

Drug-induced enterocolitis in an adult patient



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Clinical Implications

- Clinicians must keep in mind the diagnosis of drug-induced enterocolitis when dealing with a patient with acute gastrointestinal symptoms resembling food protein-induced enterocolitis syndrome after receiving a dose of amoxicillin or clavulanic acid. The challenge test should be carried out in a specialized setting.

TO THE EDITOR:

Food protein-induced enterocolitis syndrome (FPIES) is one of the non-IgE-mediated gastrointestinal reactions to food proteins and the one that has the potential for severe acute reactions. These disorders present with digestive symptoms, and manifest later than IgE-mediated reactions, usually 1 to 3 hours after eating the offending food. T-lymphocytes appear to be involved in their pathogenesis, causing intestinal permeability to be affected by the secretion of proinflammatory cytokines, which results in local inflammation and fluid shift that, in some cases, may lead to lethargy, hypotension, and even shock. The exact prevalence of FPIES is unknown and it is probably underdiagnosed, but it appears to be lower than that of IgE-mediated food allergy.¹ It occurs mainly in young children and only some cases have been described in adults, usually due to seafood, egg, or fish.² Until now, there are only 2 reports about enterocolitis caused by drugs, both in infants.^{3,4}

A 60-year-old male patient was referred to our allergy department for a suspected beta-lactam allergy. Nine months earlier he suffered an episode of vomiting, diarrhea, and malaise approximately 1 hour after taking the first dose of amoxicillin-clavulanic acid for a dental procedure. He was admitted in an emergency department, but he could not provide more information about the reaction. He reported a similar prior reaction with the same drug a few months earlier.

In the allergy study performed, specific IgE to penicillin G and amoxicillin was negative (<0.35 kU/L; ImmunoCAP, Phadia, Uppsala, Sweden)⁵ and basal tryptase was 3.62 mcg/L (normal levels <13.5 mcg/L). Skin tests with the intravenous formulation of amoxicillin-clavulanic acid (Sandoz Farmacéutica, Madrid, Spain) at a concentration of 250 mg/mL for the prick test and of 25 mg/mL for intradermal (ID) were negative. Skin tests were also negative with benzylpenicilloyl octa-L-lysine (5×10^{-5} mmol/L for prick and ID; Diater Laboratories, Madrid, Spain) and sodium penicilolate (2×10^{-2} mmol/L for prick and ID; Diater Laboratories).

A controlled oral challenge test was performed with amoxicillin-clavulanic acid. Because an immediate reaction or a

digestive intolerance to amoxicillin-clavulanic acid was expected, oral doses of 125 mg, 250 mg, and 500 mg were given to the patient with a 30-minute interval between each dose. Approximately 3 hours after receiving the first dose and 2 hours after the last dose of the drug, he presented with nausea, abdominal and groin pain, and persistent vomiting followed by profuse sweating, low oxygen saturation (81%), low blood pressure (70/50 mm Hg), and drowsiness, although he was conscious all the time and no resuscitation maneuvers were required. No throat or respiratory symptoms were reported and the physical examination was normal, with no wheezing, angioedema, urticaria, or uvular swelling; abdominal palpation was also normal. Blood pressure and hypoxemia were normalized in approximately 30 minutes after fluid therapy (1,000 mL normal saline), oxygen therapy (50% O₂), 2 doses of 0.3 mL intramuscular epinephrine (1 mg/mL) administered at a 15-minute interval, and intravenous corticosteroids (hydrocortisone 300 mg). Nausea and vomiting disappeared within an hour after treatment with intravenous ondansetron (8 mg), and abdominal pain subsided in approximately 2 to 3 hours, but he was monitored in the hospital's emergency department for 24 hours, being completely asymptomatic on discharge.

Approximately 1 hour after the onset of the reaction, a differential white blood cell count showed 2,900 neutrophils/mm³, and a tryptase level of 3.75 mcg/L. Serum glucose, creatinine, urea, amylase, bilirubin, aspartate amino transferase, alanine amino transferase, sodium, potassium, and creatine phosphokinase showed normal values except for amylase 207 IU/L (normal levels 28-100 IU/L) and potassium 2.6 mmol/L (normal levels 3.5-5 mmol/L). Troponin was normal (<0.01 ng/mL) and venous blood gasometry detected metabolic acidosis (pH 7.25, bicarbonate 17.5 mmol/L, and base excess -9.2). Chest x-ray, electrocardiogram, and echocardiogram were normal.

