

Incidence of Resensitization after Tolerating Penicillin Treatment in Penicillin-Allergic Patients

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ABSTRACT

The incidence of resensitization to penicillin in patients with a history of penicillin allergy appears to be low but the approach to patients is controversial. We sought to determine the incidence of penicillin resensitization in patients with a history of penicillin allergy who had negative skin tests to penicillin determinants and received an initial uneventful course of β -lactam antibiotics. We identified 254 patients who had negative penicillin skin testing to the major and minor penicillin determinants from January 1, 1994 to October 1999 and then reviewed their hospital and/or clinic records to determine if the patient had received subsequent treatment with β -lactams or cephalosporins after the initial course of antibiotics. Of 254 patients, we were able to review 33/35 (94.3%) patients' charts to evaluate adverse reactions to the antibiotics. These 33 patients received a total of 77 subsequent courses of β -lactam antibiotics and 19 subsequent courses of cephalosporins. Thirty of the 33 patients (90.9%) received at least one course of a parenterally administered cephalosporin or β -lactam antibiotic. Seven of the 33 patients received only cephalosporin antibiotics. None of the identified patients had evidence of an immunoglobulin E-mediated reaction. Three of the 33 patients (9.1%) developed cutaneous skin eruptions during subsequent antibiotic treatment. Two of these three patients had subsequent uneventful treatment with β -lactam antibiotics. The third patient who developed a

nonblistering eruption underwent repeat penicillin skin testing, which remained negative. These data suggest that penicillin resensitization in previously allergic patients is very low and do not support the notion that penicillin skin testing should be performed before each subsequent course of β -lactam antibiotics. (Allergy and Asthma Proc 25:161–164, 2004)

It has been estimated that between 1 and 10% of patients report an allergy to penicillin.¹ Furthermore, hospitalized patients often report medication allergies. Approximately 25% of hospitalized patients who had an order written for an antimicrobial agent reported an allergy to at least one antimicrobial agent, with penicillin being the most common, reported by >15% of patients.² Eighteen to 68% of patients with a convincing history of an immediate allergic reaction to β -lactam antibiotics have immunoglobulin E (IgE) antibodies to the major and/or minor penicillin determinants.^{3,4} Therefore, generally, it has been accepted that β -lactam antibiotics should be given to penicillin-allergic patients only when there is a strong indication and no suitable alternatives are available or are feasible. These patients require penicillin skin testing and/or test dosing before the administration of any β -lactam antibiotics. If penicillin skin testing using both major and minor determinants is negative, the risk of an immediate IgE-mediated reaction is <1%.³ If epicutaneous or intradermal testing is positive, desensitization can be done by experienced physicians using one of the published protocols.^{5–8}

One area where there is some research but continuing controversy is the subsequent risk of resensitization after the penicillin-allergic patient has received an uneventful course of β -lactam antibiotics. Although four studies reveal low rates of resensitization with oral penicillin^{9–12} or no resensitization,¹³ a study by Parker *et al.* reported that 3 of 18 penicillin-allergic patients appeared to be resensitized as their skin tests to penicillin determinants became positive

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1–12 months after treatment with intravenous (i.v.) β -lactams.¹⁴ Although there is no standardized approach for the patient with a history of penicillin allergy, who has had negative penicillin skin tests and has tolerated an uneventful course of β -lactam antibiotics, one of the current approaches is penicillin skin testing and test dosing before each subsequent course of β -lactam antimicrobials. This practice is time-consuming, expensive, and may delay treatment. Retesting may be unnecessary if the actual rate of resensitization and potential for harm to patients is low. The purpose of this study was to determine the incidence of penicillin resensitization in patients with a history of penicillin allergy who had negative immediate skin tests to penicillin determinants and received an initial uneventful course of β -lactam antibiotics.

