

Hypersensitivity to clavulanic acid in children

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ABSTRACT

We present 10 cases (6 males and 4 females) of children aged 4 to 12 years, who were diagnosed with allergy to clavulanic acid (CL) and treated in the Paediatric Allergy Section of the University Hospital Dr. Peset in Valencia from 2000 to 2005. The children reported symptoms of urticaria and angio-oedema after receiving orally-administered amoxicillin/clavulanic acid (A-CL) for an infection. Diagnosis was based on the confirmation of an IgE-mediated aetiology by an oral challenge test with amoxicillin-clavulanic acid. Following negative skin test results and CAP for penicilloyl G and V, amoxicillin, ampicillin and cefaclor < 0.35 KU/l, those patients who were allergic to clavulanic acid (positive oral challenge test) were shown to be tolerant to orally-administered Cefuroxime axetil.

Key words: Hypersensitivity. Clavulanic acid. Children.

INTRODUCTION

Beta-lactam antibiotics are commonly prescribed drugs and allergic reactions to them have been reported frequently. Their common molecular structure is the beta-lactam ring, which is linked to a second ring of varying structure.

Clavulanic acid is a beta-lactamic antibiotic with a potent inhibitory action against beta-lactamases, but with poor antibacterial activity. In clinical practice it is associated with amoxicillin, which has a potent antimicrobial activity. Studies carried out up to now indicate that clavulanic acid deteriorates into unstable metabolites that have a low immunogenicity character and few cases of allergies to this compound, either delayed¹ or immediate² reactions have been reported.

In our outpatient clinic, it is not possible to determine IgE specific to clavulanic acid, nor to make an intradermal test with clavulanic acid alone, because there is no commercial compound available containing only this molecule. Furthermore, at the moment there is no standard test to clavulanic acid and the sensitivity of specific IgE when this test is available is low.

However, in the last years there have been a number of reports of allergy to clavulanic acid in the combination clavulanic acid-amoxicillin. It is important to distinguish this kind of allergy because of the clinical implications of an amoxicillin allergy diagnosis.

The aim of this study was to describe several cases of clavulanic acid allergy in children who had previously tolerated amoxicillin, the process of diagnosis and the therapeutical alternatives that we proposed. Although it is known that a clear cross-reactivity between A-CL and cefuroxime axetil does not exist, it was decided to use TPO with cefuroxime axetil in

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order to cover a similar spectrum of action with the A-CL. All the children included in the study tolerated amoxicillin subsequently without problems.

OBJECTIVES

To present a series of cases of children who experienced an adverse reaction suggestive of IgE-mediated hypersensitivity following oral administration of amoxicillin/clavulanic acid, and in whom a hypersensitivity to clavulanic acid was identified.

PATIENTS AND METHODS

A retrospective descriptive study of children diagnosed with allergy to clavulanic acid ($n = 10$) in the Paediatric Allergy Section of the University Hospital Dr. Peset, in Valencia (Spain), from 2000 to 2005.

In order to diagnose the patients we designed a protocol consisting of the following: complete medical history; complementary examination (after receiving informed consent from parents/tutors): haemogram; total IgE; specific IgE (CAP-System) to amoxicillin, ampicillin, penicilloyl G, V and cefaclor; Skin prick test (SPT) 10 mg/ml and intradermal (ID) Test 1mg/ml (0.02 mL) for beta-lactams (PPL, MDM, amoxicillin, ampicillin, amoxicillin/clavulanic acid (A-CL)) and cefuroxime prick and Intradermal-reaction (ID) 2 mg/ml.

Children were considered to be allergic to A-CL when they demonstrated a reaction to this drug, which can be IgE-mediated, that was immediate or delayed. The specific IgE (CAP-System) was considered to be positive when greater than 0.35 KUA/l. Skin Prick tests were considered positive with a wheal of 3mm diameter which appeared after 15-20 min. with a negative response obtained from the saline control (0.9 % saline) and a positive response from the histamine. In the patients in whom an intradermal-reaction (ID) was carried out, the size of the wheal was recorded prior to and 20 minutes after the test. Results were considered positive when an increase in the wheal diameter (5 mm) was observed. The skin tests were measured at 15-20 minutes (immediate reaction), 6-8 hours (semi-delayed reaction) and 48-72 hours (delayed reaction). In order to establish a criterion for specificity and to rule out irritant reactions in the skin tests with A-CL, we used 20 healthy controls each paired in age and gender with one of our patients, and in whom the skin tests gave negative results for the same concentrations used for the diagnosis of our series of cases.

In the cases where it was indicated (negativity in the previous tests), the Oral Tolerance Test (OTT) was performed with orally-administered amoxicillin at gradually increasing doses (1/100 of the therapeutic dose, 1/10 of the therapeutic dose and the therapeutic dosage in the hospital, at intervals of 1 hour, (to evaluate immediate and accelerated reactions), and the therapeutic dose was subsequently recommended to be taken at home every 12 hours for 7 days (to evaluate delayed reactions). Subsequently, OTT was performed with A-CL, following the same method as described previously. The children's parents were warned that, in case of reaction, they should discontinue the medication and self-administer an oral antihistamine and/or a corticoid, and consult our team. The OTT was considered positive if an adverse reaction became evident (urticaria and/or angio-oedema, maculopapular exanthema, multiform erythema, etc.) during the course of the treatment or once the treatment was terminated. Such adverse reactions occurred during the first 30 minutes following the oral administration; therefore all the cases were considered to be immediate reactions. Subsequently, the patients tolerated amoxicillin without any evidence of adverse reaction.

