13-Year-Old Girl With Recurrent, Episodic, Persistent Vomiting: Out of the Pot and Into the Fire

Diana Felton, MD; Naamah Zitomersky, MD; Shannon Manzi, PharmD, NREMT; Jenifer R. Lightdale, MD, MPH

**abstract**

Cyclic vomiting syndrome (CVS) is a well-established cause of recurrent vomiting in the pediatric population. Severe vomiting with chronic cannabis use, known as cannabinoid hyperemesis syndrome, has recently been more widely recognized as an etiology of persistent episodic vomiting. In turn, patients presenting with frequent episodes of CVS are now increasingly being screened for cannabinoid use. Because patients with persistent vomiting are also frequently prescribed a proton pump inhibitor (PPI) for their gastrointestinal symptoms, it is important to be aware of the potential for a PPI to cause an interaction that can lead to false-positive urine cannabinoid screening. We describe a case of a false-positive urine cannabinoid screen in a patient with CVS who received a dose of intravenous pantoprazole. The primary reference regarding drug screen interference from PPIs can be found in the pantoprazole package insert that refers to pre–Food and Drug Administration approval data. Although multiple sources on the Internet report the possibility of positive cannabinoid screens from pantoprazole, there are no known published reports of the phenomenon in the medical literature.

Cyclic vomiting syndrome (CVS) is an idiopathic disorder characterized by recurrent, stereotypical episodes of vomiting with intervening normal health. Essential clinical features of CVS are as follows: ≥3 discrete episodes of vomiting; intervals of normal health between episodes; stereotypical episodes with regard to timing of onset, symptoms, and duration; and the absence of an identifiable organic cause for vomiting. The prevalence of CVS in school-aged children worldwide may be as high as 1.9%. Cannabis hyperemesis syndrome (CHS) is increasingly recognized as a cause of recurrent, episodic vomiting in chronic cannabinoid users and is included in the differential diagnosis of CVS. CHS is characterized by episodic nausea, vomiting, and abdominal pain, as well as compulsive bathing with hot water. The episodes are separated by periods of being symptom free and completely resolve with cannabinoid cessation. The clinical presentation of CHS and CVS is similar. Therefore, it may be clinically indicated to use urine toxicology screening to assess for cannabinoid use as a potentially reversible cause of cyclical vomiting. Positive urine screening for cannabinoid exposure in a pediatric care setting may also trigger protocols to ensure child protection. The following case report describes a case of a pediatric patient with severe cognitive impairment and CVS who was reported to the Massachusetts Department of Children and Families before it became clear that a urine drug screen for cannabinoids had been falsely positive. Knowledge of the potential for some proton pump inhibitors (PPIs) to cause...
a false-positive urine cannabinoid screen is helpful for clinicians caring for patients with CVS.

**CASE REPORT**

A 13-year-old girl presented to the emergency department (ED) for a fourth episode of acute vomiting over a 6-week period. In addition to a previous diagnosis of CVS, the patient’s medical history included intrauterine stroke, global developmental delay, seizure disorder, and gastroesophageal reflux disease. The patient was nonverbal and nonambulatory. According to her parents, who were her primary caretakers, the current episode began the day before in typical fashion when the patient refused to eat or drink. She was noted by her family to appear uncomfortable and, upon ED presentation, was retching and vomiting.

The patient had multiple previous episodes of CVS, typically lasting 3 days. They were characterized by severe vomiting every 15 minutes for the first day, with gradual lengthening of the interval between vomiting over the next 2 days, with full resolution by day 3. She had been hospitalized multiple times to receive intravenous fluids and antiemetic therapy.

Previous workup for CVS included multiple abdominal plain films that revealed a persistent moderate stool burden as well as normal complete blood counts and chemistry panels. Other serum laboratory testing had included thyroid studies and levels of amylase, lipase, ammonia, lactate, pyruvate, serum ketones, uric acid, creatinine, and cortisol, which were all unrevealing. Tests of serum amino acids, as well as urine organic acids, did not show a pattern recognizable for a known disorder. Stool testing for *Helicobacter pylori* was negative. An MRI 8 days before presentation was normal, without evidence of elevated intracranial pressure. The patient’s family history was positive for migraines in her mother, father, and both grandmothers.

On this ED visit, the patient was ill appearing, moderately dehydrated, and gagging repeatedly. She was afebrile, with a heart rate of 84 beats per minute and blood pressure of 100/75 mm Hg. Abdominal examination revealed a soft, nontender abdomen. Laboratory studies showed a mild leukocytosis (white blood cell count: 122,000 cells per μL; range: 55,000–93,000 cells per μL) with normal hemoglobin, hematocrit, and platelets. Serum electrolytes, renal function, and glucose were normal, as were lactic acid and liver enzymes.

The patient was given ondansetron 4 mg intravenously, pantoprazole 40 mg intravenously, diazepam 7.5 mg intravenously (due to missed oral doses of her antiepileptic medications), and a 20-mL/kg bolus of normal saline. The treating clinician opted to send a urine toxicology screen to evaluate for possible CHS. The urine sample was obtained 2.5 hours after administration of pantoprazole. The urine toxicity screen was expectedly positive for benzodiazepines (a result of administered diazepam) but unexpectedly positive for cannabinoids, prompting the admitting team to involve social services and file a protective order with the Department of Children and Families. Given the patient’s severe physical and developmental limitations, it was clear that she was unable to access or administer cannabinoids herself. A review of the patient’s home medications (including divalproic acid, clonidine, lacosamide, oxcarbazepine, and risperidone) and multiple discussions with the family did not reveal a source for the positive urine cannabinoid screen. The patient’s vomiting improved over 24 hours, and she was discharged from the hospital. Two days later, confirmatory testing via gas chromatography–mass spectrometry for cannabinoids returned negative, identifying the initial screening test as falsely positive for cannabinoids. With the involvement of consulting toxicology physicians, pantoprazole was identified as a possible source for the false-positive toxicity screen.

