Cholinergic Crisis after Rodenticide Poisoning

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Rodenticides have historically been common agents in attempted suicides. As most rodenticides in the United States (U.S.) are superwarfarins, these ingestions are generally managed conservatively with close monitoring for coagulopathy, and if necessary, correction of any resulting coagulopathy. However, alternate forms of rodenticides are imported illegally into the U.S. and may be ingested either accidentally or in suicide attempts. We present an unusual case of poisoning by the illegally imported rodenticide, "Tres Pasitos." The main ingredient of this rat poison is aldicarb, a potent carbamate pesticide that causes fulminant cholinergic crisis. This case is relevant and timely because carbamates and organophosphates are still used as insecticides and emergency physicians (EP) working in rural areas may have to evaluate and manage patients with these poisonings. As international travel and immigration have increased, so has the possibility of encountering patients who have ingested toxic substances from other countries. In addition, there has been increased concern about the possibility of acts of terrorism using chemical substances that cause cholinergic toxidromes.[1,2] EPs must be able to recognize and manage these poisonings. This report describes the mechanism of action, clinical manifestations, laboratory evaluation and management of this type of poisoning. The pertinent medical literature on poisoning with aldicarb and similar substances is reviewed. [West J Emerg Med. 2010; 11(5): 524-527.]

CASE REPORT

A 29-year-old male presented to the emergency department (ED) after a suicide attempt by ingesting a large amount of rat poison, which according to emergency medical services (EMS) occurred just prior to arrival. Although EMS had been told that the patient had ingested a rat poison, the exact type of rodenticide was unknown.

Upon arrival to the ED, the patient was diaphoretic and in moderate respiratory distress. His vital signs were as follows: temperature 36.0 ^{0}C, blood pressure 113/99 mm Hg, heart rate 100 beats/minute, respiration rate 28 breaths/minute and oxygen saturation 88% on room air.

On arrival he was awake but appeared to be confused and was not answering questions. Excessive secretions were noted. His neck was supple. He had respiratory distress with harsh breath sounds and rhonchi throughout both lung fields. He was tachycardic but had a regular rhythm. The abdomen was soft and non-tender with increased bowel sounds. The patient had urinated on himself. He was moving all extremities but had

some muscle fasciculations. His skin was diaphoretic, but no rash or track marks were evident. He was confused, uncooperative and not speaking. The pupils were 2 mm and non-reactive to light. Cranial nerves otherwise appeared to be intact. It was difficult to assess his motor, sensory and cerebellar function because he was very uncooperative. Initially he was moving all his extremities.

An initial bedside serum glucose analysis was 186 mg/dL. Other laboratory values were as follows: serum sodium 138 mmol/L, potassium 2.9 mmol/L, chloride 101 mmol/L, bicarbonate 17 mmol/L, glucose 247 mg/dL, blood urea nitrogen 16 mg/dL, and creatinine 1.0 mg/dL. Complete blood count showed a white blood count of $12.8 \times 10^3/\mu L$ with 58% neutrophils and 33% lymphocytes, hemoglobin level of 17.2 g/dL and platelet count of $311,000 \times 10^3/\mu L$. Creatine kinase (CK) was 191 U/L (40-210) and CK-MB was 1.96 ng/ml (0.0-4.99) with a CK-MB index of 1% (0.0-2.49). Troponin I level was < 0.20 µg/L (0-2). His liver function tests showed that bilirubin, AST, ALT, and lipase were all within the normal

range. Urine analysis was normal and the urine toxicology screen was negative. The coagulation profile was normal. His electrocardiogram showed sinus tachycardia without ischemic changes or QRS or QT prolongation. A plasma cholinesterase level was drawn and sent to the laboratory.

Fifteen minutes after being initially assessed, his condition rapidly deteriorated. He developed excessive salivation with large amounts of foamy white secretions, which continually spewed from his mouth, making it very difficult to keep his airway clear, even with mechanical suctioning. His oxygen saturation dropped into the low 80s, despite receiving high flow oxygen, and he was subsequently intubated. He was given 2 mg lorazepam intravenously (IV) prior to intubation to sedate him, and he was given another 2 mg of it after he was intubated.

