Cross-reactivity and tolerability of aztreonam and cephalosporins in subjects with a T cell–mediated hypersensitivity to penicillins

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Background: The few studies performed in adults with T cell–mediated hypersensitivity to penicillins have found a rate of cross-reactivity with cephalosporins ranging from 2.8% to 31.2% and an absence of cross-reactivity with aztreonam.
Objective: We sought to evaluate the possibility of using cephalosporins and aztreonam in subjects with documented delayed hypersensitivity to penicillins who especially require them.
Methods: We conducted a prospective study of 214 consecutive subjects who had 307 nonimmediate reactions to penicillins (almost exclusively aminopenicillins) and had positive patch test and/or delayed-reading skin test responses to at least 1 penicillin reagent. To assess cross-reactivity with cephalosporins and aztreonam and the tolerability of such alternative β-lactams, all subjects underwent skin tests with cephalexin, cefaclor, cefadroxil, cefuroxime, ceftriaxone, and aztreonam. Subjects with negative responses were challenged with the alternative β-lactams concerned.
Results: All subjects had negative skin test results to cefuroxime, ceftriaxone, and aztreonam and tolerated challenges. Forty (18.7%) of the 214 subjects had positive skin test responses to at least 1 aminocephalosporin. Of the 174 subjects with negative responses, 170 underwent challenges; 1 reacted to cefaclor.
Conclusions: These data demonstrate a rate of cross-reactivity between aminopenicillins and aminocephalosporins (ie, cephalexin, cefaclor, and cefadroxil) of around 20%, as well as the absence of cross-reactivity between penicillins and cefuroxime, ceftriaxone, and aztreonam in all subjects with T cell–mediated hypersensitivity to penicillins, almost exclusively aminopenicillins. Therefore these subjects could be treated with cefuroxime, ceftriaxone, and aztreonam. In those who especially require cephalosporin or aztreonam treatment, however, we recommend pretreatment skin tests because negative responses indicate tolerability. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Aztreonam, cephalosporins, challenges, cross-reactivity, nonimmediate reactions, penicillins, tolerability, skin tests*

Abbreviations used
MDM: Minor determinant mixture
TEN: Toxic epidermal necrolysis

Penicillins are the antibiotics that most frequently provoke hypersensitivity reactions mediated by a T-cell pathogenic mechanism, usually occurring more than 1 hour after drug administration (ie, nonimmediate).[1,2] The most frequent reactions are maculopapular or morbilliform exanthemas, particularly during treatment with amoxicillin or ampicillin. A T cell–mediated pathogenic mechanism has also been demonstrated in other nonimmediate reactions, such as acute generalized exanthematous pustulosis and toxic epidermal necrolysis (TEN).[3,4]

Studies performed since 1990 on samples of at least 30 subjects with a documented IgE-mediated hypersensitivity to penicillins have demonstrated a rate of positive responses to skin tests[5-8] or serum specific IgE assays[9] with cephalosporins ranging from 0% (0/41 subjects)[6] to 27.1% (73/269 subjects).[9] In some of these studies,[5-8] participants with penicillin allergy and negative skin test responses with cephalosporins, such as cephalexin, cefazolin, cefuroxime, ceftazidime, and ceftriaxone, underwent challenges with the cephalosporins concerned. Of a total of 241 subjects, only 2 in the study by Caimmi et al[8] reacted to cefuroxime.

In other studies[10-13] patients with penicillin allergy underwent challenges with cephalosporins, such as cefamandole, cephalexin, cefadroxil, and ceftriaxone, without performing skin tests with the cephalosporin concerned. The highest rate of positive challenges (38%) was observed in the study by Miranda et al,[12] who administered cefadroxil to 21 subjects allergic to amoxicillin.

