CASE REPORT

Selective Sensitization to Clavulanic Acid and Penicillin V

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Abstract

Allergic reactions to ß-lactam antibiotics have been reported frequently and may occur because of sensitization to unique haptens or to determinants shared with other drugs. A woman who received 1 tablet of amoxicillin–clavulanic acid developed wheals and flares although she had previously tolerated the same preparation well. Levels of specific immunoglobulin (Ig) E to penicillin V, penicillin G, amoxicillin, and ampicillin were undetectable. Skin tests to amoxicillin, penicillin major determinant and minor determinant mixture were negative. The patient tolerated oral challenge with 500 mg of amoxicillin but developed wheals and flares when challenged with amoxicillin–clavulanic acid 500/125 mg. A histamine release test was negative with amoxicillin but positive with the amoxicillin–clavulanic acid and clavulanic acid. A prick test to the combination was positive. Specific IgE to penicillin V later became positive while remaining negative to other ß-lactams. No inhibition was obtained using penicillin V against clavulanic acid and amoxicillin but was complete when penicillin V was used in the solid-phase and as the inhibitor. No cross-reactivity was proven between these sensitizations.

Key words: Amoxicillin. ß-lactams. Clavulanic Acid. Penicillin V. Sensitization.

Resumen

Las reacciones alérgicas frente a betalactámicos han sido frecuentemente descritas y pueden producirse por sensibilización selectiva a un hapteno o a determinantes comunes con otros fármacos. Una mujer comenzó con erupción de habones pruriginosos tras la administración de un comprimido de amoxicilina–clavulánico, pese a que previamente había tolerado dicho fármaco sin incidencia. Los niveles de inmunoglobulina (Ig) E específica frente a penicilina V, penicilina G, amoxicilina y ampicilina fueron indetectables. Las pruebas cutáneas frente a amoxicilina, determinantes mayores y menores de penicilina fueron también negativas. La paciente toleró 500 mg de amoxicilina, pero comenzó con erupción de habones pruriginosos tras la administración de amoxicilina–clavulánico 500/125 mg. El test de liberación de histamina fue negativo frente a amoxicilina, pero positivo frente a amoxicilina–clavulánico y frente a ácido clavulánico. La prueba cutánea con amoxicilina–clavulánico fue positiva. La IgE específica frente penicilina V fue positiva posteriormente, manteniéndose negativa frente al resto de betalactámicos. No se objetivó inhibición enfrentando penicilina V frente a ácido clavulánico y amoxicilina, pero se obtuvo una inhibición completa utilizando la penicilina V como fase sólida y como inhibidor.
No se demostró reactividad cruzada entre ambas sensibilizaciones.

Palabras clave: Ácido Clavulánico. Amoxicilina. Betalactámicos. Penicilina V. Sensibilización.

Introduction

ß-lactam antibiotics are among most widely prescribed drugs and allergic reactions to them have been reported frequently. Their common molecular structure is the ß-lactam ring, which is linked to a second ring of varying structure. Side rings may also be attached. Allergic reactions may occur because of sensitizations to unique haptens or to determinants shared with other drugs [1,2]. Cross-reactivity between ß-lactams has been widely described.

We report the case of an adverse reaction after the intake of amoxycillin–clavulanic acid.

Case Description

A 46-year-old woman received a capsule of amoxycillin–clavulanic acid (500/125 mg) (Augmentine, GlaxoSmithKline SA, Madrid, Spain) 3 months before attending our clinic. She reported that 30 minutes after intake of the first tablet, she

started developing itching, wheal, and flares, which were first located on her groins and armpits but which spread over her entire body surface within a few minutes. She had previously taken the same drug several times with good tolerance. Her medical history included nasal polyposis and allergy to *Anisakis simplex* with a specific immunoglobulin (Ig) E titer of 50.4 kU/L from a serum total IgE of 620 kU/L.

We performed radioallergosorbent tests (CAP System, Pharmacia, Uppsala, Sweden) for specific IgE to penicillin V, penicillin G, amoxicillin and ampicillin with negative results to all of them. Skin prick tests (SPT) and intradermal tests to amoxicillin, penicillin major determinant (penicilloyl polylysine), and penicillin minor determinant mixture (Diater, Madrid, Spain) were also performed with negative results.

After giving informed consent in writing, the patient also underwent oral challenge with progressively increasing doses of amoxicillin up to 500 mg with no reaction. We then decided to challenge with Augmentine. Ten minutes after a half capsule of the 500/125 mg formulation, itching and generalized wheal and flare formation started. Symptoms were relieved by administration of adrenaline, steroids and antihistamines.