In those cases with positive oral challenge to A-CL, an OTT was carried out with orally-administered cefuroxime axetil following the method described above, once negative results had been obtained with a CAP-SYSTEM study for cefaclor and skin test for cefuroxime.

RESULTS

From 2000 to 2005, 10 children with allergy to clavulanic acid (6 males and 4 females) aged 4 to 12 years, were treated in the Paediatric Allergy Section at the Dr. Peset University Hospital, in Valencia. Their clinical symptoms were urticaria, angio-oedema or urticaria-angio-oedema. These symptoms appeared in all the patients immediately after oral administration of the drug. To conduct the study it is necessary to collect sufficient and accurate data with respect to clinical symptoms and the chronological relationship between the administration of the drug and the symptoms.

If the medical history is suggestive of a reaction due to hypersensitivity, once the patient has been informed (and his/her parents or guardians) of the possible risks associated and their consent subsequently obtained, the allergy test may be performed. Skin tests must be evaluated for immediate (1-45 min, an average of 20 min), accelerated (8 hours) and delayed (48-72 hours) reactions.

In our 10 patients we found immediate reactions to A-CL in children who had previously tolerated the same compound. These patients complained of urticaria or urticaria-angio-oedema some hours after A-CL therapy had been initiated.

In all cases, specific IgE testing, prick-testing and the ID test for beta-lactam agents were negative. Cases ($n = 10$) proved to be tolerant to oral administration of doses of 50 mg/kg/day of amoxicillin over 7 days. As clavulanic acid in its isolated form was not available, we performed the prick and ID tests for A-CL in all cases. After the negativity of the skin test was demonstrated, the patients received oral A-CL (50mg/kg/day), where the reactions previously mentioned were revealed. In accordance with findings published by other authors, we found that there was not an added risk among patients with a history of reactions to other drugs. The patients tolerated amoxicillin without any evidence of adverse reaction.

DISCUSSION

A reliable diagnosis is complicated, on the one hand by the difficulty in finding a preparation that contains exclusively clavulanic acid for performing the skin tests, and on the other hand due to the lack of in vitro tests for detecting specific IgE that are valid for this molecule. In this way, diagnosis is based on the exclusion of sensitivity to amoxicillin after having a reaction to A-CL. In such circumstances we can speculate that the clavulanic acid molecule is responsible for the reaction.

The response to the skin test decreases 10 % annually after the allergic reaction and 78 % of patients with previous reactions to penicillin give negative results in skin tests performed after 10 years of having avoided this medication. In our series of cases, the period of time between the reaction and the performing of the test was approximately a year, which leads one to believe that the results of the skin tests were accurate, and made it not necessary to repeat the skin tests one month after provocation to rule out false negatives.

Faced with a diagnosis of allergy to clavulanic acid, it is necessary to find alternative therapies that cov-

er the antimicrobial spectrum of the A-CL combination. The cross-reactivity between penicillin and cephalosporin is estimated to be 10 % for first generation cephalosporins and 1-3 % for third generation cephalosporins³. In our case, we recommended orally-administered cefuroxime-axetil following a negative result in skin tests and determination of specific IgE for cefaclor, due to the lack of availability of specific IgE for cefuroxime. Therefore, given the similar spectrum of action of clavulanic acid and cefuroxime-axetil in those infections for which clavulanic acid tends to be the first option, the latter medication may be prescribed as an alternative^{4,5}.

Due to the null cross-activity of clavulanic acid with other beta-lactamases, once tolerance to amoxicillin is confirmed, we can recommend the selective avoidance of clavulanic acid.

In summary, we highlight that: 1) although allergy to clavulanic acid is infrequent, this molecule should be held in suspicion when studying the cause of an adverse reaction to amoxicillin/clavulanic acid. 2) we could confirm hypersensitivity to clavulanic acid by a positive oral challenge to amoxicillin-clavulanic acid and amoxicillin tolerance after that. 3) Given the negligible cross-reactivity of clavulanic acid with other beta-lactamases, it is not necessary to forbid the rest of the antibiotics that belong to the same family.

REFERENCES

1. Kamphof WG, Rustemeyer T, Bruynzeel DP. Sensitization to clavulanic acid in Augmentin. *Contact Dermatitis*. 2002;47:47.
2. Raison-Peyron N, Messaad D, Bousquet J, Demoly P. Selective immediate hypersensitivity to clavulanic acid. *Ann Pharmacother*. 2003;37:1146-7.
3. Romano A, Guéant-Rodriguez RM, Viola M, Pettinato R, Guéant JL. Cross-Reactivity and Tolerability of Cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Int Med*. 2004;141(1):16-22.
4. Ponvert C, Weilenmann C, Wassenberg J, Walecki P, Bourgeois ML, De Blic J, Scheinmann P. Allergy to betalactam antibiotics in children: a prospective follow-up study in retreated children after negative responses in skin and challenge tests. *Allergy*. 2007;62(1):42-6.
5. González de Olano D, Losada Peña A, De la Hoz Caballer B, Vázquez González AC, Diéguez Pastor MC, Cuevas Agustin M. Selective sensitization to clavulanic acid and penicillin. *J Invest Allergol Clin Immunol*. 2007;17(2):119-21.