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CASE REPORT

Toxicology

Accidental organophosphate poisoning: A case series of 2 pediatric coumaphos exposures

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Abstract

Introduction: Pediatric organophosphate insecticide poisonings are rare in the United States, and life-threatening toxicity is rarely seen. We report 2 accidental ingestions of the organophosphate insecticide coumaphos that resulted in life-threatening symptoms.

Case Reports: A 7-year-old boy and 10-year-old girl both presented from home after accidental ingestion of 1 "spoonful" of coumaphos 20% liquid (Asuntol; Bayer de Mexico, S.A. de C.V., Mexico D.F., Mexico). There were no other known ingestions. Both became rapidly symptomatic, with the boy developing dyspnea, vomiting, and depressed mental status and the girl developing headache and nausea. Soon afterward, the boy had witnessed cardiopulmonary arrest and the girl developed altered mental status and flaccid paralysis. Both were treated initially with atropine, but required no additional doses. On arrival to the pediatric intensive care unit (ICU), both patients received pralidoxime with subsequent plasma exchange and continuous venovenous hemodiafiltration (CVVHDF). Transient anemia, coagulopathy, transaminitis, and hyperglycemia developed in both patients. The girl was extubated on hospital day 6 and the boy on hospital day 11. The girl's course was complicated by aspiration pneumonia and an isolated seizure. The boy's course was complicated mainly by anoxic brain injury, associated seizures, neuroagitation, spasticity, and autonomic instability. The girl was discharged on hospital day 16 and remains asymptomatic 32 days after ingestion. As of 90 days after ingestion, the boy remains admitted to inpatient rehabilitation.

Discussion: The clinical benefit of pralidoxime, plasma exchange, and CVVHDF is uncertain in these cases. The optimal treatment regimen for organophosphate insecticide toxicity remains poorly defined.

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KEYWORDS
accidental ingestion, cholinergic, critical care, insecticide, organophosphate, pediatrics, poisoning, toxicology

1 | INTRODUCTION

Pediatric organophosphate insecticide poisonings are rare in the United States, with only 550 exposures in patients aged younger than 12 years reported to poison centers in 2020. Life-threatening toxicity is rarely seen. In 2020, only 15 cases of all ages were classified by US poison centers as having life-threatening effects, and no mortality was reported.[1]

Coumaphos, or 3-chloro-7-hydroxy-4-methyl-coumarin O,O-diethyl phosphorothioate, is a diethyl organothiophosphate insecticide that, similar to other organophosphates, produces acute cholinergic toxicity.[2–4] To our knowledge, acute coumaphos toxicity has not been reported in children previously or in adults for >40 years.[4]

We report 2 accidental pediatric ingestions of the organophosphate insecticide coumaphos that resulted in life-threatening symptoms. The patients' mothers provided case report consent.

2 | CASES

2.1 | Case 1

A 7-year-old 30.4 kg (body mass index [BMI], 19.46 kg/m^2) boy with no past medical history presented from home after accidental ingestion of 1 "spoonful" of coumaphos 20% liquid (Asuntol; Bayer de Mexico, S.A. de C.V., Mexico D.F., Mexico; Figure 1) after the product was confused with over-the-counter cough syrup. The family noted that the coumaphos was used to kill cockroaches and was brought to the United States from Mexico when the family moved. There were no other known ingestions.

The patient immediately developed vomiting and dyspnea. At ≈30 minutes after ingestion, paramedics found him unresponsive with tachypnea, miosis, salivation, lacrimation, and urinary incontinence. Vital signs were the following: blood pressure (BP), 125/83 mmHg; heart rate (HR), 68 beats per minute (BPM); respiratory rate (RR), 32 respirations per minute (RPM); and oxygen saturation (SpO_2), 87% on room air. He then developed bradycardia, bradypnea, and hypoxia during transport followed by cardiopulmonary arrest on arrival at the emergency department (ED). Spontaneous circulation returned after intubation and 15 minutes of cardiopulmonary resuscitation that included administration of 3-mg intravenous atropine.

He was transferred to the pediatric ICU (PICU); en route, he had myoclonic jerking, which improved after treatment with a total of 4-mg intravenous midazolam. An epinephrine infusion was started for hypotension and continued until hospital day (HD) 3.

