Anaphylaxis to Clavulanic Acid: A 7-Year Survey

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Clavulanic acid (CLV) is a β-lactam antibiotic with weak antibacterial activity, although it is a potent inhibitor of β-lactamases. The combination amoxicillin-CLV (AX-CLV) is widely used in clinical practice, and while most allergic reactions are due to amoxicillin [1,2], some allergic reactions to CLV may be selective. CLV was initially considered to have low immunogenicity, but in 1995, Fernandez-Rivas et al [3] reported the first 2 cases of selective anaphylaxis to CLV. Since then, other case reports showing selective hypersensitivity to CLV have been published [1,2,4-8].

Skin prick tests (SPTs) and intradermal tests (IDTs) followed by drug provocation testing (DPT) are the main diagnostic methods used to confirm hypersensitivity after immediate allergic reactions to β-lactams [9]. The purified CLV extract for testing (DAP Clavulanic, Diater) has been commercially available since 2012.

Hypersensitivity reactions to CLV are usually restricted to the skin, although rare anaphylactic reactions, some of which may be life-threatening, can occur [1-5,7]. Therefore, anaphylaxis to CLV must be carefully studied and selective hypersensitivity to CLV evaluated, since when confirmed, it enables the use of amoxicillin and other penicillins [1,7,8]. Nevertheless, studies on anaphylaxis to CLV are scarce.

The aim of this study was to evaluate and describe the frequency and clinical characterization of case reports of anaphylaxis to CLV based on the drug allergy work-up in patients with anaphylaxis caused by AX-CLV.

The study population comprised patients aged ≥6 years who were referred to the Drug Allergy Center of CUF-Descobertas Hospital, Lisbon, Portugal with suspected anaphylaxis to AX-CLV over a 7-year period (January 2011 to June 2018). Clinical data with a detailed description of symptoms and circumstances of the reaction were collected in the clinical history. The diagnostic procedures followed the recommendations of the European Network of Drug Allergy/ European Academy of Allergy and Clinical Immunology [9,10].

Skin tests were performed using solutions of benzylpenicilloyl octa-L-lysine (PPL) and sodium benzylpenilloate (minor determinant [MD]) (DAP Penicillin, Diater), penicillin G, amoxicillin, and cefuroxime. Solutions were prepared daily. In patients with suspected anaphylaxis to CLV, skin tests with purified CLV extract (DAP Clavulanic, Diater) were also performed. Other β-lactams (penicillin derivatives and cephalosporins) were tested according to suspicion. SPTs were the first step of investigation. If these were negative, IDTs were carried out with increasing dilutions until the appearance of a positive skin response or until the maximum concentration was reached (purified extracts of PPL 5×10^{-5} mM, MD 2×10^{-2} mM, amoxicillin 20 mg/mL, and CLV 20 mg/mL) [10]. Histamine (10 mg/mL) was used as positive control for SPT and 0.9% saline solution as a negative control. First readings were taken after 15 and 20 minutes for SPT and IDT. Skin tests were performed at least 4 weeks after the clinical reaction.

Patients underwent DPT with the culprit drug when SPTs and IDTs were negative. In those where SPTs and IDTs were selectively positive for CLV, DPT was performed with amoxicillin in a stepwise manner (increasing every 20 to 30 minutes) until the therapeutic dose was reached (maximum of 1 g of amoxicillin and 125 mg of CLV). All tests were performed by allergists with experience in recognition and management of acute reactions.

During this 7-year period, we identified 6 confirmed cases of anaphylaxis to CLV. Data on clinical characteristics and the drug allergy work-up are shown in the Table. These patients represent 3.6% of all cases of drug-induced anaphylaxis (166 patients) and 9.7% of all cases of drug-induced anaphylaxis to β-lactams (62 patients) during the 7-year period. The other 56 patients with β-lactam anaphylaxis were distributed as follows: amoxicillin, 35; penicillin, 7; flucloxacillin, 3; cefazolin, 9; cefuroxime, 1; and cephradine, 1.

All 6 patients with anaphylaxis to CLV had the reaction immediately after intake of AX-CLV (within 60 minutes) and were admitted to the emergency department for treatment. The median (IQR) age at the anaphylactic episode was 35.5 (16-65) years, and 4 patients were female. They all had mucocutaneous manifestations associated with respiratory, gastrointestinal, or cardiovascular involvement.

The allergology work-up confirmed anaphylaxis to CLV by positive IDT results to CLV in 5 patients and positive DPT with CLV (after negative skin tests) in 1 patient who experienced an anaphylactic reaction after 25 mg of CLV, with a negative DPT result to amoxicillin.

