Tolerance to cephalosporins and carbapenems in penicillin allergic patients

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

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

Skin tests were made with the concentrations recommended by the ENDA [2]. First, prick tests were performed, followed by intracutaneous tests in case of negative prick-tests. Substances tested were penicilloyl-polylysine 5 x 10^{-5} mM (PPL) (Diater SA, Madrid, Spain), minor determinant mixture (MDM) 2 x 10^{-2} mM (Diater SA, Madrid, Spain), Amoxicillin 20 mg/ml (Normon, Barcelona, Spain), Cefuroxime 2 mg/ml (Normon, Barcelona, Spain), Ceftriaxone 2 mg/ml (Fresenius Kabi SAU, Barcelona, Spain), and Imipenem-Cilastatin 0.5 mg/ml (Fresenius Kabi SAU, Barcelona, Spain). Prick-tests and intracutaneous tests were also carried out with the causative drugs: Penicillin G 10,000 IU/ml (ERN SA, Barcelona, Spain), Ampicillin 20 mg/ml (Normon, Barcelona, Spain), Clavulanic Acid 20 mg/ml (Diater SA, Madrid, Spain).

Specific IgE against penicillin G, penicillin V, ampicillin and amoxicillin was performed by ImmunoCAP (Thermo-Fisher, Uppsala, Sweden). Values higher than 0.35 kU/L were considered positive.

Challenge tests with Cefuroxime 500 mg (p.o.), Ceftriaxone 1 g (i.v.) and Imipenem 1 g (i.v.) were carried out in all subjects with negative skin tests to these drugs. Each of the challenge tests was made on a different day. Cefuroxime was administered in two doses of 250 mg separated by half an hour. Ceftriaxone and Imipenem were administered intravenously dissolved in 100 ml of saline and run in one hour. In all cases, the patients were monitored at the hospital for one hour after completing the

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challenge test, and they were instructed to communicate as soon as possible any eventual delayed reaction within the following day.

We studied 137 patients (79 women) (age 51 ± 14 years), who presented with anaphylaxis (n = 51) or urticaria/angioedema (n = 86) within one hour after the administration of penicillins (124 patients Amoxicillin or Amoxicillin-Clavulanic, 7 cases Penicillin G, 1 Ampicillin, 2 Amoxicillin and Ampicillin, 1 Amoxicillin and Cefuroxime, and 2 unknown).

132 patients had positive skin tests with betalactams (1 Cefuroxime, 1 Ceftriaxone, 27 PPL, 11 MDM, 116 Amoxicillin).

28 patients showed positive sIgE (> 0.35 KU/L) (24 Penicillin G, 23 Penicillin V, 21 Ampicillin, 28 Amoxicillin).

5 patients with negative skin tests had a positive oral challenge with Amoxicillin.

136 patients had negative skin tests with Cefuroxime, 136 with Ceftriaxone and 46 patients, negative skin tests with Imipenem.

Challenge test was carried out with Cefuroxime in 136 patients, and also with Ceftriaxone in 125 patients (the remaining patients with negative skin tests did not accept the challenge test); only 46 patients were challenged with Imipenem (as we decided to include the latter for challenge tests in the last year), all of them with negative skin tests, and good tolerance in all cases.

Cross-reactivity between penicillins and cephalosporins is frequent only with aminocephalosporins (cephalexin, cefaclor, cefadroxil) and cefamandole, given the fact that they share the same side chain as penicillins [3,4]. Cross-reactivity with other cephalosporins such as cefuroxime or ceftriaxone, as well as carbapenems, is infrequent [5-9]. The cross-reactivity between cephalosporins and between cephalosporins and other betalactams have been recently reviewed (7). In our series of 137 patients, only one patient who had reactions with both amoxicillin and cefuroxime showed a positive skin test to cefuroxime, with tolerance to it in the remaining cases. Besides, only one patient showed a positive skin test with ceftriaxone, with tolerance in the 125 patients tested.

The diagnosis of penicillin allergy implies for many patients the prohibition of all betalactam antibiotics due 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 rising health costs [1].

To date, different articles have been published that, collectively, bring together a total of 465 patients with penicillin allergy that tolerate the administration of cephalosporins such as cefuroxime and ceftriaxone, as well as different carbapenems (Imipenem, Ertapenem, Meropenem) (n=459) with a risk of cross-reactivity lower than 1 % [6-9]. Adding the data of our series, we can affirm that the risk of cross-reactivity

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with these drugs in patients allergic to penicillin, when they show negative skin tests to them, is practically non-existent.

In summary, the data from all the published series of patients and from our own data support the recommendation of the open use of cefuroxime, ceftriaxone and carbapenems in patients with penicillin allergy and negative skin tests with these drugs, without the need to perform previous exposure tests.

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