Based on the history and physical examination findings, which were consistent with an overdose of a cholinergic agent – probably an organophosphate or carbamate – the patient was given 2 mg of atropine IV, without any effect. He was then given another 2 mg IV every five minutes until his secretions were dry. He received a total of 16 mg of atropine IV in the ED. He was also given 1 gram of pralidoxime as an IV infusion over 30 minutes. He was hydrated with intravenous normal saline and his hypokalemia was corrected with potassium chloride.

When the staff realized that he had possibly taken an organophosphate, they double gloved and donned gowns and masks. All of the patient's clothes were removed and discarded in plastic bags. He was washed with soap and water. After he was intubated, a nasogastric tube was inserted. He was lavaged and 50 grams of activated charcoal was administered down the nasogastric tube. None of the EMS or ED personnel developed any signs or symptoms of cholinergic poisoning.

After intubation and treatment with atropine, pralidoxime and lorazepam, the patient's respiratory status showed marked improvement. His oxygen saturation was 100%. He was admitted to the intensive care unit, where he did not require any further treatment with atropine or pralidoxime. He was weaned off the ventilator and extubated without difficulty on hospital day 4. He remained stable and was transferred to the medical floor where psychiatry was consulted. The patient was then admitted for attempting to suicide by ingesting a rat poison called "Tres Pasitos." Its active ingredient is aldicarb, a very potent carbamate. His initial serum cholinesterase level was 103 units/ml (normal range 350-934), confirming the clinical diagnosis. This level was not repeated, because his clinical status greatly improved.

Eventually, he was cleared by psychiatry and discharged home with appointments for close follow up in the medical and psychiatry clinics. When the patient was seen in the medical clinic one week after discharge, he had no complaints, and no evidence of residual toxicity was found on examination. No further testing was performed.

DISCUSSION

Rodenticides come in many forms with a "superwarfarin" being a common type of rodenticide used in the U.S. In 2008, 3.8% of the reports of poisonings were related to pesticides.[3] Other types of rodenticides are phosphides, phosphorus, strychnine, thallium, sodium fluoroacetate and cholinesterase inhibitors. Because cholinesterase inhibitors are no longer registered for rodenticidal use in the U.S., cholinergic symptoms and signs are uncommon in patients who report ingesting a rodencticide. Although illegal in the U.S., "Tres Pasitos" is bought and sold legally in certain Latin American countries and often imported unlawfully for sale in this country. The name "Tres Pasitos" (Spanish for "three little steps") signifies the rapid lethal effects to mice, i.e. they can only take three little steps before dropping dead. Fatal intoxication with aldicarb, the active ingredient in "Tres Pasitos," has been reported.[4] Poisonings in the U.S. from "Tres Pasitos" has occurred between 1994-1997, when the New York City Poison Control Center was consulted regarding 25 patients who developed cholinergic toxicity after ingesting "Tres Pasitos."[5] Aldicarb is also used as a potent insecticide, and poisonings from exposure to this substance in agricultural areas and toxicity from the ingestion of aldicarb contaminated food have also been reported.[6]

With increases in immigration to the U.S. and international travel, it is reasonable to assume that there may be an increase in toxic substances brought to this country from other nations. Just as we should get a travel history in patients who present with fever or diarrhea, we should also consider the possibility of poisoning by an imported toxin when evaluating a patient with an unusual toxidrome.

Concern now exists for the possibility of terrorist attacks using chemical agents. In fact, two incidents of attacks using the cholinesterase inhibitor nerve agent, sarin, have occurred in the recent past.[7,8] The actions, clinical manifestations and management of poisoning by these agents are very similar to those of pesticides, such as organophosphates and carbamates like aldicarb. Therefore, it is very important that EPs be able to quickly recognize and manage cholinergic toxicity.

