Delayed selective reaction to clavulanic acid: a case report

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Summary. Clavulanic acid, an inhibitor of beta- lactamases, is widely used for antimicrobial therapy in association with beta-lactam antibiotics. Despite this, very few adverse reactions to the molecule have been described so far. We report a case of not-immediate reaction to clavulanic acid in a young adult who previously tolerated it. The patient complained of generalized itchy erythema two days after completing a course of amoxicillin-clavulanate therapy, and had no previous clinical history of adverse reactions to drugs. Intradermal and skin prick tests with beta-lactam determinants were negative, as well as the oral tolerance test with amoxicillin. Since no commercial preparation of clavulanic acid alone is available, we performed intradermal and skin prick test with the association amoxicillin-clavulanate, that elicited a delayed (24 and 48 hours) response. IgE-mediated reactions to clavulanic acid are rare, since this molecule is poorly allergenic. Based on the onset time and the specificity of the response we hypothesize that a delayed (possibly T-cell mediated) reaction has occurred.

Key words: Clavulanic acid, amoxicillin, beta-lactams, drug reaction.

Introduction

Clavulanic acid (CLA), derived from *Streptomyces clavuligerus* has a beta-lactam structure resembling that of the penicillin nucleus. Although it has only a weak antibacterial activity, it is a potent "suicide" inhibitor of bacterial beta-lactamases [1]. CLA is largely used in medical practice in association with beta-lactams, amoxycillin (AX) in particular. Nevertheless, despite the large use of the drug very few immediate allergic reaction to CLA have been reported so far, all due to an IgE mediated reaction [2-4]. In this report we describe a case of a not-immediate (delayed in time) reaction to CLA.

A 34-year-old woman received a 7-day course of AX/CLA (875/125 mg) for intercurrent dental surgery. Two days after stopping the treatment she complained of generalized itchy erythema. This reaction disappeared within a few days, with the administration of oral cetirizine (10 mg) and methylprednisolone (8 mg). Her clinical history was negative for adverse drug reactions, and she had previously received AX/CLA on several occasions without any problem. The personal and family history of atopic diseases was negative as well. Skin prick test (SPT) performed with a panel of common aeroallergens (including dust mites, cat and dog epithelia, grasses, parietaria, olive, birch, hazelnut and moulds) provided negative results.

As diagnostic workup, prick (SPT) and intradermal (ID) tests were performed with benzylpenicilloil poly-L-lysine, minor determinant mixture (MDM) (Allergopen; Allergopharma, Hamburg, Germany), and AX at 2 and 20 mg/ml. The results of these test were all negative. Moreover IgE specific to benzylpenicilloyl and phenoxymethylpenicilloyl, AX an ampicillin (CAP-System, Pharmacia) were negative. No late reactions were observed after ID and after a patch test with penicillin and AX. Subsequently an oral tolerance test with AX up to 1 g was also carried out without any reaction. For these reasons we suspected a selective reaction to CLA. Since no pharmaceutical preparation of CLA alone is available in Italy, we performed the SPT and ID test with an association of AX/CL (50/10 mg) at various dilutions (Table 1). No immediate reaction was elicited, whereas a late (24 and 48 hours) positive response appeared. The SPT and ID tests,

Table 1. Diagnostic tests.

Test	20'	24 h	48 h
PPL			
SPT	Negative	Negative	Negative
ID	Negative	Negative	Negative
MDM			
SPT	Negative	Negative	Negative
ID	Negative	Negative	Negative
AX 1 mg			
SPT	Negative	Negative	Negative
ID	Negative	Negative	Negative
AX 2 mg			
SPT	Negative	Negative	Negative
ID	Negative	Negative	Negative
AX 20 mg			
SPT	Negative	Negative	Negative
ID	Negative	Negative	Negative
AX/CL 50/10 mg			
SPT 1:10	Negative	3 x 2 mm	4 x 4 mm
ID 1: 10	Negative	4 x 3 mm	5 x 4 mm
SPT	Negative	4 x 5 mm	5 x 4 mm
ID	Negative	7 x 5 mm	7 x 5 mm
AX 50 mg			
SPT	Negative	Negative	Negative
ID	Negative	Negative	Negative

carried out with the same procedure in 10 healthy subjects to exclude irritative reactions, provided negative results.

We describe one case of not-immediate reaction after oral intake of a commercial preparation of AX/CLA, and showed a selective sensitivity to CLA. The results of SPT to benzylpenicilloyl-polylysine, minor determinant mixture, benzylpenicillin and AX, as well as RAST response to penicilloyl G and V and AX were negative, and the patient tolerated oral AX. However, skin response to AX/CLA was positive, thus our patient reacted exclusively to CLA. IgE-mediated reactions to CLA are rare, since this molecule is *per se* poorly immunogenic and allergenic [5], and not-immediate reactions have never been described. Based on the selectivity of the event and its time of onset we hypothesize that a delayed (possibly T-cell mediated) reaction has occurred. Nevertheless, neither could we establish the mechanism that was the determinant(s) causing the reaction. In this regard, CLA metabolism originates various products, but in this case they were not cross-reactive with the determinants of benzylpenicillin. As the only prevention measure, both the patient and her physician were advised to avoid the use of drugs containing clavulanic acid.

References

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