A 17-Year-Old Girl With Cough-Pulseless After Drug Overdose.

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A 17-Year-Old Girl With Cough—Pulseless After Drug Overdose

A 17-year-old girl with a history of depression, but no prescribed antidepressants, arrives to the emergency department (ED) in cardiac arrest. After an argument with her father, the girl admitted to swallowing 12 tablets of a medication. Her father had found her within 10 minutes of the ingestion; she seemed drowsy and complained of nausea and dizziness. During transport to the ED, approximately 30 minutes after drug ingestion, she rapidly developed generalized convulsions and then became apneic.

An initial assessment in the ED finds the girl to be unresponsive and pulseless. Chest compressions are started, and a bag-valve-mask is applied for assisted ventilation. Naloxone, 2 mg intravenously (IV), is administered without response. A bedside blood glucose measurement is 228 mg/dL. The defibrillator's cardiac monitor reveals ventricular fibrillation. Advanced cardiac life support protocol is initiated, and 2 defibrillations (200 J) are delivered. The following medications are administered IV: 1 mg 1:10,000 epinephrine, 2 ampoules sodium bicarbonate (50 mEq/ampoule) and 100 mg calcium chloride. Approximately 10 minutes into the resuscitation, her rhythm converts to sinus with a palpable pulse. The girl's vital signs following return of spontaneous circulation (ROSC) include heart rate, 108 beats per minute; blood pressure, 134/58 mm Hg; respirations, 14 breaths per minute; and tympanic temperature, 100 ° F. After ROSC, the girl's Glasgow Coma Scale is 3. Her pupils are mid-position and reactive, her skin is not flushed, she has normal bowel sounds, and the remainder of the physical examination is essentially unremarkable.

The girl is endotracheally intubated after administration of etomidate, 20 mg IV, and succinylcholine, 100 mg IV. Sedation is maintained with a propofol infusion. An electrocardiogram (ECG) demonstrates the following: sinus tachycardia, QRS interval 114 milliseconds, and QTc interval 540 milliseconds. Laboratory studies obtained after ROSC measured pH 7.14, pCO_2 72.7 mm Hg, pO_2 25 mm Hg (venous sample), HCO_3 24.8 mmol/L, and base excess −6 mmol/L. Electrolytes are within normal reference range. Serum acetaminophen, salicylate, and ethanol are undetectable. A rapid urine immunoassay for drugs of abuse detects THC only. A chest radiograph confirms successful endotracheal tube placement without abnormality. A postcardiac arrest hypothermia protocol is initiated.

Having achieved cardiovascular stability, preparations are begun to transition the girl to the intensive care unit. The girl's father reports that his daughter was recently prescribed a "cough medicine" by her pediatrician and has the bottle in his hand.

Can you pick your poison?

Disclosure: The authors declare no conflict of interest.

Authors interested in submitting a case study in pediatric poisoning for the *Pediatric Emergency Care* feature *Pick Your Poison* are encouraged to contact the Section Editor, Kevin C. Osterhoudt, MD, via E-mail at OsterhoudtK@email.chop.edu.

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CASE CONCLUSION AND DISCUSSION

This teenage girl presented with a seizure and cardiac arrest shortly after ingesting 12 prescribed "cough medicine" pills. After ROSC, her ECG was notable for a widened ECG QRS interval as well as QT prolongation. Although numerous cough medications are available on the market, several critical aspects of the clinical history can further differentiate the poison. First, a relatively small amount of pills resulted in severe toxicity. Second, the onset of toxicity was very rapid. And third, the drug was not purchased over-the-counter, but instead by a prescription. A succinct review of cough medications will assist in determining the ingestion in this case.

Commonly available cough medications include both peripherally and centrally acting antitussives. Centrally acting medications work to inhibit the cough center in the brain stem and consist of codeine, hydrocodone and dextromethorphan. Peripherally- acting antitussives or expectorants can affect peripheral cough receptors, change the consistency of the mucous, or act on the respiratory tree. Common medications include guaifenesin, antihistamines, and benzonatate.[1]

Codeine and hydrocodone are both μ receptor agonists. Typical signs of toxicity would be characterized by an opioid toxidrome including pupillary miosis, coma, and respiratory depression. This patient was apneic during prehospital transport but immediately prior was awake and alert. Acute, sudden onset of apnea in an awake patient generally occurs secondary to a cardiac event—in this case, ventricular fibrillation—rather than through gradual depression of respiratory drive. Furthermore, antitussive doses of opioids are generally lower than analgesic doses[1]; 12 pills would not be expected to produce significant sudden toxicity. Finally, naloxone was also administered without response and respiratory depression associated with these medications should respond promptly.

Dextromethorphan and antihistamines, such as diphenhydramine and chlorpheniramine, are common active ingredients in many over-the-counter cough preparations. Relatively sudden cardiac arrest would be highly unlikely after ingestion of 12 tablets of these medications. Dextromethorphan, widely available in cold and cough pharmaceuticals, has developed some notoriety as a drug of abuse.[2] Dextromethorphan is an *N*-methyl-D-aspartate receptor antagonist, and smaller ingestions (2 mg/kg) have reported effects of euphoria whereas larger ingestions (>15 mg/kg) can produce ataxia and visual hallucinations.[3] Antihistamine toxicity can also manifest antimuscarinic symptoms such as salivation, diarrhea, and dermal flushing, but this patient exhibited none. Diphenhydramine is one of the more commonly prescribed antihistamines and has been associated with cardiac arrest and seizures, but this is typically in the setting of massive ingestions.[4]

Guaifenesin, a common cough expectorant, is purported to work by directly affecting the consistency of mucous and perhaps by enhancing the cough reflex. Commonly reported adverse effects include headache, nausea, and vomiting. Guaifenesin overdoses are probably common but significant guaifenesin toxicity seems to be rare; one published case report suggested central nervous system depression, and subsequent asystole, developed in a patient approximately 2 hours after guaifenesin overdose.[5] The current patient's ventricular fibrillation occurred much more rapidly and does not fit this pattern.

