Tolerance to Cephalosporins and Carbapenems in Penicillin-Allergic Patients

Sánchez de Vicente J, Gamboa P, García-Lirio E, Irazabal B, Jáuregui I, Martínez MD, Segurola A, Seras Y, Galán C
Servicio de Alergia, Hospital Universitario Cruces, Osakidetza, Barakaldo, Spain

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Allergy to penicillins is the most frequent drug hypersensitivity reaction. A diagnosis of allergy to ß-lactams often leads to the use of broad-spectrum antibiotics as an alternative, with an increased risk of developing antimicrobial resistance and adverse effects and increased health costs [1]. Hence, we think that it is of paramount importance to offer penicillin-allergic patients safe options with other ß-lactams in order to avoid those risks. This paper reports our results after testing tolerance to cephalosporins and carbapenems in a large series of patients with confirmed penicillin allergy.

We included 137 patients with a history of immediate reaction (<1 hour) to any penicillin and penicillin allergy confirmed either by positive skin test results with at least 1 of the penicillin reagents (n=132) or negative skin test and specific IgE results to penicillins, but a positive oral challenge test result with the causative drug (n=5).

Skin tests were based on the concentrations recommended by the European Network on Drug Allergy [2]. Prick tests were performed first, followed by intradermal tests when the prick test result was negative. The substances tested were penicilloyl-polylysine 5×10^{-5} mM (PPL) (Diater SA), minor determinant mixture (MDM) 2×10^{-2} mM (Diater SA), amoxicillin 20 mg/mL (Normon), cefuroxime 2 mg/mL (Normon), ceftriaxone 2 mg/mL (Fresenius Kabi SAU), and imipenem-cilastatin 0.5 mg/mL (Fresenius Kabi SAU). Prick tests and intradermal tests were also carried out with the causative drugs: penicillin G 10 000 IU/mL (ERN SA), ampicillin 20 mg/mL (Normon), and clavulanic acid 20 mg/mL (Diater SA).

Specific IgE against penicillin G, penicillin V, ampicillin, and amoxicillin was determined using ImmunoCAP (Thermo Fisher). Values higher than 0.35 kU/L were considered positive.

Challenge tests with cefuroxime 500 mg (po), ceftriaxone 1 g (iv), and imipenem 1 g (iv) were carried out in all patients with negative skin test results to these drugs. Each of the challenge tests was performed on a different day. Cefuroxime was administered in 2 doses of 250 mg separated by half an hour. Ceftriaxone and imipenem were administered

intravenously dissolved in 100 mL of saline over 1 hour. In all cases, patients were monitored at the hospital for 1 hour after completing the challenge test and instructed to report as soon as possible any eventual delayed reaction within the following day.

We studied 137 patients (79 women) (mean [SD] age, 51 [14] years), who presented with anaphylaxis (n=51) or urticaria/angioedema (n=86) within 1 hour after administration of a penicillin (124 patients with amoxicillin or amoxicillin-clavulanic acid, 7 cases with penicillin G, 1 with ampicillin, 2 with amoxicillin and ampicillin, 1 with amoxicillin and cefuroxime, and 2 unknown).

Positive skin test results were observed with ß-lactams (1 with cefuroxime, 1 with ceftriaxone, 27 with PPL, 11 with MDM, and 116 with amoxicillin).

Positive sIgE (>0.35 kU/L) was observed in 28 patients (24 with penicillin G, 23 with penicillin V, 21 with ampicillin, and 28 with amoxicillin).

The oral challenge with amoxicillin was positive in 5 patients with negative skin test results.

Skin test results were negative with cefuroxime in 136 patients, with ceftriaxone in 136 patients, and with imipenem in 46 patients.

A challenge test was carried out with cefuroxime in 136 patients and with ceftriaxone in 125 patients (the remaining patients with negative skin test results refused to undergo the challenge test). Only 46 patients were challenged with imipenem (as we decided to include the latter for challenge tests in the last year); the skin test was negative and tolerance good in all cases.

Cross-reactivity between penicillins and cephalosporins is frequent only with aminocephalosporins (cephalexin, cefaclor, cefadroxil) and cefamandole, given that they share the same side chain as penicillins [3,4]. Cross-reactivity with other cephalosporins such as cefuroxime and ceftriaxone, as well as carbapenems, is infrequent [5-9]. Cross-reactivity between cephalosporins and between cephalosporins and other ß-lactams was recently reviewed [7]. In our series of 137 patients, only 1 patient who had experienced reactions to both amoxicillin and cefuroxime had a positive skin test result to cefuroxime, which was tolerated in the remaining cases. Besides, only 1 patient had a positive skin test result with ceftriaxone. Tolerance was good in the 125 patients tested.

For many patients, a diagnosis of penicillin allergy implies the prohibition of all ß-lactam antibiotics owing to the risk of cross-reactivity. This often leads to the use of alternative second-line drugs, with the risk of increasing bacterial resistance and health care costs [1].

Articles published to date collectively bring together a total of 465 patients with penicillin allergy who tolerated cephalosporins such as cefuroxime and ceftriaxone, as well as carbapenems (imipenem, ertapenem, meropenem) (n=459), with a risk of cross-reactivity lower than 1% [6-9]. Adding the data from our series, we can affirm that the risk of cross-reactivity with these drugs in penicillin-allergic patients is practically nonexistent when skin test results are negative.

In summary, data from published case series and our own data support the recommendation for open use of cefuroxime, ceftriaxone, and carbapenems in patients with penicillin allergy and negative skin test results with these drugs. Previous exposure tests should be unnecessary.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Pedro M Gamboa
Hospital Universitario Cruces
Servicio de Alergia
Plaza de Cruces s/n
48903 Barakaldo, Spain
E-mail: pedromanuel.gamboasetien@osakidetza.eus

