inotrope infusion failed to restore a sustained effective cardiac rhythm. Thirty minutes after initial arrest, a single 100 mL bolus (1.5 mL/kg) of 20% intralipid was administered intravenously and the same dose repeated 2 minutes later. After approximately 1 minute a sustained palpable pulse could be observed. Over the subsequent 15 minutes, QRS duration decreased and sinus rhythm was restored. An additional period of VT developed 90 minutes later, but resolved with adrenaline and only 1 minute of chest compressions. ILE was continued up to a total dose of 300 mL when extrasystoles disappeared.

While under ventilatory support, the patient was kept sedated using midazolam and fentanyl infusions for 24 hours. The need for vasopressor support and atropine started to decrease gradually (Table 2), concurrent with improvement in level of consciousness to GCS score of 9 after 72 hours. Patchy infiltrates and haziness in her chest X-ray started to disappear and oxygenation improved. In addition, cultures of endotracheal tube secretions were found to be sterile.

Measurement of PChE level was repeated every day and PChE began to rise after the 3rd day and returned to normal values on the 7th day (Figure 1). The patient was extubated from ventilator with GCS score of 15 on the 5th day of admission after following a weaning protocol. By the end of the 7th day, her mental status, pupilary signs and hypersecreation improved and atropine was discontinued.

After regaining consciousness, the patient admitted that ingestion of the poison was with suicidal intention. Following recovery, she was evaluated by psychiatrists and it was revealed that ingestion of poison was an impulsive act due to poor social and financial support from family.

Table 2. Atropine requirement in ICU

Day	Atropine Requirement
Day 1	2 mg every 15 to 30 min
Day 2	1mg every 15 to 30 min
Day 3	0.5 mg every 15 to 30 min
Day 4	1 mg every 1 to 6 hours
Day 5	0.5 mg every 12 to 24 hours
Day 6	Discontinued

DISCUSSION

Poisoning with anticholinesterase agents usually presents with non-specific gastrointestinal symptoms of vomiting, diarrhea and abdominal pain. Subsequent clinical effects are multi-systemic depending upon the dose of the poison ingested and involve muscarinic, nicotinic and central receptor stimulation (3,6). The spectrum of clinical findings ranges from muscle fasciculation, cramps and twitching to weakness and paralysis requiring mechanical ventilation (3,6). In addition, OP induced cardiac complications include tachycardia or bradycardia (depending on whether nicotinic or muscarinic effects predominate), prolonged QTc and PR interval and arrhythmias (7,8). The mechanism of cardiotoxicity caused by OP poisoning is not fully determined. Ludormirsky et al described three phases of OP cardiotoxicity (9): phase 1; a brief period of increased sympathetic tone, phase 2; a prolonged period of parasympathetic activity, and phase 3; in which QT prolongation followed by torsade de pointes ventricular tachycardia and ventricular fibrillation occurs.

For the patient we presented in this paper, the diagnosis of OP poisoning was based on history and confirmed by the clinical picture and decreased level of PChE. The patient had bradycardia and hypotension which rapidly progressed to VT. According to our institutional protocol, both atropine and pralidoxime should be administered in the treatment of OP poisoning. Pralidoxime was given as per WHO protocol comprised of 30 mg/kg loading dose over 30 minute followed by 8mg/kg/h continuous infusion for maximum of 7 days (10). However, our patient continued to deteriorate despite administration of atropine and pralidoxime as well as vasopressor support in the first day of admission. Intralipids are readily available in the operating room of department of surgery of our hospital because of previous successful experiences with local anesthetic toxicity. ILE therapy was immediately started once repeated attempts of standard cardiopulmonary resuscitation failed to produce sustainable perfusing cardiac rhythm. Two doses of this treatment resulted in restoration of hemodynamic state and sinus rhythm (Figure 2). For the present case, ILE was administered according to the guideline of the Association of Anesthetists of Great Britain and Ireland which recommends intravenous injection of bolus 1.5 mL/kg intralipid followed by infusion of 0.25 mL/kg/min increasing to 0.5 mL/kg/min (11). We used this treatment as there has been no established evidence of adverse events from the use of high dose ILE as antidote for humans to date. However, some low-intensity complications such as allergic reactions, elevated liver enzymes, thrombocytopenia, hyperthermia are the anticipated side-effects following use of ILE that are satisfactorily responsive to supportive treatments (12,13). Intralipid solution is constituted of soybean oil, egg phospholipids and glycerine and is available in 10%, 20% and 30% concentrations. Intralipids can reverse cardiotoxicity by drug sequestration, increasing intracellular calcium concentration and augmenting myocardial free fatty acid uptake which contribute to improved cardiac performance (13). To the best of our knowledge, this is the first report of OP poisoning with severe cardiac toxicity in humans reversed by intralipids. However, an experimental study on a rat model with parathion poisoning has proven positive effects of ILE therapy in diminishing the acute effects of this type of OP compound (14).