As far as T cell–mediated hypersensitivity to penicillins is concerned, 5 studies assessed cross-reactivity with cephalosporins in a total of 240 adults with such hypersensitivity by performing delayed reading skin tests, patch tests, or both with cephalosporins and, in case of negative responses, challenges.[14-18] In these studies the rate of positive responses to cephalosporin allergologic tests ranged from 2.8% (2/71 subjects)[17] to 31.2% (5/16).[15]

Few studies have evaluated cross-reactivity with aztreonam in samples larger than 10 subjects with IgE-mediated hypersensitivity to penicillins, performing allergologic tests and challenges with it in a total of 297 such subjects.[19-22] In 2 of these studies,[19,20] 3 participants had positive allergologic test responses with aztreonam; 2 of them tolerated aztreonam challenges, whereas the third participant did not undergo the challenge. In

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these studies,[19-22] of a total of 294 subjects with negative skin test responses to aztreonam, 293 underwent challenges and tolerated them.

Four studies did not find any cross-reactivity with aztreonam in subjects with T cell–mediated hypersensitivity to penicillins.[14,16,18,23] Specifically, the largest of these studies[18] evaluated 97 subjects with such hypersensitivity by performing both patch tests and delayed-reading skin tests with aztreonam. None of these participants had positive responses to aztreonam allergologic tests; 72 of them underwent aztreonam challenges and tolerated them.

The present prospective study was conducted to evaluate the possibility of using cephalosporins and aztreonam in patients with a documented T cell–mediated allergy to penicillins. To address this question, a large group of such subjects was evaluated by using delayed-reading skin tests with cephalosporins (cephalexin, cefaclor, cefadroxil, cefuroxime, and ceftriaxone) and aztreonam to assess the cross-reactivity. Subjects with negative responses were challenged to ascertain whether negative responses could be a reliable indicator of the tolerability of these alternative β-lactams.

METHODS

Patient selection

We studied all participants older than 14 years who were recruited to the allergy units of the Complesso Integrato Columbus, Rome, Italy; Oasi Maria Santissima, Troina, Italy; and Istituto Dermopatico dell'Immacolata, Capranica, Italy between January 2000 and June 2014 because of histories of nonimmediate reactions to penicillins. The inclusion criterion was a positive patch test and/or delayed-reading skin test response to at least 1 penicillin reagent. An indication for cephalosporin or aztreonam treatment was not a criterion of inclusion. Exclusion criteria were pregnancy and severe cardiovascular, renal, or respiratory compromise. Before the study, all subjects received information about possible risks of allergologic tests, and written informed consent was obtained from each patient or the parents of those less than 18 years of age. The respective institutional review boards approved the protocol.

Skin and patch tests

On the first day, skin prick and intradermal tests were carried out with penicilloyl-polylysine (Allergopharma, Reinbeck, Germany), minor determinant mixture (MDM; Allergopharma), and benzylpenicillin (Grünenthal Pharma AG, Mitlödi, Switzerland). The final concentrations were 5×10^{-5} mol/L, 2×10^{-2} mol/L, and 10,000 IU/mL, respectively. Because Allergopharma ceased production of penicillin reagents, from July 2005, we used Diater S.A. (Madrid, Spain) reagents: penicilloyl-polylysine (final concentration, 1.07×10^{-2} mol/L) and MDM (benzylpenicillin, sodium benzylpenicilloate, and benzylpenicilloic acid; final concentration, 1.5 mol/L). Since May 2011, the composition of MDM has changed and now contains only sodium benzylpenicilloate.

Patch tests were also administered with benzylpenicillin, ampicillin, and amoxicillin (5% in petrolatum; F.I.R.M.A., Florence, Italy); piperacillin (at a concentration of 200 mg/mL in 0.9% NaCl) was also used in subjects with adverse reactions to it, as previously described.[24,25]

Two days later, ampicillin (Amplital, Pfizer Srl, Latina, Italy) and amoxicillin (Amoxil, GlaxoSmithKline, Brentford, United Kingdom), at concentrations of 1 and 20 mg/mL, after dilution in 0.9% NaCl, were used for skin prick and intradermal tests. Piperacillin (Piperital; Istituto Biochimico Italiano S.p.A., Aprilia, Italy) at concentrations of 1 and 20 mg/mL, after dilution in 0.9% NaCl was also used in subjects with adverse reactions to it, as previously described.[25]

In subjects with positive patch test responses to 1 or more of the aforementioned semisynthetic penicillins, only the concentration of 1 mg/mL was used.

