Tres Pasitos: "Three Little Steps" to Aldicarb Poisoning

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Cholinergic crisis is suspected in a girl who presents with the clinical findings known as SLUDGE. Her illness began after she consumed a beverage the night before. This report reviews the agents that can cause cholinergic crisis, the appropriate antidotes, and priorities in management. Safety precautions for health care personnel are also discussed.

Case

A 13-year-old girl with an unremarkable medical history presents to the emergency department via ambulance with continuous vomiting and diarrhea. The patient recalls feeling ill after drinking a beverage with her mother the night prior to presentation. Shortly after, she developed uncontrollable vomiting and diarrhea and then passed out. The paramedics report that the girl's aunt heard her calling for help early the next morning and found her covered in her own emesis, feces, and urine.

In the emergency department, her vital signs are as follows: blood pressure, 120/77 mm Hg; heart rate, 71 beats/min; respiratory rate, 24 breaths/min; and temperature, 97.3°F. Her oxygen saturation is 100% on high-flow oxygen. On physical examination, the patient appears very ill and continues to gag. She is responsive to noxious stimuli, and her pupils are 2 mm and sluggishly reactive to light. She is diaphoretic and covered in her own excrements. The cardiac exam is unremarkable and her lungs are clear. Her abdomen is soft, nondistended, and nontender with normal bowel sounds. Her cranial nerves are intact and her muscle tone and strength are normal.

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What is the toxicologic differential diagnosis for altered mental status with profound gastrointestinal hyperactivity?

The clinical signs and symptoms that this girl displays can be summarized as SLUDGE: salivation, lacrimation, urination, diarrhea, gastrointestinal upset, and emesis. Additional findings of this "syndrome" include the more life-threatening bradycardia, bronchorrhea, and bronchospasm, often deemed the "killer B's." These clinical findings result from an excess of acetylcholine at postganglionic muscarinic receptors within the parasympathetic nervous system. Stimulation of nicotinic receptors at the autonomic ganglia and at the neuromuscular junction can cause mydriasis, tachycardia, hypertension (signs of sympathetic overactivity), and fasciculations, muscle weakness, or paralysis, respectively. In reality, the clinical effects of excess acetylcholine can be variable because acetylcholine receptors are found in both the parasympathetic and sympathetic nervous system. The SLUDGE syndrome of muscarinic toxicity is a reflection of parasympathetic pathway activation, whereas nicotinic receptor activation causes sympathetic effects. Though the parasympathetic pathway is usually emphasized in classical "cholinergic" teaching, excessive sympathetic activity often predominates.

Some mushrooms, such as the ivory funnel (*Clitocybe dealbata*), and some *Inocybe* species contain muscarine and can cause a SLUDGE syndrome. Muscarine is a quaternary ammonium parasympathomimetic that does not readily cross the blood-brain barrier.

Infectious food "poisoning" can cause severe gastrointestinal effects and is responsible for a significant number of hospitalizations and deaths in the United States. Certain bacterial food poisonings are due to liberated toxins. Examples include *Staphylococcus* species, *Bacillus cereus*, *Escherichia coli*, *Salmonella* species, *Vibrio cholera*, *Shigella* species, *Yersinia* species, and *Campylobacter jejuni*. Some echinoderms, such as the starfish, can cause vomiting due to asteriotoxin.

FAST TRACK

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Other foodborne toxins can cause gastrointestinal illness but also cause neurologic symptoms ranging from allodynia to life-threatening issues such as paralysis. Ciguatoxin, found in dinoflagellate-consuming reef fish, classically causes vomiting and diarrhea and an unpredictable course of neurologic illness. (See "Case Studies in Toxicology: A Toxic Fish Dinner" in the October 2011 issue of *Emergency Medicine* [pp 20-22].) Patients often report lasting paresthesias. Conversely, more serious food poisoning can occur after consumption of the Japanese puffer fish (fugu). Specific organs harbor tetrodotoxin, and if the fish is prepared improperly, consumption can cause death due to paralysis.

Plants can also cause gastrointestinal symptoms following consumption and may occasionally be associated with systemic findings. Many plants, such as raw tomatoes and potatoes (both of the Solanaceae family), can cause direct irritation to the gastric and intestinal mucosa. Nicotine and related nicotine-like alkaloids can cause nausea, vomiting, and diarrhea, due to stimulation of intestinal cholinergic receptors. Plants containing cellular toxins, such as *Colchicum autumnale* (autumn crocus; colchicine) or *Ricinus communis* (castor bean; ricin), most prominently affect the rapidly dividing cells of the gastrointestinal tract.[1] Other plants produce gastrointestinal effects only following systemic absorption. This includes *Cephaelis ipecacuanha*, from which ipecac is derived, which acts via the chemoreceptor trigger zone in the brain.

Metal salts, such as those of lithium, iron, arsenic, and mercury, cause prominent and early nausea, emesis, and diarrhea. The directly oxidative effects of the metal ions damage the gastric mucosa, produce hematemesis and gastrointestinal bleeding, and further increase absorption into the circulation to cause systemic toxicity. Iron ions, for example, can disrupt oxidative phosphorylation and cause metabolic acidosis following systemic distribution. Additional systemic symptoms include coagulopathy, hepatic dysfunction, myocardial depression, and neurotoxicity.