ILE has been considered as an effective therapeutic method for reversal of toxicity caused by overdose of

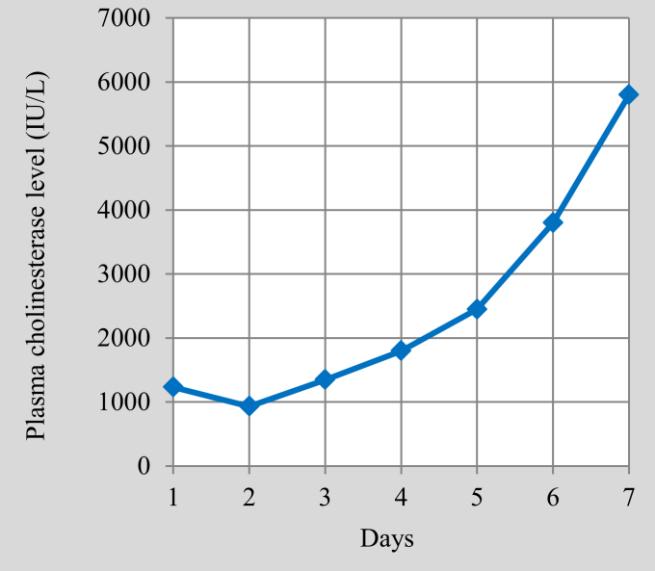

Figure 1. Trend in plasma cholinesterase level of the patient

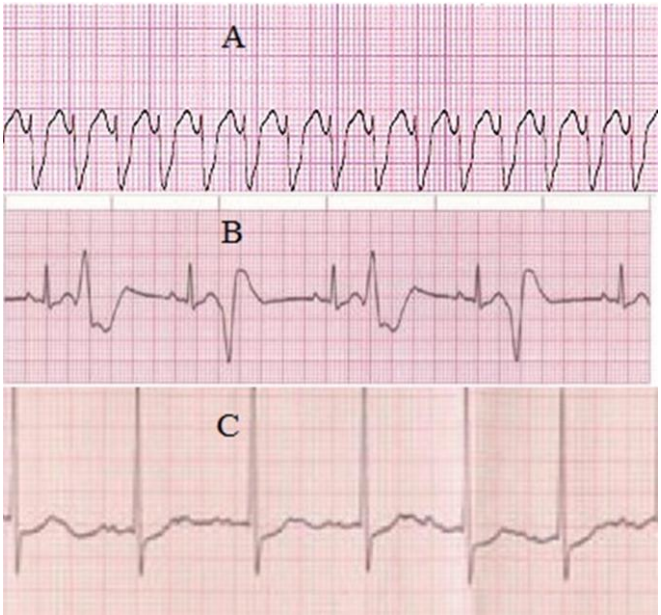

Figure 2. (A) Electrocardiogram (ECG) at the onset of ventricular tachycardia before lipid emulsion administration, (B) ECG at 1 minute after bolus intralipid showing supraventricular extrasystoles with intermittent bigeminy, (C) ECG after 90 minutes of lipid emulsion showing sinus rhythm with respiratory variation and supraventricular extrasytoles are no longer present

lipophilic substances (5). Most OP compounds are highly lipid soluble (15). At present, there is lack of effective methods to treat severe OP poisoning. Several factors can contribute to difficulty in treatment of OP poisoning (6,16-18): Firstly, absorption of OP compounds from the gastrointestinal tract is rapid and occurs within minutes of ingestion; secondly, the ingested dose of OPs in fatal cases might be too large for the amount of treatment given; thirdly, the anticholinesterase effects of these poisons are poorly reversible to standard treatments. Current treatments in severe OP poisoning is only partially effective with case fatality of over 10% even in the best medical facilities (17,18).

Several studies supported the use of intralipid as an antidote for local anesthetic drugs toxicity (4,11,13,19). While the exact mechanism of antidotal actions of ILE is not clearly identified, the "lipid sink" theory may give a potential explanation (15,20,21). The theory explains that infusion of a large amount of lipids to the blood can move the lipophilic substances away from the affected tissues and dissolve them in the plasma resulting in alleviation of the toxic effects (5,13).

Deliberate self-poisoning with OPs usually results in plenty of ingestion and consequently severe poisoning. OP compounds that are absorbed from the bowel might be drawn into this lipid sink (15). Another possible advantage of administration of large quantity of lipids is that they can provide energy substrates for the patients who are intubated and unconscious to receive calories by mouth (15). At present, the benefit of ILE is difficult to be assessed, but on the basis of limited animal and human data, this may range from minimal to life-preserving (22,23). While awaiting for human data on antidotal use of ILE for OP toxicity, the best approach would be to assess the effectiveness of this treatment in animal subjects with comparable size to humans. Lastly, we endorse the suggestion of Picard and Harrop-Griffiths that unless convincing evidence of effectiveness of ILE for poisoning with other toxic agents rather than local anesthetic drugs are provided, ILE should only be given by the judgment of treating physician when the patient is constantly deteriorating and his/her life is in danger despite receiving maximal available standard treatments (23). Moreover, large trials are required to validate the effectiveness of ILE and to find out the best dosing regimen of this treatment for OP poisoning.

CONCLUSION

ILE therapy is an accepted antidotal treatment for lipophilic drugs toxicity. This was the first human case report which showed that ILE may be effective in reversal of systemic toxicity caused by OP poisoning.

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