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CASE REPORT

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Drug-induced enterocolitis, a new condition under consideration

Lucía Hernando Marín, Ana María Segura Machado, Marta Castro Ramos, Javier Torres-Borrego*

Pediatric Allergy and Pulmonology Unit, Children's University Hospital Reina Sofia, Cordoba, Spain

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Abstract
Drug-induced enterocolitis syndrome (DIES), little known due to its recent description, is analogous to food protein-induced enterocolitis syndrome (FPIES). Both processes are more frequent in pediatric age and share diagnostic criteria, the main one being the appearance of persistent vomiting 1-4 hours after ingestion of the drug or food, in the absence of IgE-mediated allergy symptoms.

Clinical Case 1

A 12-year-old adolescent was referred to our Pediatric Allergology Unit with suspected hypersensitivity to amoxicillin, which was prescribed in March 2024 for a dental infection at 50 mg/kg. Five hours after the first dose, he presented with multiple vomiting. He had tolerated amoxicillin previously, in 2017 and 2018. One week later, amoxicillin was prescribed again for the same indication. Two hours after the first dose, he presented with repeated vomiting, lethargy, pallor, and hypotension. He was attended to in the emergency department, and he improved after ondansetron and oral rehydration. In our unit, the allergic etiology was considered unlikely and, with prior informed consent, a controlled oral challenge test (COCT) with amoxicillin was prescribed, with no reaction in the initial 2 hours. Five hours later, he had incoercible vomiting. He was attended to in the emergency department, and he required intravenous rehydration and metoclopramide. Tryptase, specific IgE, and basophil activation test with amoxicillin were normal. Subsequently, tolerance to cefuroxime was tested in a new COCT.

***Corresponding author**: Javier Torres Borrego, Pediatric Allergy and Pulmonology Unit, Children's University Hospital Reina Sofia, Murcia, Spain. *Email address*: jtorbo@yahoo.es

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Clinical Case 2

A 9-year-old schooler was referred to our department with suspicion of reaction to NSAIDs. In August 2023, oral ibuprofen was prescribed to him for otitis. One hour after taking it, he had lip edema and vomiting. He had previously tolerated it without symptoms. In October 2023, 1 hour after taking oral metamizole, he had nausea and vomiting, epigastric pain, pharyngeal pruritus, and lethargy. In the emergency department, he received ondansetron and intravenous rehydration. Two weeks later, he underwent COCT with ibuprofen in another center, presenting with abdominal pain and vomiting. With prior consent, in March 2024, a new COCT with ibuprofen was performed in our unit, showing abdominal pain, vomiting, pallor, and lethargy, and he was treated with antihistamine and oral corticosteroid. With these antecedents, COCT was performed with acetylsalicylic acid (ASA), according to the pertinent protocol.[1] At 60 minutes after the last dose, he had lip edema, sialorrhea, and dysphagia, with partial response to oral antihistamine and corticosteroid, which yielded with intramuscular adrenaline. Tolerance to paracetamol was proven, awaiting PEOC with COX-2 inhibitor.

Discussion

First described in 2014,[2] the diagnosis of DIES (Table 1) is eminently clinical, with the appearance of gastrointestinal symptoms 1–4 hours after ingestion of the drug, mainly vomiting, which usually lead to dehydration and lethargy, and require emergency care.[3] The literature is full of reports of isolated cases, most of them associated with amoxicillin,[4] being tolerant to other beta-lactams (penicillin and cephalosporins).

The pathophysiology of DIES is poorly understood. By equivalence with FPIES, the alteration of the intestinal mucosa would favor the entry of the antigen,[1,5] with activation of CD4+ TH17 lymphocytes,[5] with serum IL-17 being a potential diagnostic biomarker.[6] The usefulness of the lymphocyte transformation test (LTT) has been proposed in the diagnosis of DIES,[7] FPIES,[8] and in hypersensitivity to drugs.[9]

As in the first case, unlike FPIES, most patients had previously tolerated amoxicillin.[5] The second case raises some diagnostic questions. On the one hand, there are few reports of DIES with drugs other than amoxicillin,[4,7,10] and on the other hand, we have not been able to find any report associated with multiple drugs. Although the clinical criteria for DIES due to NSAIDs are met, it is also compatible with hypersensitivity to ibuprofen, metamizole, and ASA, or with anaphylactic reaction. These entities should also be included in the differential diagnosis.[2] Although the patient presented with lip edema with ibuprofen and ASA, digestive symptoms predominated, which could be a consequence of edema in the gastrointestinal mucosa, justifying the efficacy of adrenaline due to its vasoconstrictor effect. DIES has been treated with paracetamol, administered orally and rectally.[7,10]

The DIES is an entity that deserves attention among pediatricians. The diagnosis is clinical, in patients with uncontrollable vomiting after ingestion of a drug, especially amoxicillin. The controlled exposure test is the diagnostic gold standard, although the LTT is emerging as a confirmatory test. Treatment is based on corticosteroids, antiemetics, suerotherapy, and drug avoidance, although it is not known whether spontaneous tolerance may occur in the future.

Table 1 The DIES diagnostic criteria. The major and at least three of the minor criteria must be met (adapted from 1).

Major Criteria	Minor Criteria
Uncontrolled vomiting 1–4 hours after drug ingestion, with absence of IgE-mediated allergy symptoms[1,2]	1. Second episode of vomiting after re-exposure to the same drug[1,2] 2. Vomiting after ingestion of a different drug[2] 3. Lethargy[1,2] 4. Marked pallor[1,2] 5. Emergency room attendance[1,2] 6. Intravenous fluids treatment[1,2] 7. Diarrhea within 24 hours 8. Hypotension 9. Hypothermia

[1,2]Criteria presented by patients 1 and 2.

Author Contributions

All authors contributed equally to this article.

Conflict of Interest

The authors declare no conflicts.

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