Case Continuation

Features of the history and physical examination assisted in narrowing the differential diagnosis. For example, there was no history of plant or mushroom ingestion. Since the vomiting and diarrhea persisted for hours without metabolic acidosis or classic neurologic findings, metal salt ingestion was unlikely. Furthermore, the combination of miosis, intractable vomiting, diarrhea, and urinary incontinence immediately raised suspicion for cholinergic crisis. Although the patient did not have bronchorrhea, bradycardia, or bronchospasm in the emergency department, it is common, as suggested above, to have incomplete findings.

What agents can cause cholinergic crisis?

Some insecticides are strong acetylcholinesterase inhibitors. The World Health Organization classifies insecticides into five groups, ranging from "extremely hazardous" to "unlikely to present acute hazard" in normal use.[2] Parathion, for example, is a very hazardous cholinesterase inhibitor (organophosphorus; OP) insecticide that has resulted in numerous fatalities worldwide. Some countries, such as the United States, have banned pesticides deemed to be highly toxic, such as those with high potency or long duration of action.[3] However, "less toxic" cholinesterase inhibitor pesticides can be found in insect baits (including roach baits), shampoos for head lice, and products for pets.[4] Temephos, for instance, is widely available in the United States to control mosquito outbreaks. Hazardous pesticides remain available in other parts of the world due to their low cost and high effectiveness for agricultural purposes. Sometimes these compounds are smuggled into the United States for specific uses. For example, though prohibited for public use in the United States, aldicarb is imported from the Dominican Republic as *tres pasitos* (Figure). Cholinergic crisis following exposures was noted in New York City's Dominican population starting in the 1990s.[5] Aldicarb is one of many carbamate insecticides; other common ones include carbaryl, carbofuran, and methomyl. The mechanism of action of the carbamate insecticides is nearly identical to that of the OP insecticides. Generally, cholinergic crisis from carbamate poisoning may be indistinguishable from that caused by the OPs. However, with carbamates, the duration and severity of clinical poisoning tends to be less. The reduced impact of poisoning from carbamates is a result of spontaneous and rapid hydroxylation of the carbamate-cholinesterase bond, thereby releasing the esterase to metabolize acetylcholine. This contrasts with the OP insecticides, whose spontaneous hydrolysis of the enzyme-OP bond is slow and incomplete. To make OP poisoning more difficult to treat, after an initial reversible period, some OP compounds can become irreversibly bound to the acetylcholinesterase enzyme ("aging"), making reversal impossible, even when appropriate antidotes are administered.

Several therapeutic medications are cholinesterase inhibitors. When administered in excess, they can cause cholinergic symptoms. Examples include medications used to treat myasthenia gravis (pyridostigmine) or Alzheimer's disease (donezepil). Prescribers should be aware that overuse of these agents can precipitate cholinergic crisis.

FIGURE. Typical samples of *tres pasitos* in unmarked packages with no instructions or warnings.

What are the most important steps in caring for the patient?

Caregivers should protect themselves from contamination if OP or carbamate poisoning is suspected. Donning personal protective equipment, including impermeable gowns and gloves, is wise. Patients with dermal exposures should be undressed and thoroughly washed with soap and water. Health care personnel can become poisoned by inhaling insecticide that is on the surface of a contaminated patient; dermal contact is another route of poisoning.

Addressing airway, breathing, and circulation should be the first priority. The most common cause of death in cholinergic crisis is respiratory failure secondary to bronchorrhea. Early intubation is indicated for patients who exhibit neuromuscular paralysis, respiratory failure, or severely altered mental status. Orogastric lavage can be attempted early after ingestion. Lavaged contents and emesis may contain the toxic substance and should be handled cautiously.

What are the antidotes for cholinergic crisis?

Atropine competitively inhibits acetylcholine binding at the muscarinic receptors in the central and peripheral nervous systems. Atropine has no effect at the nicotinic receptors and will not reverse muscle weakness or paralysis. Atropine should be given intravenously, and the dose should be titrated in relation to bronchial secretions. Adult dosing can start at 1 mg IV, whereas children can receive 0.02 mg/kg IV, with a minimum dose of 0.1 mg. Rapid escalation by doubling the previous dose every 2 to 3 minutes may be necessary to control bronchorrhea, and mitigating this symptom is one of the primary end points of therapy.[6,7]

Pralidoxime releases the cholinesterase inhibitor and restores the ability of cholinesterase to metabolize acetylcholine. Dosing regimens vary, but a reasonable approach is a loading dose of 30 mg/kg IV (up to 2 g) followed by a maintenance infusion of 8 to 10 mg/kg/h (up to 650 mg/h). Rapid administration of pralidoxime can cause cardiac and respiratory arrest. Ideally, if organophosphate toxicity is suspected, pralidoxime should be administered early, prior to aging of the OP-cholinesterase bond.[7,8] Use of pralidoxime in carbamate poisoning is controversial since spontaneous hydrolysis is expected. However, the clinical differentiation of carbamate and OP poisoning is very difficult, and use of empiric therapy is reasonable.

Case Conclusion

The patient received atropine 3 mg IV and rapidly improved. Shortly after the patient arrived to the emergency department, her mother arrived with similar but more severe findings. The mother was intubated and received antidotal therapy. The daughter recovered and the mother was extubated approximately 1 week later. The mother admitted having *tres pasitos* in the home. Laboratory analysis of the serum of both patients, sent at the time of admission, confirmed the presence of aldicarb. **EM**

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