Drug-Induced Enterocolitis Syndrome due to Amoxicillin-Clavulanic Acid with good tolerance to Penicillin.

Short title: Enterocolitis to Amoxicillin-Clavulanic

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0500

Key words: Drug Induced Enterocolitis Syndrome. Amoxicillin-Clavulanic Acid. Drug Provocation Test. Eosinophil Cationic Protein.

Palabras clave: Amoxicilina-clavulánico. Proteína catiónica del eosinófilo. Provocación con medicamentos. Síndrome de enterocolitis inducida por fármacos.

Drug Induced Enterocolitis Syndrome (DIES) is a non-IgE mediated hypersensitivity reaction caused by a medication. To our knowledge, there are currently very few reported cases, all involving aminopenicillins [1-5]. We report a new case with the intention of raising awareness of this clinical entity, to accurately diagnose and manage patients with this condition.

We present an 18 years-old man who came to our clinic referring vomits in relation with intravenous infusion of amoxicillin-clavulanic acid and metamizole in the perioperative phase of an acute appendicitis when he was 9 years-old. The following allergological study was carried out with the written consent of the patient.

Skin prick (PT) and intradermal (ID) tests were performed with penicilloil-poly-lysine (PPL), minor determinant (MD) and clavulanic acid at the concentrations commercially available (Diater), and 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). All skin tests performed were negative, and the patient was submitted to a drug provocation test (DPT) with amoxicillin-clavulanic acid. Two and a half hours after having received a therapeutic dose of 500/125 mg (cumulative dose amoxicillin 875 mg/clavulanic acid 218.75 mg), the patient presented epigastric pain, dizziness, nausea and one vomit. A bolus of physiological saline solution, ranitidine and

doi: 10.18176/jiaci.0500

ondansetron were administered intravenously with complete resolution of symptoms in 2.5 hours.

On a different daymetamizole was studied. PT at 400 mg/ml and ID at 4 and 10 mg/ml gave negative results, and the patient was submitted to a DPT with metamizole that was well tolerated.

Three weeks later, with the impression that the digestive symptoms presented during the DPT with amoxicillin-clavulanic acid were non-specific, PT and ID were repeated for betalactamic drugs being once again, all negative. A DPT with amoxicillin-clavulanic acid was performed and 1.5 hours after having received a therapeutic dose of 500/125 mg, the patient presented abdominal pain, profuse diarrhea, nausea and repetitive vomits. 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. Vitals remained stable at all times. Three hours after the onset of symptoms and despite all the medications given, the patient persisted with profuse diarrhea. A blood sample was obtained with no relevant alterations other than a hemoglobin of 18 g/dL consistent with dehydration secondary to loses. He was transferred to the emergency room where he only received another bolus of physiological saline. He progressively improved and was discharged after 2.5 hours of observation.

The patient came back for follow up two days later, a blood test was carried out with hemoglobin being 15.4 g/dL, tryptase was 3.2 mcg/dL, serum specific IgE was measured for amoxicillin, ampicillin, cefaclor, penicillin G and V being all negative with a total IgE of 496 kU/L (ImmunoCAP, Thermofisher Scientific). Stool samples from 24 and 48 hours after the DPT with amoxicillin-clavulanic acid were sent for eosinophil cationic protein (ECP) measurement being 77.4 and 50 mcg ECP/g feces,

doi: 10.18176/jiaci.0500

respectively. Six weeks later, in basal conditions, ECP was measured on other two stool samples taken on two different days, being 1.8 and 2.1 mcg ECP/g feces, respectively.

Finally, in order to rule-out cross reactivity with other betalactams, a DPT was performed with Penicillin V and G, being 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 our patient, he complies with the major criterion (vomiting in the 1-4 h period after ingestion of the suspected drug and absence of classic IgE-mediated allergic skin or respiratory symptoms), and 5 out 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 h following the ingestion of the suspected drug) [6].Increased neutrophil count is a common finding after positive food challenge in FPIES, also described in 4 of the reported cases of DIES. Neutrophils usually peak 6 hours after ingestion of the trigger [6]. Our 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 2nd involving amoxicillin-clavulanic acid [3], and only in two of the published patients a DPT was carried out successfully with penicillin [2, 5] and cefpodoxime [5]. In our patient, the penicillin tolerance was also confirmed. This enabled us to prohibit only aminopenicillins and cephalosporins with the same side chain as amoxicillin (cefaclor, cefalexin, cefadroxil and cefprozil), allowing all other betalactamic antibiotics.

All reported cases had the DPT performed close in time to the initial reaction, but our patient had a 9 year interval between the first reaction and the positive DPT. In FPIES

doi: 10.18176/jiaci.0500

periodic re-evaluations are recommended to assess if the patient is still reactive. Rates of resolution of FPIES vary considerably, but many resolve after a few years [6]. We do not know whether this applies to DIES, but our case shows persistence over time.

It is worthy of note, that all the reported cases of DIES involve amoxicillin with or without clavulanic acid [1-5]. Compared to penicillin these drugs increase the intestinal motility of the small intestine [9], and are associated with higher frequency of gastrointestinal side effects, including diarrhea [10]. However, the gastrointestinal symptoms presented by our patient are suggestive of a DIES with an underlying specific immune mechanism. This is supported by the onset after the intake of the first therapeutic dose, the severity of the reaction, and the presence of elevated ECP in stools, in line with the described activation of eosinophils in FPIES [7,8].

In summary, we report a case of DIES induced by amoxicillin-clavulanic acid in an adult patient with a good tolerance to penicillin. Assessing the tolerance to penicillin is of importance in the management of these uncommon patients in order to avoid unnecessary restrictions of all betalactam antibiotics.

Previous Presentation

This case report was presented as a poster in the International Symposium: Avances y Perspectivasen Alergia Cutánea e Inmunología, organized by the SEAIC in Gran Canaria, Spain, Oct 23-26, 2019.

doi: 10.18176/jiaci.0500

Funding

This study was supported by Instituto de Salud Carlos III (ISCIII) co-founded by FondoEuropeo de Desarrollo Regional – FEDER for the ARADyAL research network (RD16/0006/0009).

Conflicts of Interest

Dr. FreundtSerpadeclares no conflicts of interest.

Dr. Sánchez-Morillas reports personal fees from Sociedad Madrid-Castilla La Mancha de Alergología e InmunologíaClínica; personal fees from Abelló, outside the submitted work.

Dr. Jaqueti Moreno declares no conflicts of interest.

Dr. González-Gutiérrez reports personal fees from Sociedad Madrid-Castilla La Mancha de Alergología e InmunologíaClínica; personal fees from GSK and Teva, outside the submitted work.

Dr. Cimarra reports personal fees from Sociedad Madrid-Castilla La Mancha de Alergología e InmunologíaClínica; personal fees from Novartis and ALK, outside the submitted work.

Dr. Cerecedo reports personal fees from Diater, Leti, ALK, Stallergens, and from Sociedad Madrid-Castilla La Mancha de Alergología e InmunologíaClínica, outside the submitted work.

Dr. Fernández-Rivas reports grant from European Commission, grants from Spanish Government (MINECO, ISCIII); personal fees from Aimmune, ALK, Allergy Therapeutics, Fundación SEAIC, HAL, Thermofisher Scientific, Schreiber foods, DBV,

doi: 10.18176/jiaci.0500

outside the submitted work. Dr. Fernández-Rivas has a patent PCT/ES2014/070634 issued.

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