

Clinical Communications

Drug-induced enterocolitis syndrome (DIES) with pantoprazole in an adult patient

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Clinical Implications

- Drug-induced enterocolitis syndrome is a little-known entity that has yet the potential to cause life-threatening hypovolemic shock. Severe gastrointestinal symptoms resembling food protein–induced enterocolitis syndrome after a drug intake should raise awareness for this non–IgE-mediated gastrointestinal hypersensitivity reaction.

Drug-induced enterocolitis syndrome (DIES) is a rare type of non–IgE-mediated hypersensitivity reaction to drugs that shares clinical features with an analogous and well-recognized entity, that is, food protein–induced enterocolitis syndrome (FPIES), typically triggered by dairy or soy proteins in young infants. In the acute setting, both DIES and FPIES manifest as delayed-onset (approximately 2 hours after ingestion) profuse vomiting and diarrhea that can lead to dehydration and, more severely, hypovolemic shock.¹ To our knowledge, only 4 cases of enterocolitis syndrome caused by drugs have been reported, exclusively with antibiotics, namely amoxicillin and amoxicillin-clavulanate.^{2–5} To date, this is the first report of DIES provoked by a proton pump inhibitor (PPI).

We present the case of a 69-year-old Caucasian woman who was referred to the Allergy Department of the Centre Hospitalier de l'Université Laval with a history of 2 reactions after the taking of pantoprazole. In both episodes, the patient presented to the emergency department (ED) with vomiting, profuse bloody diarrhea, and abdominal pain having developed a few hours after taking pantoprazole prescribed for gastroesophageal reflux disease. The second episode was severe enough for the patient to develop features of hypovolemia and to be admitted to the hospital. At that time, investigation for diarrhea, including transaminases, lipase, stool cultures, mesenteric artery Doppler ultrasound, esophagoscopy, and colonoscopy, found no infectious, inflammatory, or ischemic cause for her gastrointestinal (GI) symptoms, which resolved spontaneously over a few days. Pantoprazole was stopped giving the temporal relationship between the drug taking and symptoms development, and the patient was successfully treated with intravenous fluids and intravenous corticosteroids before discharge.

Three months later, because of the unexplained nature of the GI symptoms and a low degree of suspicion of drug allergy with the absence of literature supporting enterocolitis secondary to PPIs, the patient underwent an oral challenge to pantoprazole with increasing doses of 5, 10, and 20 mg with a 30-minute interval between each dose to rule out definitively a drug

hypersensitivity. Within 1 hour after the last dose, the challenge was clearly positive for reproducing the exact same violent GI symptoms: the patient developed nausea, vomiting, and diarrhea with intense abdominal pain and was transferred to the ED. She was noted to have a high blood pressure (180/77 mm Hg), a rapid heart rate (114/min), and a low blood oxygen saturation (91%). Sonography showed signs of hypovolemia with a collapse of the inferior vena cava of more than 50% with inspiration. On arrival, she received 0.3 mg of intramuscular epinephrine and 50 mg of intravenous (IV) diphenhydramine, as an initial tentative diagnosis of anaphylaxis was erroneously made in the ED. She also received IV methylprednisolone, IV antiemetics, and aggressive IV fluid resuscitation. She was briefly admitted to the intensive care unit for surveillance. She developed neither a skin rash, urticaria, or edema, nor any respiratory symptoms during her episodes.

Investigations carried out a few hours after the onset of symptoms showed a white blood cell count at the upper limit of normal (14,000/mm³) with neutrophilia (10,500/μL). Serum creatinine was elevated (2.1 mg/dL, baseline 0.8 mg/dL), presumably due to hypovolemia, and capillary blood gasometry detected a metabolic acidosis (pH 7.30, bicarbonate 19 mmol/L) with an anion gap at the upper limit of normal (16 mEq/L, normal 8–16 mEq/L). Of note, at this early stage of her reaction for which IV fluid resuscitation was started promptly, lactic acid measurement was normal (7.2 mg/dL), but interestingly enough, during the second episode, which justified her first hospitalization, lactic acid was noted to be elevated (24.3 mg/dL, normal <19.8 mg/dL). Serum glucose, lipase, bilirubin, transaminases, sodium, potassium, creatinine phosphokinase, sedimentation rate, troponin, and eosinophil count were all within the normal range.

Interestingly, abdominopelvic computed tomography scan performed during the second episode of enteric symptoms showed intestinal edema with parietal thickening from the duodenum to the distal small intestine with sparing of the terminal ileum. At that time, both functional and antigenic C1 esterase inhibitors were normal.

DIES is a rare type of hypersensitivity reaction to drugs, and only a few cases are described to date with antibiotics. To our knowledge, we report the first case of an adult patient who developed DIES with pantoprazole.

The laboratory findings, the late onset of GI symptoms (>1 hour after drug administration) that reproductively occurred at 3 different occasions after pantoprazole intake including a positive oral challenge, in combination with the lack of cutaneous and respiratory symptoms, prompted the diagnosis of DIES due to pantoprazole. Van Thuijl et al² suggested in 2019 diagnostic criteria for DIES (Table 1) adapted from Nowak-Węgrzyn et al⁶ International consensus guidelines for the diagnosis and management of FPIES. Our patient met the criteria for DIES according to these authors. Of note, neutrophilia found in our patient a few hours after drug intake is also a feature described with FPIES in the literature.⁷

Pathophysiology of DIES has not yet been described in the literature. Close clinical resemblance with FPIES could suggest a cell-mediated disorder with evidence of T-cell proliferation on

TABLE I. Diagnostic criteria for DIES

Major criteria	Minor criteria
Vomiting in the 1- to 4-h period after ingestion of the suspected drug and absence of classic IgE-mediated allergic skin or respiratory symptoms	(1) A second episode of repetitive vomiting after ingestion of the same drug
	(2) Repetitive vomiting episode 1-4 h after ingestion of a different drug
	(3) Extreme lethargy
	(4) Marked pallor
	(5) Need for an emergency department visit
	(6) Need for intravenous fluid support
	(7) Diarrhea in 24 h (usually 5-10 h) after ingested drug
	(8) Hypotension
	(9) Hypothermia

A patient has to meet the major criterion and >3 minor criteria for a diagnosis of DIES. In a patient with a single episode, a diagnostic oral drug challenge is suggested to confirm the diagnosis.

DIES, Drug-induced enterocolitis syndrome.

From Van Thuijl et al.,² adapted from Nowak-Węgrzyn et al.⁶

stimulation with food antigens in those patients. Proinflammatory cytokines with local inflammation appear to affect intestinal permeability resulting in fluid shift leading to vomiting and diarrhea, hypotension, and, in some cases, shock.⁸ Skin testing has been reported to be negative in DIES in the literature, but the small number of cases warrants further evaluation.²⁻⁵

Our case is remarkable and noteworthy in many aspects in that DIES has the potential to cause hypovolemia that can lead to life-threatening shock after a drug intake.⁵ DIES is rather little known in comparison to FPIES. Awareness and recognition of this entity, in its mild or more severe form, is important in the evaluation of a patient presenting with acute GI symptoms, not excluding any possible drug reaction.

Management is mainly supportive, and the only definitive diagnostic test is the oral challenge that should be performed in controlled settings because of the potential to induce severe reactions.

The patient was advised to avoid pantoprazole and other PPIs in the future, even though tolerance to other PPIs should ideally be tested with a specific oral challenge.

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