Aldicarb [2-methyl-2-(methylthio)-propionaldehyde O-(methylcarbamoyl) oxime], is a very potent carbamate.[9] Aldicarb is rapidly absorbed via the gastrointestinal tract.[10] It binds to and inhibits human cholinesterase, which normally breaks down acetylcholine, resulting in an excess of aceylcholine and enhancement of its physiological effects at muscarinic, nicotinic and central nervous system (CNS) receptors causing a cholinergic crisis.[11] It inhibits both red blood cell (RBC) cholinesterase and plasma pseudocholinestrase. Aldicarb has an LD_{50} (median lethal dose) in humans of 0.8 mg/kg. It is a toxic cholinergic agent that has caused many fatalities.[12] It is especially toxic to the nervous system and is excreted completely in the urine within 24 hours.

Clinical findings of toxicity reflect effects of excessive cholinergic stimulation at muscarinic, nicotinic and CNS receptors.[13] Excessive stimulation of muscarinic receptors produces the "SLUDGE" toxidrome: salivation, lacrimation, urination, diarrhea, gastric secretions and emesis. It also produces miosis, and the "triple Bs": bradycardia, bronchospasm and bronchorrhea. Bronchospasm and bronchorrea are especially dangerous, and patients can literally drown in their own secretions. In a case series of patients in Rio de Janeiro, who were poisoned by carbamates that were illegally used as rodenticides, all victims were noted to have at least two symptoms and/or signs of muscarinic toxicity described by the SLUDGE mnemonic.[14]

Aldicarb can also cause hyperactivity at nicotinic sites, especially at the skeletal muscle junctions, causing muscle fasciculations, weakness and paralysis that may lead to significant morbidity and mortality. Hyper-stimulation at the nicotinic receptors of the autonomic ganglia may cause tachycardia, mydriasis and hypertension, instead of bradycardia, miosis and hypotension that are seen when muscarinic stimulation at these sites predominates. Tachycardia may also be due to hypoxia. This is important to consider when both evaluating and treating these patients. When treating these patients with atropine, it is important to remember that the end point for atropinization is when secretions have been dried, not the presence of tachycardia or dilated pupils.[15]

CNS toxicity often occurs with aldicarb and may be manifested as delirium, lethargy, coma or, less commonly, seizures. In one study that reviewed anti-cholinesterase poisonings, including aldicarb, the most common muscarinic symptom was diarrhea, the most common nicotinic symptom was muscle fasciculation and almost half of the patients had CNS depression with a Glasgow Coma Scale of less than eight.[16] Therefore, the authors like to use a modified DUMBELS mnemonic (diarrhea, urination, miosis, muscle fasciculations, muscle weakness, mental status changes, bradycardia, bronchorrhea, bronchospasm, emesis, lacrimation and seizures) when evaluating patients for possible toxicity from aldicarb, other carbamates or organophosphates, as it describes the muscarinic, nicotinic and CNS effects of these toxins.

The diagnosis of poisoning with an anti-cholinesterase agent, such as aldicarb, in the ED must be made clinically based on the history and/or recognition of this toxidrome. Laboratory measurement of cholinesterase activity can help to eventually confirm the diagnosis. This can also be useful in following the course of this illness and for public health and epidemiologic purposes. Two types of cholinesterases, plasma (or pseudo-cholinesterase) and RBC cholinesterase, can be measured and both of their levels are decreased by anti-cholinesterase toxins. However, although plasma cholinesterase is more easily performed by most laboratories, RBC cholinesterase is more accurate and correlates better with the severity of poisoning.[17]

