The case of the slandered Halloween cupcake: Survival after massive pediatric procainamide overdose

SUZANNE R. WHITE, MD, GRACE DY, MD, JOHN M. WILSON, PhD

INTRODUCTION

This is the first report of acute pediatric procainamide overdose. Features of this 14-year-old patient’s course included early, prominent gastrointestinal symptoms, antimuscarnic findings, and the abrupt onset of seizure activity. The patient did not experience cardiac dysrhythmia or cardiovascular collapse, despite the presence of extremely high combined procainamide and N-acetylprocainamide levels. Crossreactivity between procainamide or its metabolites and amphetamine was noted on toxicologic analysis of the urine by enzyme immunoassay technique. Recovery was rapid and complete, mirroring the rapid clearance of both procainamide and N-acetylprocainamide from the blood. Although malicious tampering was initially suspected in this case based on a misleading history and the occurrence on Halloween, intentional exposure in the adolescent patient with poisoning should always be considered.

CASE

A 14-year-old African American male sought treatment at the emergency department (ED) on Halloween with abdominal pain and generalized weakness. While walking to school, he had purchased a lemon cream-filled cupcake from a local gas station. Within 2 hours of eating the cupcake, he developed abdominal pain, dizziness, and difficulty ambulating resulting from generalized weakness. The cupcake was reportedly purchased in a sealed package, but the brand name was not known. No other people were known to have consumed the same or similar products, and no other family members or classmates were ill. He arrived in the ED approximately 4 hours after ingestion. Additional symptoms on arrival included blurred vision, dry mouth, odynophagia, and cephalgia. He denied the ingestion of any other foods, medications, or recreational drugs. Before this exposure, the child had been in relatively good health except for a history of mild asthma. Neurologically, the patient was alert and answering questions appropriately. Patellar and bicep reflexes were graded as 2+. Results of motor and sensory examinations were normal.

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Thirty minutes after arrival, the patient vomited uniformly-sized, cylindrical pieces of doughy, yellow particulate matter described as the same color as the cupcake consumed earlier. Seconds after vomiting, a tonic-clonic seizure lasting less than 1 minute occurred, followed by a brief postictal period. The patient’s respiration was supported by bag-mask ventilation. Repeat vital signs after the seizure episode were as follows: blood pressure, 125/57 mm Hg; heart rate, 136 beats per minute; respiratory rate, 17 breaths per minute. The cardiac rhythm strip displayed sinus tachycardia with narrow QRS complexes. Pulse oximetry was 99%, and a bedside glucose was 143. The administration of 2 mg naloxone was not temporally associated with improvement in mental status. Over the next 10 minutes, the patient became briefly combative but was then able to follow commands and voice simple commands. He exhibited mild, residual lethargy and slurring of speech. The abdomen was soft, bowel sounds were present, and the bladder was not palpable. The skin was dry and pale.

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ditional doses. The Food and Drug Administration was contacted and initiated an investigation into possible malicious tampering with a food product. Law enforcement officials were sent to the gas station to confiscate various food products.

Laboratory results from the postictal period included the following: blood urea nitrogen, 4 mg/dL; creatinine, 0.9 mg/dL; sodium, 147 mEq/L; potassium, 3.6 mEq/L; chloride, 111 mEq/L; bicarbonate, 16.8 mEq/L; anion gap, 19; white blood cell count, 14,400/µL; hemoglobin, 13.3 g/dL; and platelets, 362,000/µL. Capillary blood gas analysis during bag-mask ventilation with 100% oxygen showed the following: pH, 7.19; PCO₂, 42.3 mm Hg; and PO₂, 123.9 mm Hg. A computed tomography scan of the head without contrast enhancement was normal. Electrocardiogram showed sinus rhythm with a PR interval of 123 milliseconds, QRS duration of 76 milliseconds, and QTc interval of 371 milliseconds.