The girl's presentation of rapid onset seizure and ventricular dysrhythmia, as well as the widened QRS complex and QT prolongation on her ECG, can all be explained by toxicity secondary to sodium benzonatate, which was, in fact, the culprit poison.

Benzonatate, 4-(butylamino) benzoic acid, is a peripherally acting antitussive which anesthetizes vagal stretch receptors in the bronchi, alveoli, and pleura.[1] It was first synthesized in 1956 and is available under the brand name Tessalon Perles (Forest Pharmaceuticals, St Louis, MO) or generically as 100- and 200-mg liquid-filled yellow capsules.[6] The normally recommended dose for adults and children older than 10 years is 100 to 200 mg by mouth 3 times daily as needed for cough, with a maximum dose of 600 mg/d. It is rapidly absorbed from the gastrointestinal tract and onset of action is typically within 15 to 20 minutes. The duration of action is reported as between 3 and 8 hours. Common adverse effects include sedation, dizziness, headache, confusion, and nausea.[6] More clinically significant toxicities, however, may result in a rapid onset of neurological or cardiovascular complications (mostly related to sodium-channel blockade) including seizures, coma, agitation, hypotension, ventricular dysrhythmia, and cardiac arrest.[7,8] This is consistent with the girl's initial presentation of a seizure and ventricular dysrhythmia with associated ECG findings of QRS and QT prolongation.

There are a number of cases of serious toxicity from benzonatate ingestion reported in peer-reviewed publications.[8–15] One 12-month-old experienced a seizure after chewing "one or two" perles; 4 other cases involving children younger than 2 years resulted in fatality. Among cases reported involving older children patients experienced a seizure, ventricular dysrhythmia, or both.

The girl described in this case was subsequently administered both a sodium bicarbonate infusion and lipid emulsion therapy (LET) (20% at 0.25 ml/kg per hour) for approximately 24 hours. A subsequent ECG demonstrated heart rate 117, QRS interval 82 milliseconds, and QTc interval 493 milliseconds. Her hospital course was complicated by a pneumothorax after central venous catheter placement, hypokalemia, and hypomagnesemia. Following the 72-hour hypothermia protocol, the girl was extubated on hospital day 3 with a Glasgow Coma Scale of 14. She demonstrated some mild short-term memory impairment but was otherwise neurologically intact. Magnetic resonance imaging of the brain showed no abnormality. The patient was discharged to an inpatient adolescent psychiatric facility at baseline mental status. Before discharge, the patient verified that she ingested benzonatate.

Management of benzonatate toxicity centers on supportive care with special attention placed on the patient's neurological and cardiovascular status. Gastrointestinal decontamination is not typically believed to be useful due to the rapid onset of toxicity and potential for clear aspiration risk. Seizures should be treated aggressively. Because benzonatate is known to be a potent sodium channel blocking drug, sodium administration and blood alkalinization are believed to be helpful, especially if QRS widening is noted.[11,16,17]

Lipid emulsion therapy (LET) is a relatively new "antidote" that has been used successfully for the treatment of local anesthetic cardiotoxicity.[18] Although there are no reported cases describing the use of LET specifically with benzonatate overdose, given the structural similarity between benzonatate and ester anesthetics, a therapeutic effect can be inferred. The beneficial mechanism of LET is not fully characterized, but a predominant theory is that of the "lipid sponge." The concept behind this mechanism is that intra-arterial lipids rapidly bind the lipophilic sodium channel blocking toxicant and extract it from the target tissues.[19] In this case, a narrowing of the QRS was witnessed after administration of LET and our patient had what we considered to be a favorable outcome.

A limitation of this case report was the lack of confirmation with a measured benzonatate serum concentration. Some previously described cases have used high-pressure liquid chromatography with tandem mass spectrometry to accurately measure serum concentration.[11] However, the presence of an empty pill bottle, direct corroboration from the patient, a consistent clinical syndrome, and the lack of other important positive findings on toxicological analysis make us confident that this case represents benzonatate toxicity.

Between 2004 and 2009, dispensed benzonatate prescriptions increased by approximately 52% from 3.1 to 4.7 million, despite a 26% decrease of total dispensed antitussive prescriptions in the same period (National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance project database).[20] Although serious outcomes from benzonatate toxicity are relatively rare, physicians are encouraged to be aware of the potential risks when prescribing benzonatate to their patients. Benzonatate perles have an attractive appearance and young children are particularly at risk of serious outcomes from exploratory ingestion. In fact, based on accumulating evidence of serious outcomes among young children, the US Food and Drug Administration issued a Drug Safety Communication in December 2010—more than 50 years after its initial approval of benzonatate as an antitussive—highlighting that exploratory ingestion of benzonatate by children younger than 10 years can result in death.[21]

In sum, sodium benzonatate toxicity can be significant and emergency health care providers should be considerate of the potential for toxicity with this drug, and the clinical manifestations and treatment of poisoning. Given the narrow therapeutic index of this medication, the risks of prescribing benzonatate—especially to younger patients—likely outweigh the marginal benefit of improving a self-limiting symptom.

Final Diagnosis: *Sodium benzonatate overdose.*

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