On PICU arrival, he was decontaminated using a solution of soap, water, and dilute bleach. He was noted to have intermittent myoclonic jerking and shivering, flaccid limbs, and hyperreflexia with clonus in the bilateral lower extremities.

Several abnormal laboratory trends were noted (Table 1). He developed anemia, requiring 2 units of packed red blood cells (RBCs). An early coagulopathy was also developed and resolved by HD 3. He had delayed lipase elevation and mild transaminitis. Finally, he had persistent, mild hyperglycemia until HD 47; an insulin level measured on arrival was 10 μU/mL (laboratory reference range <17 μU/mL).

The initial plasma cholinesterase (PC) and RBC cholinesterase (RBCc) measurements were 0.1 U/mL (ARUP Laboratories reference range 2.9–7.1 U/mL) and 1.4 U/mL (ARUP Laboratories reference range 7.9–17.1 U/mL), respectively. The trend of subsequent PC concentrations is detailed in Figure 2. Urine organophosphate metabolite concentrations were elevated (Table 2).

Pralidoxime 50-mg/kg bolus was given followed by an infusion of 10 mg/kg per hour from HDs 1 to 9. No additional atropine was required. Continuous electroencephalogram (EEG) showed frequent epileptiform discharges. Propofol, midazolam, and pentobarbital infusions were required to achieve adequate burst suppression and

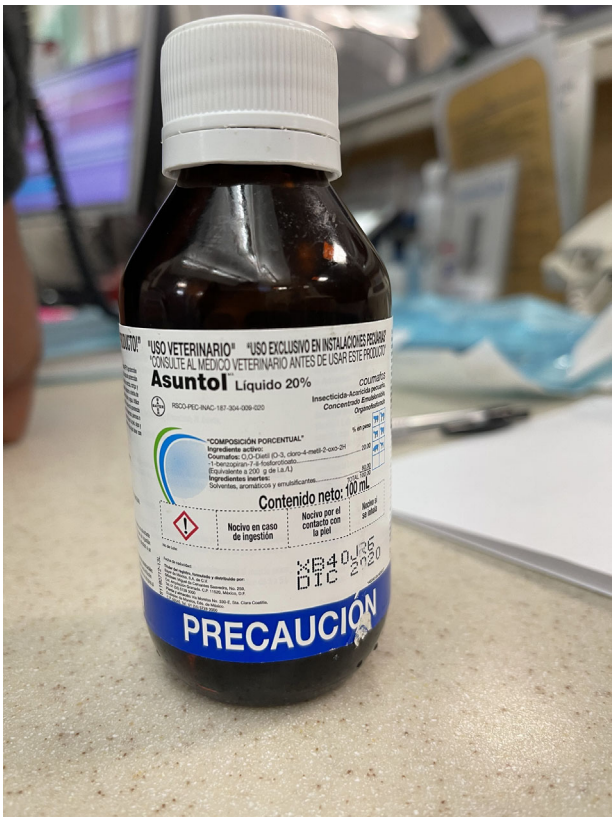

FIGURE 1 Coumaphos bottle brought to the emergency department by family

TABLE 1 Notable laboratory abnormalities

Case	Initial (HD 1)	Peak/nadir	HD of normalization/ return to baseline
1			
Hemoglobin, g/dL (reference range: 11.5–14.5 g/dL)	12.2	7.7 (HD 5)	26
Glucose, mg/dL (reference range: 70–106 mg/dL)	263	Same	47
Lipase, U/L (reference range: 23–300 U/L)	131	2464 (HD 12)	26
AST, U/L (reference range: 15–40 U/L)	76	124 (HD 14)	26
ALT, U/L (reference range: 5–45 U/L)	34	134 (HD 14)	26
INR (reference range: 0.86–1.14)	1.15	2.13 (HD 1)	3
Fibrinogen, mg/dL (reference range: 138–452 mg/dL)	307	123 (HD 1)	2
2			
Hemoglobin, g/dL (reference range: 12.5–15.0 g/dL)	11.9	9.3 (HD 9)	12
Glucose, mg/dL (reference range: 70–106 mg/dL)	139	187 (HD 5)	11
AST, U/L (reference range: 15–40 U/L)	21[a]		
ALT, U/L (reference range: 5–45 U/L)	12	112 (HD 8)	[b]
INR (reference range: 0.86–1.14)	1.34	1.89 (HD 2)	3

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HD, hospital day; INR, international normalized ratio.
[a]Value not rechecked.
[b]Value downtrending but not trended to normalization.

