Drug-Induced Enterocolitis Syndrome due to Amoxicillin-Clavulanic Acid With Good Tolerance to Penicillin

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Drug-induced enterocolitis syndrome (DIES) is a non–IgE-mediated hypersensitivity reaction caused by a medication. To our knowledge, there are very few reported cases, and they all involve aminopenicillins [1-5]. We report a new case with the intention of raising awareness of this clinical entity to facilitate accurate diagnosis and management.

An 18-year-old man came to our clinic with vomiting in relation to intravenous infusion of amoxicillin-clavulanic acid and metamizole during surgery for acute appendicitis when he was 9 years old. The allergological study we describe below was carried out with the written consent of the patient.

Skin prick tests (SPT) and intradermal tests (IDT) were performed with penicilloyl-poly-lysine (PPL), minor determinant (MD), and clavulanic acid at commercially available concentrations (Diater), as well as with penicillin G (10 000 IU/mL), amoxicillin (20 mg/mL), amoxicillin-clavulanic acid (20/4 mg/mL), cefuroxime (2 mg/mL), ceftazidime (2 mg/mL), and meropenem (1 mg/mL). The results of the skin tests were negative, and the patient underwent a drug provocation test (DPT) with amoxicillin-clavulanic acid. Two and a half hours after receiving a therapeutic dose of 500/125 mg, the patient experienced abdominal pain, profuse diarrhea, nausea, and repetitive vomiting. Two boluses of physiological saline, ranitidine (50 mg), ondansetron (8 mg), and methylprednisolone (60 mg) were administered intravenously. Loperamide (4 mg) was also given orally. The patient developed marked pallor and dizziness. His vital signs remained stable at all times. Three hours after the onset of symptoms, and despite all the medications given, profuse diarrhea persisted. A blood sample revealed no relevant abnormalities other than a hemoglobin concentration of 18 g/dL, which was consistent with dehydration secondary to loss of liquids. The patient was transferred to the emergency room, where he only received another bolus of physiological saline. His condition gradually improved, and he was discharged after 2.5 hours of observation.

A blood test performed at a follow-up visit 2 days later revealed hemoglobin 15.4 g/dL, tryptase 3.2 µg/dL, negative serum specific IgE for amoxicillin, ampicillin, ceftacor, and penicillin G and V, and total IgE of 496 kU/L (ImmunoCAP, Thermo Fisher Scientific). Analysis of stool samples taken 24 and 48 hours after the DPT with amoxicillin-clavulanic acid were sent for determination of eosinophil cationic protein (ECP) and revealed 77.4 and 50 µg ECP/g feces, respectively. Six weeks later, measurement of ECP in a further 2 stool samples taken on 2 different days yielded results of 1.8 and 2.1 µg ECP/g feces, respectively.

Finally, in order to rule-out cross reactivity with other β-lactams, a DPT was performed with penicillin V and G, both of which were well tolerated.

DIES is an uncommon and probably underreported non–IgE-mediated hypersensitivity reaction provoked by drugs. Its clinical presentation is very similar to that of food protein–induced enterocolitis syndrome (FPIES) [1-5]. Extrapolating the criteria of the 2017 International Consensus Guidelines for FPIES [5] to the present case shows that the patient fulfills the major criterion (vomiting in the 1- to 4-hour period after ingestion of the suspected drug and absence of classic IgE-mediated allergic skin or respiratory symptoms) and 5 of the 9 minor criteria (repetitive vomiting after ingestion of the same drug, marked pallor, need for emergency department visit, need for intravenous fluid support, and diarrhea in the 24 hours following ingestion of the suspected drug) [6]. Increased neutrophil count is a common finding after positive food challenge in FPIES and has also been described in 4 of the reported cases of DIES. Neutrophils usually peak 6 hours after ingestion of the trigger [6]. In the present case, the patient’s blood was collected 3 hours after taking a therapeutic dose, possibly prior to the peak.

To our knowledge, out of the few cases of DIES reported [1-5], this is the second to involve amoxicillin-clavulanic acid [3]. DPT was carried out successfully with penicillin in only 2 of the published cases [2,5] and with cefpodoxime in 1 [5]. We confirmed that the patient tolerated penicillin, thus enabling us to prohibit only aminopenicillins and cephalosporins with the same side chain as amoxicillin (cefaclor, cefalexin, cefadroxil, and cepfrotil) and to allow all other β-lactam antibiotics.

In all of the reported cases, the DPT was performed close in time to the initial reaction, although in the case we
In summary, we report a case of DIES induced by amoxicillin-clavulanic acid in an adult patient with good tolerance to penicillin. Assessing tolerance to penicillin is important in the management of such uncommon cases in order to avoid unnecessary restrictions of all β-lactam antibiotics.

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**Conflicts of Interest**

Dr. Sánchez-Morillas reports personal fees from Sociedad Madrid-Castilla La Mancha de Alergología e Inmunología Clínica and from Alk-Abelló outside the submitted work.

Dr. González-Gutiérrez reports personal fees from Sociedad Madrid-Castilla La Mancha de Alergologia e Inmunologia Clinica and from GSK and Teva outside the submitted work.

Dr. Cimarro reports personal fees from Sociedad Madrid-Castilla La Mancha de Alergología e Inmunología Clinica and from Novartis and ALK outside the submitted work.

Dr. Cerecedo reports consultancy fees from Diater, Leti, ALK, and Stallergenes outside the submitted work and personal fees from Sociedad Madrid-Castilla La Mancha de Alergologia e Inmunologia Clinica, and grants from the Spanish Government (ISCIII). Dr. Cerecedo holds a patent (PCT/ES2014/070634).

Dr. Fernández-Rivas reports grant from the European Commission and the Spanish Government (MINECO, ISCIII) and personal fees from Aimmune, ALK-Abelló, Allergy Therapeutics, Fundación SEAIC, HAL, Thermo Fisher Scientific, Schreiber Foods, and DBV outside the submitted work. Dr. Fernández-Rivas also holds a patent (PCT/ES2014/070634).

The remaining authors declare that they have no conflicts of interest.