Tolerability of aztreonam and carbapenems in patients with IgE-mediated hypersensitivity to penicillins

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Background: Studies performed on samples larger than 100 subjects with a documented IgE-mediated hypersensitivity to penicillins have demonstrated a cross-reactivity rate of approximately 1% between penicillins and both imipenem and meropenem, whereas a single study found a cross-reactivity rate of 6.2% with aztreonam in 16 such subjects.
Objective: To assess the cross-reactivity and tolerability of aztreonam and 3 carbapenems (imipenem-cilastatin, meropenem, and ertapenem) in patients with documented IgE-mediated hypersensitivity to penicillins.
Methods: A total of 212 consecutive subjects with immediate reactions to penicillins and positive results on skin tests to at least 1 penicillin reagent underwent skin tests with aztreonam and carbapenems; subjects with negative results were challenged with escalating doses of aztreonam and carbapenems.
Results: All subjects displayed negative skin test results to both aztreonam and carbapenems; 211 accepted challenges and tolerated them. Challenges were not followed by full therapeutic courses.
Conclusions: These data indicate the tolerability of both aztreonam and carbapenems in penicillin-allergic subjects. In those who especially require these alternative β-lactams, however, we recommend pretreatment skin tests, both because rare cases of cross-reactivity have been reported and because negative results indicate tolerability. (J Allergy Clin Immunol 2015;135:972-6.)

Key words: *Aztreonam, cross-reactivity, ertapenem, imipenem, meropenem, penicillin allergy, skin tests, tolerability*

Together with cephalosporins, penicillins are the antibiotics that most frequently provoke hypersensitivity reactions mediated by specific immunological mechanisms. IgE-mediated reactions usually occur within 1 hour of the last drug administration (ie, immediate reactions) and are manifested clinically by urticaria, angioedema, rhinitis, bronchospasm, and anaphylactic shock.[1]

Aztreonam, the only monobactam available for clinical use, consists of a monocyclic β-lactam ring structure without adjoining rings (Fig 1). Early immunogenicity studies demonstrated that aztreonam antibodies are directed to the side chain rather than the β-lactam ring.[2,3] They also indicated that aztreonam is weakly immunogenic and does not significantly cross-react with penicillin or cephalosporin antibodies, except ceftazidime, with which it shares an identical side chain. This position is supported by the Joint Task Force on Practice Parameters.[4] Only 3 studies of more than 10 subjects with IgE-mediated hypersensitivity to penicillins (85 subjects in total) have evaluated cross-reactivity to aztreonam by performing allergologic tests and challenges with aztreonam.[5-7] In 2 of these studies,[5,6] 3 participants had positive results to allergologic tests with aztreonam. In the study by Vega et al,[6] 2 subjects with positive results to skin tests and serum specific IgE assays, respectively, underwent aztreonam challenges and tolerated them, while in the study by Moss,[5] 1 (6.2%) of the 16 patients with cystic fibrosis and allergic to semisynthetic penicillins had a positive skin test result to aztreonam and did not undergo a challenge.

Penicillins and carbapenems have a structural similarity regarding their bicyclic core, composed of a 5-membered ring attached to the β-lactam ring (Fig 1). Until the last decade, it was considered potentially harmful to administer carbapenems to patients with IgE-mediated hypersensitivity to penicillins,[4] because a single study[8] found that 47.4% (9 out of 19) of the subjects with positive skin test results to penicillin also had positive skin test results to imipenem, and none was challenged. Subsequent studies of ours—2 including only adults[9,10] and 2 including only children[11,12]—performed on samples larger than 100 subjects with a documented IgE-mediated hypersensitivity to penicillins have demonstrated a cross-reactivity rate of approximately 1% between penicillins and both imipenem and meropenem, on the basis of positive responses to carbapenem skin testing, without challenge confirmation, causing the alarm connected with a significant allergic cross-reactivity between penicillins and carbapenems to cease.[13] There are no published data concerning cross-reactivity with ertapenem in patients with IgE-mediated hypersensitivity to penicillins.

The present prospective study was conducted to evaluate the possibility of using aztreonam and carbapenems in patients with a documented IgE-mediated allergy to penicillins. To address this question, a large group of such subjects was evaluated by skin tests with aztreonam and carbapenems (imipenem-cilastatin, meropenem, and ertapenem) to assess the cross-reactivity. Subjects who displayed negative results were challenged to ascertain whether negative results could be a reliable indicator of the tolerability of these alternative β-lactams.