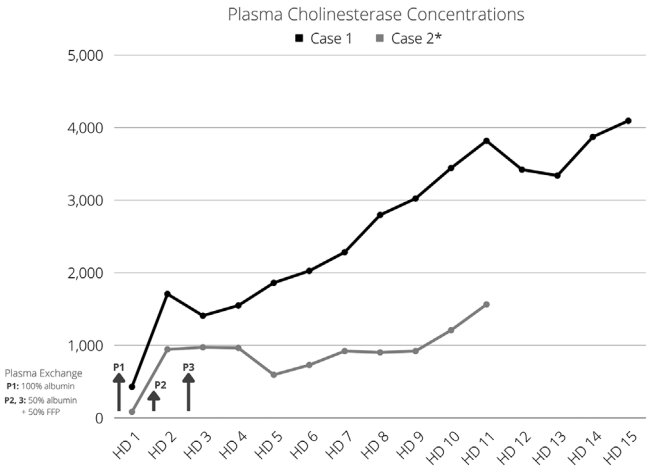

FIGURE 2 Plasma cholinesterase concentration trend (performed by Quest Diagnostics) for cases 1 and 2 relative to the timing of the plasma exchanges (P1: first plasma exchange, P2: second plasma exchange, P3: third plasma exchange). *Not trended to normalization. FFP, fresh frozen plasma; HD, hospital day

were continued until HDs 2, 3, and 7, respectively. A total of 3 plasma exchanges were performed on HDs 1 to 3: first with albumin alone and then twice with half albumin and half fresh frozen plasma. Continuous venovenous hemodiafiltration (CVVHDF) was performed on HD 1 and discontinued on HD 6. He was extubated on HD 11.

The clinical course was complicated by aspiration pneumonia and anoxic brain injury, from which he developed neuroagitation, spasticity, and autonomic dysfunction. This required transfer to inpatient rehabilitation services on HD 15, where he remains as of 90 days after ingestion.

2.2 | Case 2

A 10-year-old 66 kg (BMI, 25.78 kg/m^2) girl with a history of obesity ingested the same volume of coumaphos at approximately the same time, immediately developing headache, nausea, and anxiety. Vital signs on emergency medical services arrival 60 minutes after ingestion were BP, 147/69 mmHg; HR, 143 BPM; RR, 24 RPM; and SpO_2, 96% on room air. She was reported to be diaphoretic with normal mental status at that time.

TABLE 2 Urine organophosphate metabolites

	Urine metabolite	Amount detected	Reporting limit
Case 1	Diethylphosphate, ng/mL	970	25
	Diethylthiophosphate, ng/mL	340	10
	Total dialkyl phosphates (creatinine corrected)	75,000 nmol/g creatinine	Normal range: <680 nmol/g creatinine
Case 2	Diethylphosphate, ng/mL	3900	250
	Diethylthiophosphate, ng/mL	1400	100
	Total dialkyl phosphates (creatinine corrected)	77,600 nmol/g creatinine	Normal range: <680 nmol/g creatinine

Note: Analysis performed by NMS Laboratories.

During her ED course, she developed miosis, worsening tachypnea with coarse breath sounds and hypoxia, as well as progressive altered mental status and generalized weakness. Despite supplemental oxygen by high-flow nasal cannula and a total of 4.5-mg intravenous atropine, she required intubation for airway protection. She was decontaminated in the ED before transfer to the PICU.

En route to the PICU, she was empirically given a total of 2-mg intravenous midazolam. An epinephrine infusion was started for hypotension and continued until HD 6. Other than miosis, she had no significant examination findings on arrival.

She was treated with the same modalities as case 1. Pralidoxime 2000 mg was bolused and then infused on HDs 1 to 8 at 500 mg per hour, which are the maximum recommended doses. A total of 3 plasma exchanges were performed on HDs 1 to 3, and CVVHDF was performed on HDs 1 to 5. No additional atropine was required. Continuous EEG revealed no significant abnormalities.