We carried out a histamine release test (HRT) with an automated fluorometric method [3] with Augmentine 3.2, 16, 80, and 400 µg; amoxicillin 3.2, 16, 80, and 400 µg and clavulanic acid (Beecham, Toledo, Spain) 1.6, 8, 40, and 200 µg. HRT was negative with amoxicillin but positive with Augmentine with a 10%, 10%, 11%, and 20% release and also positive with clavulanic acid with a 10%, 10%, 11%, and 26% release over the baseline value, with a release greater than 10% considered positive. The SPT to Augmentine 100/20 mg/mL was positive (negative in 5 control subjects). We also performed SPTs to cloxacillin, tazobactam, and sulbactam with negative results (at 25 mg/mL of all drugs).

At a visit 2 months later, specific IgE determinations to penicillin V, penicillin G, amoxicillin, and ampicillin were performed again. In 2 consecutive tests the penicillin V determination was positive (1.05 kU/L and 0.95 kU/L respectively) whereas the others remained negative. SPTs to amoxicillin, penicillin major determinant and minor determinant mixture, and penicillin V were also performed again, with negative results. A CAP inhibition assay (Pharmacia) was then carried out using the commercial penicillin V as the solid-phase allergen and 10 µg of clavulanic acid and 10 µg of amoxicillin as inhibitors. No significant inhibition was obtained. In contrast, using penicillin V as the solid-phase allergen and 10 µg of penicillin V as inhibitor, we observed complete inhibition. When oral challenge was proposed, our patient refused.

Discussion

ß-lactam antibiotics are highly reactive with proteins and can haptenate carrier macromolecules. Allergy to these drugs is a frequent problem in clinical practice, concerning 0.7% to 8% of treated patients [4]. The antigenicity of these drugs is related to the chemical structure of various molecules and of their constituent parts, but mainly of benzylpenicilloyl [4]. Different degrees of cross-reactivity among the classes of ß-lactams have been established [5,6], though a selective allergic response to other ß–lactams has also been proposed [1-7].

Clavulanic acid is a ß-lactam antibiotic produced by *Streptomyces clavuligerus* that has weak antibacterial activity. It is also a ß-lactamase inhibitor and is usually combined with amoxicillin to overcome ß-lactam resistance. It differs from penicillin in its second ring, which is an oxazolidine instead of the thiazolidine ring of penicillins. In spite of the wide use of ß-lactams, and particularly of amoxicillin–clavulanic acid, only a few cases of adverse reactions have been reported, supporting the assertion that clavulanic acid has low immunogenicity [8]. In most of the adverse reactions reported, type I sensitization has been demonstrated in vitro, with HRT and in human-serum albumin-conjugated clavulanic acid [3], and in vivo with SPT [10-12]. A delayed-type sensitization has only been reported once [13]. In our patient, allergy to clavulanic acid was demonstrated with specific-IgE antibody levels, SPT, HRT, and oral challenge. In order to determine whether the oxazolidine ring was responsible for the adverse reaction, we performed an SPT with cloxacillin, a drug that contains this ring. We also did SPTs with the other ß-lactamase inhibitors, obtaining negative results in all the SPTs. Thus, the oxazolidine ring was excluded as the epitope responsible for sensitization, consistent with previous reports [9-12].

After the allergy work-up, our patient developed sensitization to penicillin V (phenoxymethylpenicillin), in which the phenyl acetic acid of benzylpenicilloyl is replaced by the phenoxymethyl side chain. Few cases of sensitization to penicillin V have been reported [14,15]. Though it was not possible to prove the clinical importance in vivo, the detection of specific IgE antibodies to penicillin V and the results of the CAP-inhibition assay suggest selective sensitization to penicillin V. No cross-reactivity was found with other ß-lactam drugs, including clavulanic acid. Although SPTs have shown higher sensitivity than CAP in detecting IgE antibodies, cases of sensitization with a positive CAP determination and negative SPT have also been reported [14,15]. We support the hypothesis that the patient developed this new sensitization after oral challenges with amoxicillin and clavulanic acid. The possibility of a false positive result should be also taken into account since it was not possible to perform an oral challenge. Nevertheless, specific IgE quantification has proven highly specific in this context [16-18] and these assays were performed twice for penicillin V; a false positive, therefore, is unlikely.

We have reported a case of IgE-mediated sensitization to clavulanic acid with clinical manifestations and sensitization to penicillin V demonstrated by specific IgE antibodies but with unknown clinical relevance. No cross-reactivity between these sensitizations was proven. Therefore, different epitopes might be involved. To our knowledge, no cases of selective sensitization to different ß-lactam drugs have been reported until now.

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