Since this hospitalization, the patient has had significant improvement in her CVS, which has been attributed to the addition of maintenance amitriptyline.

**DISCUSSION**

Our report describes a case of false-positive cannabinoid screening in a 13-year-old girl with CVS. Errant drug screens in pediatric patients can lead to unnecessary social service investigations of caretakers. In this case, our patient’s family reported considerable personal stress experienced as a result of the false-positive drug test. They have asked our health care team to educate other providers about the potential diagnostic error that can occur if urine toxicity screening for cannabinoids is performed in patients receiving pantoprazole.

Urine toxicology screens generally used in EDs are immunoassays designed to identify particular xenobiotic chemical structures.7 Urine drug screening for cannabinoids looks for metabolites of tetrahydrocannabinol (THC), including 9-carboxy-THC and 11-nor-Δ9-THC-9 carboxylic acid, which can persist in the urine for multiple days to weeks depending on the chronicity of use.8,9,10

In general, few substances besides THC metabolites cause a positive cannabinoid urine screen. Hemp-containing foods and passive inhalation of marijuana smoke have been implicated in positive THC screens.7 In addition to pantoprazole, nonsteroidal antiinflammatory drugs and the antiretroviral drug efavirenz...
have been implicated in false-positive cannabinoid screening.\textsuperscript{9,11,12} In addition, although gas chromatography–mass spectrometry currently remains a medical, legal, and regulatory gold standard, recent concern has been raised over possible false-negative confirmatory testing for THC, particularly in very young infants who may have intrauterine exposure and atypical drug metabolism.\textsuperscript{13}

Information regarding the mechanism of interference by pantoprazole in urine drug screening is scant, with all references referring to the pantoprazole package insert that describes pre–Food and Drug Administration approval data. Multiple attempts to obtain further information from the manufacturer did not yield additional information. In turn, an understanding of the interaction between the structure of pantoprazole and the immunoassay for THC remains unknown. It also remains unclear whether other PPIs could limit the reliability of immunoassays for THC, and there have been no reports of any other PPI besides pantoprazole having this effect.

**CVS**

CVS is a functional gastrointestinal disorder characterized by recurrent episodes of severe nausea and vomiting, interspersed with asymptomatic periods, which occurs in children and adults. CVS may be related to migraines, and a family history of migraines is often obtained. The pathophysiology of CVS is still under investigation. Proposed etiologies involve autonomic dysregulation, gastrointestinal dysmotility, mitochondrial enzymopathies and other metabolic defects, and neuroendocrine causes.\textsuperscript{14} Initial management involves antiemetics, intravenous fluids with glucose, PPIs, and electrolyte management. Prophylaxis with tricyclic antidepressants in the asymptomatic phase has been shown to be helpful in 75.5% of adult patients and 67.6% of pediatric patients, in a non–placebo-controlled cohort study.\textsuperscript{15} Propranolol has also been shown to be effective as prophylactic treatment in children.\textsuperscript{16} Patients presenting with symptoms of CVS often undergo extensive evaluation for alternative causes of their symptoms. Although it is important to rule out other etiologies, particularly those with life-threatening sequelae, the testing can have unintended, detrimental consequences, as occurred in this case. Parents frustrated by their child’s suffering may also turn to alternative therapies to control symptoms. Marijuana is considered a potential treatment of intractable vomiting, and its rapidly changing legal status and availability make it possible for parents to trial it in their children.

**CHS**

CHS is characterized by severe, recurrent vomiting in the setting of chronic, active cannabis use. Invariably, patients describe temporary relief with hot bathing. This syndrome develops in certain individuals after frequent and large exposures to marijuana, usually months to years of heavy use.\textsuperscript{17,18} Management involves treatment of the symptoms, while ruling out other causes of abdominal pain and recurrent vomiting and, most importantly, cessation of cannabinoid use. This syndrome has also been reported in patients who chronically use synthetic cannabinoids (ie, “spice,” “K2”).\textsuperscript{19} The pathophysiology of CHS is not well understood and is somewhat paradoxical given that cannabinoids are usually known for their antiemetic qualities. One proposed mechanism involves overstimulation of the cannabinoid receptor type 1 (CB1) in intestinal mucosa slowing gut motility and gastric emptying.\textsuperscript{4,20} The temporary relief of symptoms when bathing in hot water may be related to CB1 receptors in the hypothalamus that control thermoregulation.\textsuperscript{19} Recognizing CHS as a potential cause of CVS is important, because prevention and elimination of the condition are possible. Because the use of organic and synthetic cannabinoids is increasing, the number of patients with CHS will undoubtedly grow.

**CONCLUSIONS**

This case reflects some of the pitfalls involved in correctly diagnosing and managing patients with recurrent, episodic, persistent vomiting. It also underscores the importance of knowing the limitations of urine drug screens, because such testing may be used when patients present with a host of symptoms that can be ascribed to drug exposures. Awareness of the potential for false-positive results in urine cannabinoid screening may be particularly important as marijuana use for medical and recreational purposes becomes legalized in many states.

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