During her hospital course, she developed anemia, coagulopathy, transaminitis, and hyperglycemia, although milder than case 1 (Table 1). Her initial insulin level was 155 μU/mL, and serial lipase measurements remained within normal limits. Although her international normalized ratio was elevated, her fibrinogen remained within normal limits. The initial PC and RBCc concentrations were 0.1 U/mL (ARUP Laboratories reference range 2.9–7.1 U/mL) and 6.2 U/mL (ARUP Laboratories reference range 7.9–17.1 U/mL), respectively. The trend of subsequent PC concentrations is detailed in Figure 2. Urine organophosphate metabolite concentrations were elevated (Table 2).

She was extubated by HD 6, after which she required short-term use of continuous positive-pressure ventilation. Her course was complicated by aspiration pneumonia and a seizure on HD 7. She was transferred to the inpatient rehabilitation service on HD 12 and discharged on HD 16 without significant sequelae. The patient's mother reports she remains asymptomatic 32 days postingestion.

3 | DISCUSSION

Coumaphos is classified by the World Health Organization as highly hazardous (class Ib) by inhalation, oral, or dermal routes. There is no established median lethal dose (LD_{50}) in humans; animal studies have shown a wide range depending on the tested organism.[3,4] Toxicity is mediated by in vivo conversion into its active form, coumaphos-oxon.[5]

Organophosphate insecticide exposure was confirmed in both patients with the measurements of cholinesterase levels and urine metabolites. Both patients had similar initial inhibition of PC (0.1 U/mL) and total urine metabolites. However, they had markedly different initial RBCc measurements (1.4 vs 6.2 U/mL), and the boy's PC concentration rose higher and faster than the girl's (Figure 2). As the severity of RBCc inhibition is considered a better correlate to central nervous system cholinesterase inhibition than PC inhibition, this may help explain the boy's more severe initial presentation.[6]

It is unclear why both had the noted laboratory abnormalities. A previously published coumaphos case also had signs of pancreatitis and hyperglycemia.[2] Although it was initially hypothesized this was toxin-induced pancreatitis causing hypoinsulinemia, the conflicting insulin levels do not support this explanation. There are reports of organophosphate-associated hemolysis and coagulopathy, although the mechanisms are not well understood.[7,8] It is possible that the leaving group chlorferon or other intermediates/metabolites may be responsible in some way for these abnormalities, but unfortunately their effects are poorly characterized.

Both patients were treated with pralidoxime, CVVHDF, and plasma exchange. The infusion duration, dosing, and overall efficacy of pralidoxime are controversial.[9,10] In these cases, pralidoxime was continued for 8 days and 9 days for the girl and boy, respectively, at the recommended dosing.[9] Based on prior reports, we expected prolonged mechanical ventilation and continued pralidoxime until extubation.[2]

Organophosphates are considered poor hemodialysis candidates; however, limited evidence suggests that continuous hemodialysis may be helpful.[11] In addition, plasma exchange with fresh frozen plasma has been shown to increase PC levels with unclear clinical benefits.[12] Hemoperfusion was not available at our institution.

We cannot explain why both required only a small total atropine dose initially without need for additional doses. It is possible that pralidoxime limited the necessity for atropine, but pralidoxime was not initiated for either patient until PICU arrival multiple hours after the last atropine dose. Furthermore, pralidoxime alone is generally considered insufficient for the treatment of acute organophosphate toxicity.[10] The aforementioned previously published case required multiple doses of atropine during an 8-day period, so this does not appear to be related to an idiosyncratic effect of coumaphos.[2]

In summary, we report 2 patients with life-threatening coumaphos poisoning, both of whom survived, 1 neurologically intact. Both

presented initially with the typical signs and symptoms of organophosphate poisoning and were treated with atropine and mechanical ventilation followed by pralidoxime, plasma exchange, and CVVHDF. As noted previously, these cases highlight several unknowns that merit further evaluation. Primary among these, the optimal treatment regimen for organophosphate insecticide toxicity remains poorly defined. Further investigation as to the efficacy of pralidoxime, CVVHDF, and plasma exchange for the treatment of organophosphate insecticide poisoning is warranted.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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