Because severe anti-cholinesterase poisoning has significant morbidity and mortality, emergency management should not be delayed once the diagnosis is suspected. The most important aspect of the treatment of aldicarb poisoning is to support the airway, breathing and circulation (ABC) of the patient. Special attention must be given to the airway and breathing, as these patients may become very hypoxic from excessive secretions, bronchorrhea, bronchospasm, weakness of respiratory muscles and CNS depression. In severe cases, the patient may require intubation. In these cases the patient should be paralyzed with non-depolarizing agents, such as vecuronium, if needed, rather than succinylcholine, which is metabolized by plasma cholinesterase and may cause prolonged paralysis.[18]

After stabilization of ABCs, specific therapy involves blockade of acetylcholine effects at both muscarinic and nicotinic receptors. Atropine provides inhibition at muscarinic receptors in both the CNS and the periphery. Very large doses are often needed. Therapy is begun with a dose of 2 mg in adults and 0.02 mg/kg (minimum dose of 0.1 mg) in children. This can then be repeated every three to five minutes until drying of pulmonary secretions has occurred. An alternative way of giving atropine in very severe cases is to start with 2 to 5 mg IV in adults and 0.05 mg/kg in children and to double the dose every five minutes until secretions are dried up. As noted above, very large doses of atropine may be required, and the EP should not be afraid to use enough atropine to dry secretions. Atropine is not effective for reversing nicotinic effects. Patients can still develop respiratory failure from muscle paralysis, and these patients must be closely monitored and mechanically ventilated as needed.

The use of pralidoxime (2-PAM) in the treatment of poisoning by carbamates, including aldicarb, is somewhat controversial since, unlike organophosphates, the cholinesterase poisoned by a carbamate reactivates within a day. Therefore, pralidoxime, which markedly increases the regeneration of acetylcholinesterase and reverses both nicotinic and muscarinic toxicity, may not be needed, especially in mild to moderate poisonings. However, recent reports show that pralidoxime improves morbidity and mortality with severe poisonings from most carbamates.[9,19] It makes the patient easier to manage by decreasing the atropine requirement and by treating nicotinic toxicity. Pralidoxime therapy should therefore not be withheld in a patient with significant cholinergic toxicity, because it is thought that the poisoning may be caused by a carbamate. Benzodiazepines, such as diazepam or lorazepam, can be used to control seizures and CNS agitation.

It is also important to decontaminate patients who have aldicarb on their skin or clothing because it is rapidly absorbed through the skin. They should be totally exposed and

vigorously washed with soap and water. Anyone handling these patients or their clothing should be appropriately gowned and gloved. In the case of patients who have ingested the poison, like ours, and emesis has not occurred yet, gastric lavage with airway protection needs to be performed. Activated charcoal should also be administered through the nasogastric tube.

Although, if untreated or treated incorrectly, patients with poisoning from aldicarb can easily die, most patients do well if they are diagnosed rapidly and managed appropriately. The intermediate syndrome, muscle weakness and other neurological signs occurring after 24 hours, is rarely seen with aldicarb poisoning.[20]

Our major limitation was that we were unable to obtain confirmatory laboratory or forensic evidence that the patient ingested aldicarb. We were not able to actually get samples of the "Tres Pasitos" that he took, nor did we measure aldicarb levels or levels of its metabolites. However, based on the history, his cholinergic toxidrome, his response to the appropriate therapy and very low serum cholinesterase level, it is conclusive that he took this poison. It must be emphasized that when possible, it is very helpful to get the "bottles" when evaluating a patient with a possible poisoning or overdose.

CONCLUSION

We presented the case of a patient who ingested a rat poison, "Tres Pasitos," which was illegally imported into the U.S. This substance, which contains aldicarb, caused a life-threatening cholinergic crisis. Due to increased immigration and international travel, it should be expected that similar cases will continue to be seen in our EDs. Because our patient's cholinergic toxidrome was quickly recognized and correctly managed, he did very well.

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REFERENCES:

1. Lester J, Christos S, Kordick MF, et al. Terrorism: can emergency medicine physicians identify terrorism syndromes? *Am J Emerg Med*. 2007 Nov;25(9):1019-24.