Within 5 hours of the beginning of the reaction, blood neutrophils rose to 11,600 cells/mm³, tryptase remained normal (2.46 mcg/L), and amylase, potassium, and pH in venous blood were normalized (pH 7.35). Two months later, specific IgE to penicillin G and amoxicillin remained negative, but unfortunately, the patient refused to undergo cutaneous or any other test again.

He had tolerated beta-lactam antibiotics, including amoxicillin-clavulanic, on several occasions before the first reaction. He has never had an episode of hypotension or digestive symptoms apart from those related to amoxicillin-clavulanic acid, and he remains asymptomatic since the challenge test, following the instruction to avoid all beta-lactam antibiotics.

We report the case of an adult patient who developed a severe reaction, with shock and digestive symptoms in direct relation to a dose of amoxicillin-clavulanic acid.

The late onset of the reaction (3 hours after the first dose of the drug), the lack of cutaneous or respiratory symptoms and of demonstrable sensitization to the drug, together with the normal tryptase levels after the onset of the reaction, makes the diagnosis of anaphylactic shock unlikely. In fact, hypo-oxygenation resolved when blood pressure was normalized, so it appeared to be related to the shock and due to low peripheral perfusion, as there were no obvious respiratory signs or symptoms.

Although a negative ID test to penicillin and amoxicillin-clavulanic acid does not rule out an IgE-mediated reaction to amoxicillin or to clavulanic acid, the lack of positive testing and the fact that the reaction consisted of hypotension and abdominal symptoms is more consistent with an FPIES type of reaction, rather than an IgE-mediated reaction.

On the other hand, metabolic acidosis together with the great increase (by 8,700 cells/mm³) of the number of blood neutrophils 5 hours after the first blood sample obtained 1 hour after the onset of the reaction strongly suggests the diagnosis of enterocolitis induced by amoxicillin-clavulanic acid. Some authors consider neutrophilia, peaking 6 hours after ingestion of the causative allergen, with an increase by 5,500–16,800 cells/mm³ (or at least by 3,500 cells/mm³), as a frequent feature⁶ and one of the diagnostic criteria⁷ of FPIES. The patient was treated with 300 mg of intravenous hydrocortisone and intramuscular adrenaline 1 hour before the first blood sample that showed a normal white blood cell count. Corticosteroids can increase the neutrophil count from the day after, but, as reported,⁸ an average increase of approximately 6,000 neutrophils/mm³ would be expected later, after at least the first week of daily doses of the drug. The patient was given a single dose of 300 mg hydrocortisone and, although unlikely, it is not possible to rule out that corticosteroids were responsible for the neutrophilia detected in the patient few hours after the dose of the drug.

Until very recently, this type of reactions had only been described with food proteins and mainly in children. In the past few years, 2 cases have been published, in children of 3 and 6 years of age, and in relation to amoxicillin.^{3,4} Both had an episode of acute urticaria during a previous treatment with amoxicillin⁴ or a cephalosporin,³ but in later exposures with amoxicillin, they developed an acute episode of vomiting, diarrhea, and, in one of the patients, pallor, lethargy, and hypotension³ within 2 to 4 hours of the oral challenge test with the drug. In both cases, neutrophilia was detected in peripheral blood and tryptase levels were normal. In our case, given the seriousness of the symptoms, we considered that we should not assume the risk of a new challenge test with amoxicillin or penicillin to check for tolerance to other beta-lactam antibiotics or to rule out the implication of clavulanic acid, although, in one of the previously published cases,⁴ tolerance was confirmed to phenoxymethylpenicillin.

As far as we know, this is the first case of a likely non-IgE-mediated gastrointestinal allergy manifested as acute enterocolitis due to drugs in adults. It has only been described previously in

infants and with amoxicillin, but given the infrequent nature of these reactions, it is unknown if it could be caused by other drugs.

In the case of acute, gastrointestinal symptoms resembling FPIES after taking a drug, and especially amoxicillin, with or without clavulanic acid, we must keep this possible diagnosis in mind and not just attribute the symptoms to a possible digestive intolerance. The only diagnostic test is the controlled challenge test with the suspected drug, but because of the potential to induce severe reactions, it should be performed in a specialized setting with the appropriate resources to treat a possible severe reaction.

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication November 19, 2016; revised March 9, 2017; accepted for publication March 23, 2017.

Available online May 9, 2017.

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2017.03.024>

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