METHODS

Patient selection

Study subjects were recruited from the 290 total individuals, 15 years or older, who came to the allergy units of the Complesso Integrato Columbus,

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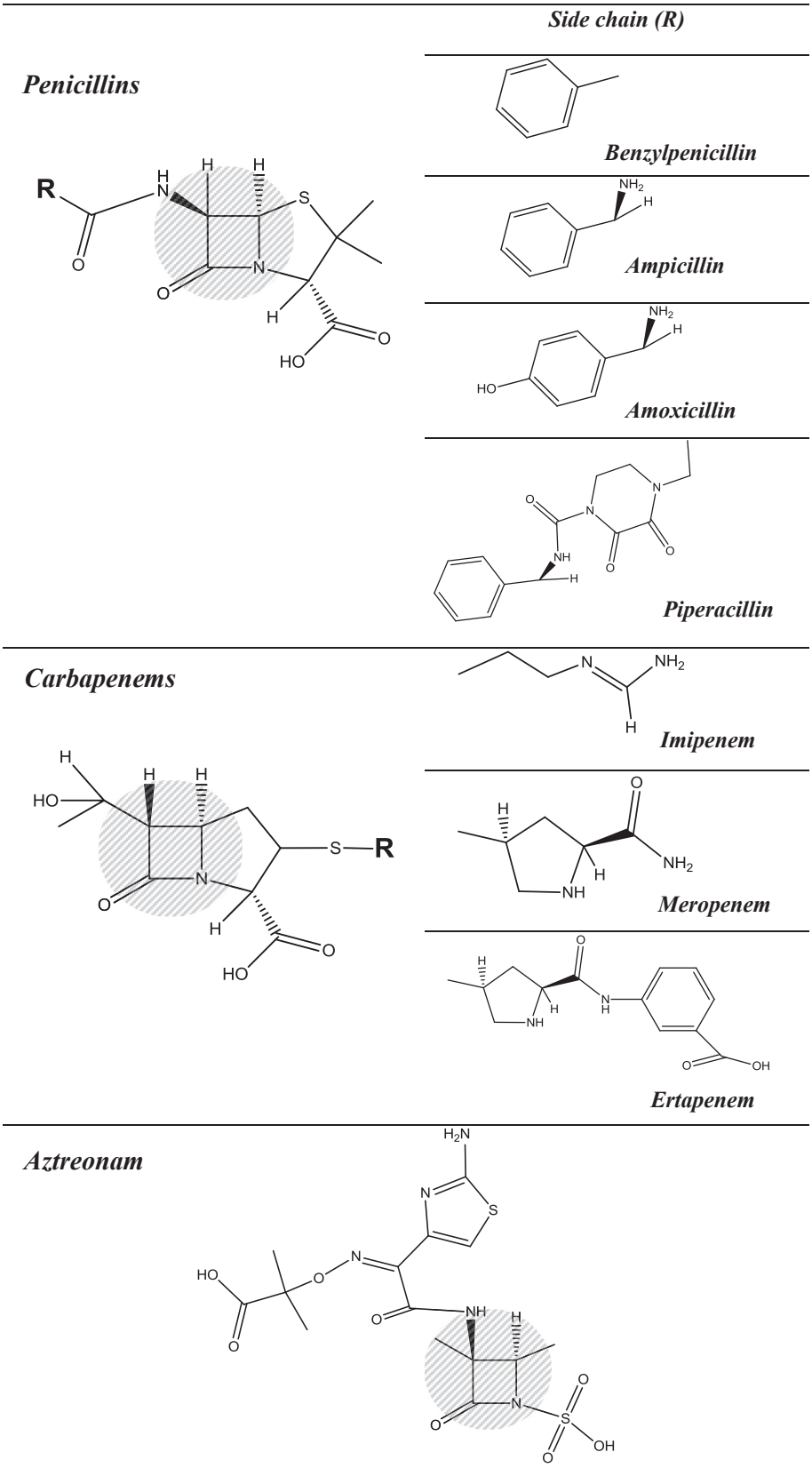

FIG 1. Chemical structures of penicillins, carbapenems, and aztreonam, with the common β-lactam ring highlighted in *gray*.