Toxicologic analysis of the urine was positive for amphetamines by enzyme-mediated immunoassay (EMIT; Syva Co., St. Louis, MO) but negative by fluorescence polarization immunoassay (FPIA; Abbott, Abbot Park, IL) and thin-layer chromatography (Toxilab; ANSYS Technologies, Lake Forest, CA). Additional testing of the urine for barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, methadone, opiates, propoxyphene, phencyclidine, and methaqualone was negative by FPIA. Serum toxicologic analysis was also negative for tricyclic antidepressants, benzodiazepines, barbiturates, acetaminophen, and ethanol by EMIT method. Serum salicylate and theophylline levels were negative by enzymatic salicylate assay (Diagnostic Chemicals, Oxford, CT) and by FPIA, respectively. Gas chromatography for methanol and ethylene glycol was negative. High-pressure liquid chromatography of the urine showed the presumed presence of a large amount of an unknown substance.

Based on the large, unidentifiable peak noted on high-pressure liquid chromatography of the urine, more in-depth analysis of the blood and urine was performed by thin-layer chromatography, identifying the substance as procainamide. This finding was confirmed by gas chromatography—mass spectrometry and quantitated by FPIA, yielding a serum procainamide level of 63 µg/mL (normal range, 4–8 µg/mL) and a serum N-acetylprocainamide level of 80.4 µg/mL (normal range, 2–8 µg/mL; normal combined procainamide and N-acetylprocainamide, 8–30 µg/mL). No other substances were detected. Repeat procainamide and N-acetylprocainamide levels at 43 hours after ingestion were less than 0.3 µg/mL and less than 0.6 µg/mL, respectively.

None of the patient’s family members, friends or relatives were known to take procainamide. The patient continued to deny intentional drug overdose, despite the appearance of vomitus consistent with partially dissolved capsules or tablets. The issue of malicious tampering with food seemed unlikely once the laboratory results were known, because an extremely large dose of procainamide (approximately 21 g) would have been necessary to produce such significantly elevated levels. This number of tablets would have been obvious to the patient during consumption of the cupcake. After a family discussion during which he was confronted with the procainamide and N-acetylprocainamide levels detected, the child admitted to an intentional drug overdose. He indicated that he was upset over recent poor report card results and that he had consumed the contents of a medication bottle discovered among other items in the attic. Further investigation into possible tampering was halted.

**DISCUSSION**

Procainamide is a class 1A antidysrhythmic drug indicated for the management of documented, life-threatening ventricular dysrhythmias such as sustained ventricular tachycardia. The drug’s actions are pharmacologically complex. It inhibits cardiac voltage-gated sodium channels, potassium rectifier currents, and, to a lesser extent, voltage-gated L-type calcium channels. Decreased automaticity of cardiac pacemaker cells with slowed conduction results. Although antimuscarinic effects are described and may result in increased atrioventricular conduction at low doses, atrioventricular block occurs at higher doses (1). These pharmacologic effects may manifest electrocardiographically as sinus bradycardia; tachycardia; prolongation of the PR, QRS, or QT intervals; or torsade de pointes. Hypotensive effects have also been noted from procainamide and are related to decreased cardiac output rather than direct vascular effect with severe intoxication (1). Procainamide’s active metabolite, N-acetylprocainamide, a class III antidysrhythmic, has an inhibitory action on potassium rectifier currents. Its presence does not result in increased PR or QRS intervals, but it does cause QT interval prolongation to a similar or greater degree than the parent compound (2). Both regular and sustained-release formulations of procainamide are available, each with a bioavailability of 85% (3). The absorptive half-life is 20 to 30 minutes in healthy volunteers (4) but may be as long as 11 hours in the overdose setting (5). Procainamide is widely distributed into tissues with a volume of distribution of 2 L/kg in adults and 2.2 L/kg in children (6). Of a dose, 45 to 65% is renally eliminated unchanged via first-order kinetics. Elimination by this route is affected by renal function, but urine pH is not (7). Roughly half of the procainamide dose, depending on acetylator status, is heptatically metabolized to N-acetylprocainamide, which is also renally excreted. A minor desethyl metabolite has also been described (3). N-acetylprocainamide has a slightly smaller volume of distribution than the parent drug (1.5 L/kg) (3). Both procainamide and N-acetylprocainamide exhibit low protein binding. Elimination half-lives in patients with normal renal function are 3.5 hours and 6.2 hours for procainamide and N-acetylprocainamide, respectively (3). In patients with end-stage renal disease, significantly prolonged elimination half-lives as long as 14 hours for procainamide and 42 hours for N-acetylprocainamide may be observed (3, 8). Half-lives in overdose may also be as long as 8.8 or 10.5 hours for procainamide (5, 9) and 35.9 hours for N-acetylprocainamide (5). The elimination half-life in children of 1.7 hours is much shorter than that in adults (6). In the newborn, however, a prolonged elimination half-life of 13.5 hours has been reported, possibly related to hepatic immaturity (10). Although accurate elimination half-life calculations for procainamide and N-acetylprocainamide were not possible in our patient, complete clearance of both the parent drug and its metabolite by 43 hours after ingestion suggests that the half-lives for both were less than 11 hours.