Table. Clinical Characteristics of the 6 Patients With Confirmed Anaphylaxis to CLV

Sex	Atopy	Age, y[a]	Timing of Reaction	Reaction	Skin Tests	DPT
Female	AR	16	30 min after AX-CLV (first dose)	Generalized uticaria, palmar pruritus, nausea, facial and hand edema, abdominal pain	IDT positive to CLV 20 mg/mL (10-mm wheal), with palmoplantar pruritus and erythema	Amoxicillin (alternative DPT - negative)
Male	AR; AA	31	30 min after AX-CLV (first dose)	Generalized urticaria, facial edema, larynx edema, dyspnea	IDT positive to CLV 20 mg/mL (10.5-mm wheal)	Amoxicillin (alternative DPT - negative)
Female	AR	65	Less than 30 min after AX-CLV (first dose)	Tongue edema, larynx edema, dyspnea	IDT positive to CLV 20 mg/mL (13-mm wheal)	Amoxicillin (alternative DPT - negative)
Male	AR	40	60 min after AX-CLV (first dose)	Cutaneous pruritus, erythema, facial and lip edema, nausea, presyncope	IDT positive to CLV 5 mg/mL (10.5-mm wheal)	Amoxicillin (alternative DPT - negative)
Female	AR	17	Less than 30 min after AX-CLV (first dose)	Generalized urticaria, facial edema, vomiting, diarrhea	IDT positive to AX 20 mg/mL (25-mm wheal) IDT positive to CLV 20 mg/mL (15-mm wheal)	Cefuroxime (alternative DPT - negative)
Female	AR	45	20 min after AX-CLV (first dose)	Generalized urticaria, edema of limb extremities, dyspnea	SPT and IDT negative	Positive to CLV (culprit DPT) with anaphylaxis[b] Amoxicillin (alternative DPT - negative)

Abbreviations: AA, allergic asthma; AR, allergic rhinitis; AX-CLV, amoxicillin-clavulanic acid; CLV, clavulanic acid; DPT, drug provocation test; IDT, intradermal test; SPT, skin prick test.

[a]Age at anaphylaxis.

[b]Thirty minutes after a cumulative dose of 25mg of CLV, the patient experienced palmar pruritis, facial and hand erythema, intense abdominal pain, rhinitis and diarrhea, which resolved with intramuscular epinephrine 0.5 mg, an oral antihistamine (cetirizine 20 mg) and a corticosteroid (prednisolone 60 mg).

Of the 5 patients with positive IDT results to CLV, 4 had a negative IDT result with amoxicillin and other β-lactams and a negative DPT result with amoxicillin; 1 patient had a positive IDT result to both components, amoxicillin and CLV.

The 5 patients with confirmed selective hypersensitivity to CLV underwent an alternative DPT with amoxicillin in which the result was negative. These patients corresponded to 15.6% of the total of 32 patients who experienced anaphylaxis after administration of AX-CLV. The patient with hypersensitivity to both drugs underwent an alternative DPT with cefuroxime, although the result was negative.

Allergic reactions to β-lactams are the most frequent cause of IgE-mediated drug hypersensitivity [2,9]. The combination AX-CLV is increasingly implicated in clinical practice, and although amoxicillin is the main inducer, CLV can be the culprit drug [1-7]. To date, reports focusing on CLV-induced anaphylaxis are scarce. However, 2 large studies investigated selective hypersensitivity to amoxicillin and CLV [1,7], and 1 report provided data on 9 cases with selective hypersensitivity to CLV [2].

We evaluated a large group of patients with anaphylaxis to β-lactams and confirmed that 15.6% were selectively allergic to CLV (5 of 32 patients with anaphylaxis after taking AX-CLV). Consequently, they only need to avoid CLV and tolerate penicillin and its derivatives. Previous Spanish studies found a higher frequency of selective hypersensitivity to CLV, ranging from 29% [1] to 35% [7] of immediate allergic reactions (urticaria to anaphylaxis) after taking AX-CLV.

In conclusion, it is important to evaluate selective anaphylaxis to CLV. Our study shows that CLV can be responsible for anaphylaxis and that almost all cases of CLV anaphylaxis were IgE-mediated. In these situations, skin tests with purified CLV extract are very useful and must be included in the diagnostic work-up of anaphylaxis to AX-CLV. This approach enables the use of amoxicillin and other penicillins, which is important in daily clinical practice, as it provides patients with alternatives. It also has an impact on health care costs.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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