Cross-reactivity of beta-lactam antibiotics

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During a drug history, the most common drug allergies cited are those experienced after the administration of a penicillin, with a reported allergy incidence of 1% to 10% in patients who receive drugs in this class (1). Penicillins, as well as other beta-lactam antibiotics such as cephalosporins, carbapenems, and monobactams, contain a beta-lactam ring (2). The safety of administering beta-lactam antibiotics to penicillin-allergic patients is highly debated and is based mainly on anecdotal information regarding the incidence of cross-reactivity.

Another factor complicating safety is the validity of the reported allergy. For example, patients experiencing gastrointestinal upset with penicillin administration often mistakenly report this reaction as an allergy on subsequent interview. In addition, <20% of patients who report penicillin allergies have a positive result when given a penicillin skin test (3). However, Preston et al studied the accuracy of self-reported penicillin allergy at their institution (1). Patients enrolled in the study were determined to be allergic or intolerant through an interview conducted by a pharmacist. Of the 117 patients enrolled in the study who reported having a penicillin allergy, the majority (82.9%) were classified as having a true allergy, and 17.1% were classified as intolerant.

The purpose of this paper is to discuss the available data concerning the safety of administering cephalosporins, carbapenems, and monobactams to penicillin-allergic patients.

CEPHALOSPORINS

Penicillins contain a bicyclic nucleus, which includes the beta-lactam ring and a thiazolidine ring. Cephalosporins also contain a beta-lactam ring, but a dihydrothiazine ring replaces the thiazolidine ring in the bicyclic nucleus (2). Early case reports demonstrated a high incidence of in vitro cross-reactivity (up to 20%) between penicillins and cephalosporins (4). Cephalosporins involved in these reports included cephalothin and cephaloridine. Both agents are first-generation cephalosporins and have side chains similar to those of benzyl penicillin, which may explain the high incidence of cross-reactivity (3). However, at the time of these early studies, formulations of cephalothin and cephaloridine contained trace amounts of penicillin (4). Petz et al demonstrated a 4-fold increase in the incidence of cephalosporin reactivity—including cephaloridine, cephalothin, and cephalexin—in patients allergic to penicillins (8.1%) compared with patients not allergic to penicillins (1.9%) (5). When this incidence is compared with the overall incidence of allergic reactions to cephalosporins (4%), there is a 2-fold increase of reactivity in patients allergic to penicillins (4). The cross-reactivity of first- and second-generation cephalosporins with penicillin is higher than that of third-generation cephalosporins. This is thought to be due to the decreased immunogenicity associated with bulky side chains in the structure of the newer agents (2). The high in vitro cross-reactivity with penicillins and cephalosporins does not correlate with in vivo reactivity (6). Of 94 patients with positive penicillin skin tests who were subsequently administered a cephalosporin, only 1 patient experienced cross-reactivity manifested by bronchospasm and urticaria (6). If a cephalosporin is warranted in a penicillin-allergic patient, skin tests, test doses, and desensitization protocols may be used (7).

CARBAPENEMS

Carbapenems, including imipenem and meropenem, also contain a bicyclic nucleus with a beta-lactam ring (6). A review of cross-reactivity with beta-lactam antibiotics found a high degree of immunologic reactivity between penicillins and imipenem. Sixty patients underwent skin testing to antigenic determinants of penicillin and imipenem (8). Twenty of the 60 patients developed IgE-mediated responses to penicillin. Of these, 9 developed IgE-mediated responses to imipenem, for an overall cross-reactivity of 45%. One case report described an immediate hypersensitivity reaction to imipenem in a patient allergic to penicillin and aztreonam (9). The clinical relevance of this cross-reactivity is unknown. However, based on the magnitude of reactivity between the 2 agents, some authors recommend that imipenem not be administered to penicillin-allergic patients (2).

MONOBACTAMS

Aztreonam is a monobactam antibiotic that contains a beta-lactam ring. However, unlike other beta-lactam antibiotics, aztreonam does not contain a bicyclic-ring structure (6). To date, aztreonam has not demonstrated clinical cross-reactivity in penicillin-allergic patients (2, 8). Ceftazidime has a side chain identical to that of aztreonam, and clinical cross-reactivity has been demonstrated in vitro (8, 9). The clinical significance of this has

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not been studied; however, patients who are allergic to aztreonam should not be administered agents with similar side chains (9).

SUMMARY

Based on available information, our institution recommends that patients who report a penicillin allergy and are placed on a regimen containing a cephalosporin or imipenem should be interviewed again to determine the presence and nature of the allergic reaction. Patients who have experienced pronounced allergic reactions with penicillins—such as anaphylaxis, angioedema, or bronchospasm—should not receive therapy containing a cephalosporin or imipenem. Aztreonam may be safely administered to patients with a history of penicillin allergy. Caution is warranted, however, in patients who are allergic to ceftazidime and are subsequently placed on aztreonam therapy. In those cases, the patient should be observed closely during the administration of the first full dose of aztreonam.

1. Preston SL, Briceland LL, Lesar TS. Accuracy of penicillin allergy reporting. *Am J Hosp Pharm* 1994;51:79–84.
2. Shepherd GM. Allergy to beta-lactam antibiotics. *Immunology and Allergy Clinics of North America* 1991;11:611–633.
3. Phillips E, Louie M, Knowles SR, Simor AE, Oh PI. Cost-effectiveness analysis of six strategies for cardiovascular surgery prophylaxis in patients labeled penicillin allergic. *Am J Health Syst Pharm* 2000;57:339–345.
4. Anne S, Reisman RE. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. *Ann Allergy Asthma Immunol* 1995;74:167–170.
5. Petz LD. Immunologic cross-reactivity between penicillins and cephalosporins: a review. *J Infect Dis* 1978;137(Suppl):S74–S79.
6. Kishiyama JL, Adelman DC. The cross-reactivity and immunology of beta-lactam antibiotics. *Drug Saf* 1994;10:318–327.
7. Drugdex, vol 102. Englewood, Colo: Micromedex, edition expires December 1999.
8. Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. *Ann Intern Med* 1987;107:204–215.
9. Neftel KA, Cerny A. Beta-lactam antibiotics other than penicillins and cephalosporins. In Dukes MNG, ed. *Meyler's Side Effects of Drugs*, 12th ed. Amsterdam: Elsevier, 1992:632–634.