Intentional drug overdose with procainamide in the pediatric population has not been previously described. Neither a MEDLINE search (from 1966) nor a review of the American Association for Poison Control Centers Toxic Exposure Surveillance System Annual Reports (from 1983) yielded reports of acute intentional pediatric procainamide overdose. Similarly, experience with acute procainamide overdose in adults is extremely limited, reported only twice. In the first case (9), a 79 year old with coronary artery disease and renal insufficiency ingested 19 g procainamide and developed lethargy, wide complex dysrhythmia, and vomiting within 45 minutes of ingestion. Symptoms progressed to coma and hypotension within 2 hours of ingestion. Treatment involved tracheal intubation, vasopressors, gastric decontamination, and peritoneal dialysis. Procainamide levels peaked at 77 mg/L 3 hours after ingestion. N-acetylprocainamide levels were not measured. The half-life of procainamide was found to be 8.8 hours. The second case of acute procainamide overdose involved a
67-year-old woman with an extensive cardiac history who ingested 7 g (5). Nausea, vomiting, lethargy, junctional tachycardia, severe hypotension, and oliguria developed. The patient was treated with hemodialysis, which reportedly doubled procainamide clearance and increased N-acetylprocainamide clearance fourfold.

Our patient’s examination results differed from those of the reported adult cases, with more prominent gastrointestinal distress, abrupt onset of seizure activity, notable antimuscarinic findings (eg, tachycardia, mydriasis, dry mucous membranes), and a lack of cardiac dysrhythmia, QRS or QT prolongation, or hypotension. Seizures have not previously been noted with acute procainamide toxicity. Because antidysrhythmic agents are known to have greater toxic effect on the diseased myocardium, we hypothesize that, despite extremely high drug levels, a relative sparing of healthy myocardial tissue occurred in our patient. Theoretically, in the absence of cardiovascular collapse, greater partitioning of the drug to the central nervous system may have resulted in a predominance of neurologic symptoms. Alternatively, seizure activity may have represented unique pediatric sensitivity to the anticholinergic effects of procainamide, as has been described with other agents (11). Antimuscarinic toxicity has been described in one other case of procainamide toxicity, resulting from drug accumulation with chronic administration in an adult (12). Perhaps procainamide should be considered along with other agents in the differential diagnosis of children seeking treatment with symptoms of antimuscarinic toxicity (delirium, hallucinations, coma, mydriasis, anhidrosis, tachycardia, urinary retention, or ileus).

As illustrated in our case, procainamide and N-acetylprocainamide are not typically detected through routine toxicologic analysis. If procainamide toxicity is suspected, procainamide and N-acetylprocainamide levels should be specifically requested. Interestingly, the crossreactivity observed between procainamide or N-acetylprocainamide and amphetamines in our case corresponds to the structural similarity of these compounds (Fig. 1). This crossreactivity has been described previously but at much higher concentrations of N-acetylprocainamide and procainamide than were noted in our patient (215 and 855 mg/L, respectively) (13). For therapeutic monitoring, one report suggests that combined serum concentrations of 42 mg/L indicate risk for severe cardiotoxicity, and that those greater than 60 mg/L are associated with lethargy and hypotension (5). In our case, the procainamide level of 63 mg/L and N-acetylprocainamide level of 80.4 mg/L represent the highest combined levels reported (143.4 mg/L). However, because both adult patients described and our pediatric patient survived despite markedly elevated serum levels, we question the prognostic value of procainamide and N-acetylprocainamide levels in the acute overdose setting.

