Anaphylaxis to clavulanic acid: seven-year survey

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

Skin prick tests(SPT) and intradermal tests (IDT) followed by drug provocation test (DPT) are the main diagnostic methods used to confirm hypersensitivity after immediate allergic reactions to β-lactams (9). The purified CLV extract (*DAP®Clavulanic, Diater, Madrid, Spain*) for testing isavailable commercially since 2012.

Hypersensitivity reactions to CLVare usually restricted to skin, but although rare anaphylactic reactions can occur (1-5,7), being potentially life-threatening. Therefore,anaphylaxisto CLV must be carefully studied and evaluating selective hypersensitivity to CLV is important, since when confirmed, 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 andclinical characterization of case reports of anaphylaxis to CLV, describing the drug allergy work-up activityperformed in patients with anaphylaxis to AX-CLV.

The authors included in this descriptive study a group of patients(more than six-year old)who were referred to Drug Allergy Center of CUF-Descobertas Hospital (Lisbon, Portugal) with suspected anaphylaxis toAX-CLV, over a seven-year period (January-2011 to June-2018). Clinical data with a detailed description of symptoms and circumstances of the reaction werecollected in clinical files. The diagnostic procedures followed the ENDA/ EAACI (*European Network of Drug Allergy / European Academy of Allergy and Clinical Immunology*)recommendations(9,10).

Skin tests were accomplished using solutions, daily prepared, of benzylpenicilloyloctа-L-lysine (PPL) and sodium benzylpenilloate - minor determinant (MD)(*DAP®Penicillin, Diater*), penicillin G, amoxicillin and cefuroxime. 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. SPT were the first step of investigation and, if negative, IDT were carried out with increasingdilutions,

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until appearance of positive skin response or until reaching the maximum concentration (purified extracts of PPL $5x10^{-5}$mM, MD $2x10^{-2}$mM, amoxicillin 20mg/mL and CLV 20mg/mL) (10). Histamine (10mg/mL) was used as positive control for SPT and 0.9% saline solution as 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.

The patients underwent DPT with the culprit drug, when SPT and IDT were negative. In those where SPT or IDT were positive selectively for CLV, a DPT with amoxicillin was performed. DPTwas made in stepwise manner (increasing each 20 to 30minutes) until reaching the therapeutic dose (maximum of amoxicillin 1g and CLV 125mg). All tests were performed by allergists, with experience in recognition and management of acute reactions.

During this seven-year period we identified 6 confirmed cases of anaphylaxis to CLV. Data on clinical characteristics and drug allergywork-up isshown in Table 1. This corresponds to 3.6% from the total of drug-induced anaphylaxis (166 patients during this seven-year period) and 9.7% from the total of drug-induced anaphylaxis to β-lactams (62 patients). The other 56 patients with β-lactamanaphylaxis were: amoxicillin-35, penicillin-7, flucloxacillin-3, cefazolin-9, cefuroxime-1 and cephradine-1.

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

The allergy workup confirmed anaphylaxis to CLV by positive IDT to CLV in five patients,and positive DPT with CLV (after negative skin tests) in one patient that havean anaphylactic reactionafter 25mg of CLV, being the DPT to amoxicillinnegative.

Regarding the five patients with positive IDT to CLV,four patients had negative IDT to amoxicillin and other β-lactams, and had negative DPT with amoxicillin; one patient had positive IDT to both components, amoxicillin and CLV.

The five patients with confirmedselective hypersensitivity to CLV performed an alternative DPT with amoxicillin that was negative, corresponding to 15.6% from the total of 32 patients that have anaphylaxis after administration of AX-CLV. The patient with hypersensitivity to both, amoxicillin and CLV, performed an alternative DPT with cefuroxime which 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 inclinical practice, and although amoxicillin is the main inducer, CLV can be the culprit drug (1-7).Until now, reports focusing in CLV-induced anaphylaxisarescarce.There are, however, two large studies that investigated selective hypersensitivity to amoxicillin and CLV (1,7) and one report of 9 caseswith selective hypersensitivity to CLV (2).

We have evaluated a large group of patients with anaphylaxis to β-lactamsand confirmed that 15.6% of them were selective allergic to CLV (5 from 32 patients with anaphylaxis after taking AX-CLV), which means they only need to avoid CLV and tolerate penicillin and its derivatives. Previousspanish studies have found a higher frequency of selective hypersensitivity to CLV accounting for 29% (1) to 35% (7) of the immediate allergic reactions (from 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 almost all cases of CLVanaphylaxis

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were IgE mediated. In these situations, skin tests with purified CLV extract have shown to be very useful and must be included in the work-up diagnosis of anaphylaxis to AX-CLV. This allows the use of amoxicillin and other penicillins which is important in daily clinical practice when offering alternative drugs to patients, having impact on healthcare costs.

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Table 1. Clinical characteristics of the 6 patients with confirmed anaphylaxis to CLV

Sex	Atopy	Age*	Timing of reaction	Reaction	Skin tests	DPT
F	AR	16	30 minutes after AX-CLV (firstdose)	Generalizeduticaria, palmar pruritus, nausea,facial and hands oedema,abdominal pain	IDT Positive to CLV 20mg/mL (10mm wheal), with palmoplantarpruritus and erythema	Amoxicillin (alternativeDPT - negative)
M	AR; AA	31	30 minutes after AX-CLV (firstdose)	Generalizedurticaria, facial oedema, larynx oedema, dyspnea	IDT Positive to CLV 20mg/mL (10.5mm wheal)	Amoxicillin (alternativeDPT - negative)
F	AR	65	Less 30minutes after AX-CLV (firstdose)	Tongue oedema, larynx oedema, dyspnea	IDT Positive to CLV 20mg/mL (13mm wheal)	Amoxicillin (alternativeDPT - negative)
M	AR	40	60 minutes after AX-CLV (firstdose)	Cutaneous pruritus, erythema, facial and lip oedema, nausea,presyncope	IDT Positive to CLV 5 mg/mL (10.5mm wheal)	Amoxicillin (alternativeDPT - negative)
F	AR	17	Less 30 minutes after AX-CLV (firstdose)	Generalizedurticaria, facial oedema, vomiting, diarrhea	IDT Positive to AX 20mg/mL (25mm wheal) IDT Positive to CLV 20mg/mL (15mm wheal)	Cefuroxime (alternativeDPT - negative)
F	AR	45	20 minutes after AX-CLV (firstdose)	Generalizedurticaria, oedema of limb extremities, dyspnea	SPT and IDT negative	Positive toCLV (culpritDPT) with anaphylaxis ** Amoxicillin (alternativeDPT - negative)

*Age at anaphylaxis. ** Thirty minutes after cumulative dose of 25mg of CLV, the patient had palmar pruritis, facial and hands erythema, intense abdominal pain, rhinitis and diarrhea, which resolved with intramuscular epinephrine 0,5mg, and oral antihistamine (cetirizine 20mg) and corticosteroid (prednisolone 60mg).
AA: allergic asthma; AR: allergic rhinitis; AX-CLV: Amoxicillin-clavulanic acid; CLV: clavulanic acid; DPT: drug provocation test; F: feminine; IDT: intradermal test; M: masculine; SPT: skin prick test.

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