2. Lawrence DT, Kirk MA. Chemical terrorism attacks: update on antidotes. *Emerg Med Clin North Am.* 2007 May;25(2):567-95.

3. Bronstein AC, Spyker DA, Cantilena LR Jr, et al. 2008 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): *26th Annual Report. Clin Toxi*col (Phila). 2009 Dec;47(10):911-1084

4. Proenca P, Teixeira H, de Mendonca MC, et al. Aldicarb poisoning: one case report. *Forensic Sci Int*. 2004 ;146 Suppl:S79-81.

5. Centers for Disease Control and Prevention (CDC). Poisonings associated with illegal use of aldicarb as a rodenticide - New York City, 1994-1997. *MMWR Morb Mortal Wkly Rep* 1997;46:961-3.

6. Mendes CA, Mendes GE, Cipullo JP, et al. Acute intoxication due to ingestion of vegetables contaminated with aldicarb. *Clin Toxicol* (Phila). 2005;43:117-8.

7. Okudera H, Morita H, Iwashita T, et al. Unexpected nerve gas exposure in the city of Matsumoto: report of rescue activity in the first sarin gas terrorism. *Am J Emerg Med*. 1997 Sep;15(5):527-8.

8. Reutter S. Hazards of chemical weapons during war: new perspectives. *Environ Health Perspect* 1999; 107: 985-90

9. Nelson LS, Perrone J, DeRoos F, et al. Aldicarb poisoning by an illicit rodenticide imported into the United States: Tres Pasitos. *J Toxicol Clin Toxicol*. 2001;39:447-52.

10. Covaci A, Manirakiza P, Coucke V, et al. A case of aldicarb poisoning: a possible murder attempt. *J Anal Toxicol*. 1999;23:290-3.

11. Risher JF, Mink FL, Stara JF. The toxicologic effects of the carbamate insecticide aldicarb in mammals: a review. *Environ Health Perspect*. 1987;72:267-81.

12. Burgess JL, Bernstein JN, Hurlbut K. Aldicarb poisoning. A case report with prolonged cholinesterase inhibition and improvement after pralidoxime therapy. *Arch Intern Med*. 1994 ;154:221-4.

13. Clark, R. Insecticides: Organic Phosphorus Compounds and Carbamates. In: Goldfrank's Toxicologic Emergencies, 7th Edition; Goldfrank, L.R., Flomenbaum, N.E., Lewin, N.A., Howland, M.A., Hoffman, R.S., Nelson, N.S., Eds.; McGraw Hill Companies, Inc: 2002.

14. Lima JS, Reis CA. Poisoning due to illegal use of carbamates as a rodenticide in Rio de Janeiro. *J Toxicol Clin Toxicol*. 1995;33:687-90.

15. Eddleston, M, Roberts, D, Buckley, N. Management of severe organophosphorus pesticide poisoning. *Crit Care 2002*; 6:259.

16. Ragoucy-Sengler C, Tracqui A, Chavonnet A, et al. Aldicarb poisoning. *Hum Exp Toxicol*. 2000 ;19:657-62.

17. Eckert S, Eyer P, Herkert N, et al. Comparison of the oxime-induced reactivation of erythrocyte and muscle acetylcholinesterase following inhibition by sarin or paraoxon, using a perfusion model for the real-time determination of membrane-bound acetylcholinesterase activity. *Biochem Pharmacol*. 2008 Feb 1;75(3):698-703.

18. Nelson TC, Burritt MF: Pesticide poisoning, succinylcholine induced apnea and pseudocholinesterase. *Mayo Clin Proc* 1986;61:750-5.

19. Hoffman RS, Manini AF, Russell-Haders AL, et al. Use of pralidoxime without atropine in rivastigmine (carbamate) toxicity. *Hum Exp Toxicol*. 2009 Sep;28(9):599-602.

20. Paul N, Mannathukkaran TJ. Intermediate syndrome following carbamate poisoning. *Clin Toxicol* (Phila). 2005;43(7):867-8.