On a different day, all subjects with positive patch and/or delayed-reading skin test responses underwent skin testing with aztreonam (Primbactam, Guidotti, Pisa, Italy), cephalexin (Keforal, Crinos S.p.A., Milan, Italy), cefaclor (Panacef, Valeas, Milan), cefadroxil (Duracef, Juste, S.A.Q.F., Madrid), cefuroxime (GlaxoSmithKline, Verona, Italy), and ceftriaxone (Fidia farmaceutici S.p.A., Abano Terme, Italy) at a concentration of 2 mg/mL in 0.9% NaCl. After June 2004, we used cephalexin, cefaclor, and cefadroxil at concentrations of 2 and 20 mg/mL in 0.9% NaCl.

For injectable compounds, we used the intravenous form under sterile conditions, whereas for noninjectable cephalosporins, we prepared a solution, as previously described.[26]

The concentrations used for cephalosporins proved to be nonirritating in previous studies.[26-32]

We also administered patch tests with cephalexin, cefaclor, and cefadroxil at 5% in petrolatum (F.I.R.M.A.).

In skin tests all reagents were initially tested on volar forearm skin by using the skin prick method, and reactions were considered positive when a wheal larger than 3 mm in diameter with surrounding erythema was present 20 minutes later. When skin prick test responses were negative, 0.02 mL of the reagent solution was injected intradermally on volar forearm skin, and readings were made at 20 minutes and 48 hours. Positive controls for skin prick and intradermal tests were performed with histamine (10 and 1 mg/mL, respectively); normal saline was used as a negative control, as previously described.[24]

Responses on intradermal tests were considered positive when an increase of greater than 3 mm in initial wheal diameter accompanied by erythema was present 20 minutes later.[33] Late reactions to intradermal tests were considered positive when an infiltrated erythema with a diameter of greater than 5 mm was present.[4]

In patch testing all reagents were applied to uninvolved skin on the interscapular region of the patient's back by using acrylate adhesive strips with small plates attached for test allergens (Curatest, Lohmann GmbH & Co. KG, Neuwied, Germany), as previously described.[24,25] Occlusion time was 48 hours. Readings of patch tests were made 15 minutes after removal of the strips and 48 hours later. Positive reactions were scored as follows: + (erythema, infiltration, possibly discrete papules), ++ (erythema, infiltration, papules, and vesicles), and +++ (intense erythema, infiltration, and coalescing vesicles).[4,33]

Aztreonam and cephalosporin controlled administrations (challenges)

In participants with negative allergologic test responses with the alternative β-lactams concerned, we performed controlled intramuscular administrations of therapeutic doses of aztreonam (1 g) and ceftriaxone (1 g), as well as oral administrations of cefuroxime axetil (500 mg), cephalexin (1 g), cefaclor (500 mg), and cefadroxil (500 mg), each on a different day and in the above order. We administered an initial dose of one hundredth of the therapeutic dose. In cases with negative responses, 1 week later, we administered a dose of one tenth and, if the responses were again negative, after another week a full dose, as previously described.[4,31,34] After the first 30 challenges with each β-lactams, we modified this workup, administering an initial dose of one tenth of the therapeutic dose, and if the response was negative, we administered a full dose 1 week later. After 30 additional challenges, we administered an initial dose of one tenth of the therapeutic dose, and, if the response was negative, we administered a full dose 1 hour later.

In case of a positive response to an aminocephalosporin, the other doses were not administered. Challenges with aminocephalosporins were not performed in subjects who had experienced TEN or acute generalized exanthematous pustolosis.

Patients were carefully monitored during all allergy testing and for 6 hours after challenges. They were also advised to return to show any positive responses.

Statistical analysis

We collected the data prospectively and analyzed them with Stata software (StataCorp, College Station, Tex). Our goal was to assess the cross-reactivity with cephalosporins and aztreonam and its potential determinants in patients