Existing treatment recommendations for procainamide toxicity are derived primarily from experience related to chronic drug and metabolite accumulation in patients with cardiac or renal disease. The following general recommendations for acute procainamide overdose represent the opinions of the authors, based on literature review and experience. As with the treatment of all poisoned patients, early stabilization of airway, breathing, and circulation and a search for rapidly reversible causes of coma take precedence. The administration of naloxone would likely not be beneficial. Based on experience with poisonings involving other sodium channel–blocking agents, such as cyclic antidepressants or cocaine, flumazenil should be avoided to prevent the potential unmasking of proconvulsant effects. A rapid 12-lead electrocardiogram may provide useful diagnostic clues. QRS widening or rightward axis shift of the terminal portion of QRS complex may indicate the presence of a sodium channel antagonist like procainamide. In turn, this finding may prompt treatment with serum alkalinization with sodium bicarbonate, which has previously been shown to reverse conduction defects in the setting of chronic procainamide toxicity (14) and also in acute overdoses involving other sodium channel antagonists. Given that the urinary excretion of procainamide is not dependent on pH, there appears to be no role for urinary alkalinization in an attempt to enhance drug elimination. Torsade de pointes could be managed with magnesium and potassium supplementation, isoproterenol infusion, or pacer-mediated increased intrinsic heart rate (1). Class IA, IC and III antidysrhythmics could theoretically potentiate the effects of procainamide and should be avoided. Hypotension should be treated initially with fluids and, if refractory, with inotropes or vasoconstrictors, as ideally guided by pulmonary catheter readings. Seizures would best be treated with benzodiazepines or barbiturates (1).

Given the propensity for procainamide and N-acetylprocainamide to induce conduction disturbances, phystostigmine is not recommended. The role of gastrointestinal decontamination in procainamide overdose is not clear. Ipecac should be avoided in this setting, because abrupt onset of seizures or lethargy may predispose to pulmonary aspiration. The use of multiple-dose charcoal therapy or whole bowel irrigation with polyethylene glycol solutions has not been studied but could be considered in patients ingesting the sustained-release formulations of procainamide.

Experience with chronic procainamide toxicity suggests that patients without predisposing renal impairment exhibit rapid declines in serum concentration upon drug discontinuation. Intrinsic pediatric
plasma clearance of procainamide in children with normal renal function is 19.4 mL/min/kg (6). If renal impairment is present, however, procainamide and its active metabolite are amenable to extracorporeal removal based on their properties of low protein binding and relatively low volumes of distribution. Anecdotal cases showing increased drug clearance with hemodialysis, hemoperfusion, or continuous arteriovenous hemofiltration have been reported. Peritoneal dialysis was ineffective in clearing procainamide after acute overdose, possibly related to reduced perfusion of the splanchnic vasculature in patients who are hypotensive or on vasopressor therapy (8, 9). Clearance rates of procainamide and N-acetylprocainamide by hemodialysis have been reported at 47 to 88 mL/min and 22 to 104 mL/min, respectively (5, 8, 15–17). Comparative clearance rates by hemoperfusion are reported to range from 47 to 103 mL/min for procainamide and from 47 to 151 mL/min for N-acetylprocainamide (8, 15, 16). Braden et al. (15) proposed superiority of hemoperfusion over hemodialysis for N-acetylprocainamide clearance based on rates averaging 145 mL/min. Other investigators report markedly increased elimination with the combination of hemoperfusion followed by hemodialysis yielding clearances of 135 mL/min for procainamide and 107 to 137 mL/min for N-acetylprocainamide (8, 16). Although continuous arteriovenous hemofiltration has been proposed as the therapy of choice for extracorporeal removal of N-acetylprocainamide, reported clearance rates of 23 mL/min are only slightly higher than intrinsic renal clearance rates (18).

**CONCLUSIONS**

This case illustrates that patient history surrounding intentional drug overdose may be inaccurate. Although it must be remembered that intentional drug overdose is much more common than malicious poisoning and that initial allegations of food tampering are often proven false, poison centers must remain vigilant, with a heightened index of suspicion for poisonings occurring around Halloween. All credible cases of suspected product or food tampering should be reported to law enforcement officials immediately. This occurrence also reinforces the need for continued poison prevention education about the proper disposal of unused medications in an effort to prevent their access by children.

**REFERENCES**