METHODS

We reviewed our division records, which have been recorded prospectively, of all the patients penicillin tested either in the hospital or as outpatients from January 1, 1994 to October 1999. At our institution, penicillin testing is done by percutaneous testing to benzyl-penicilloyl-polylysine (PrePen; Hollister Stier, Spokane WA) and the minor determinants benzyl-penicilloyl *n*-propylamine, sodium benzylpenicilloate, and potassium benzylpenicillin G (6000 units/mL). Skin tests were read at 20 minutes. If percutaneous testing was negative, intradermal testing to the same substances (0.01 mL) was done. A wheal of 4 mm with surrounding erythema was considered a positive result and testing was stopped. If intradermal testing was negative, a test dose of 1/1000 the prescribed dose was given, and if the patient tolerated this dose without difficulty, a full dose of the chosen β -lactam was given. A wheal of ≥ 4 mm without erythema was designated as an indeterminate result. A modified test-dose regimen was used in those patients.

Patients referred for penicillin testing were either seen at Northwestern Memorial Hospital, the Lakeside VA Hospital, or referred to the allergy clinic at the Northwestern Medical Faculty Foundation. A list of the patients with negative or indeterminate penicillin testing who had received an initial course of β -lactam antibiotics uneventfully at Northwestern Memorial Hospital was submitted to the pharmacy and, using a pharmacy database, a list of all subsequent antibiotics given to each patient while he/she was an inpatient was generated. After receiving approval from the Institutional Review Board, the inpatient charts of all the patients who had received subsequent penicillin or cephalosporin antibiotics were reviewed. For the patients initially evaluated at the Lakeside VA Hospital, the pharmacists were able to access the patient's medication profiles via the computerized pharmacy records to determine if subsequent penicillins or cephalosporins had been given to each patient. Then, the charts of these patients were reviewed. As for the patients referred to the Allergy Clinic, we reviewed the clinic charts of all the patients who had

undergone penicillin testing for evidence of subsequent administration of β -lactam or cephalosporin antibiotics. These charts could contain records from primary care physicians and/or specialists, depending on where the patient sought care. If there was any indication from the clinic chart that the patient had been hospitalized, the hospital chart also was reviewed.

All of the charts were reviewed for documentation of subsequent treatment with penicillins or cephalosporins, the number of doses of these antibiotics, evidence of untoward reactions (from progress notes, physical exams, and phone messages), and medications administered for a possible untoward reaction (*i.e.*, corticosteroids, antihistamines, etc.). A course of antibiotics was defined as the prescribed dose required to treat the underlying problem. This could be just a few days if the physician was waiting for culture results or a week, a month, a single dose (such as a single intramuscular injection or as prophylaxis on-call to the operating room), etc. If an antibiotic was changed, but the dosing remained continuous, as occurs when a patient is being changed from i.v. to oral antibiotics, it was considered one course.

Although it was assumed that the pharmacy database was an accurate account of the antibiotics prescribed to patients, we found it to be incomplete. There were some patients who we thought had received one course of subsequent antibiotics, but when the chart was reviewed, the patient had received additional courses of antibiotics.

RESULTS

There were 254 patients initially considered penicillin allergic (convincing or unknown history) who had negative or indeterminate penicillin skin testing followed by an initial course of penicillin or cephalosporin antibiotic. Of these 254 patients, 214 were evaluated while inpatients at Northwestern Memorial Hospital and 27 patients were evaluated in the allergy clinic. Thirteen were evaluated as inpatients at the VA hospital. Of the 254 patients, 35 patients (13.8%) received a documented subsequent course of penicillin or cephalosporin. Of these 35 patients, we were able to review the charts of 33 patients (94.3%). Overall, these 33 patients received 77 subsequent courses of β -lactam antibiotics and 19 subsequent courses of cephalosporin antibiotics. Of the 33 patients, 26 patients (78.8%) received their initial course of β -lactam or cephalosporin antibiotics via parenteral administration. In regard to subsequent cephalosporin or β -lactam administration, 7 of the 33 patients (21.2%) received subsequent cephalosporins only. Nineteen of the 33 patients (57.6%) received more than one subsequent course of β -lactam antibiotics. Thirty of the 33 patients (90.9%) had received at least one course of parenteral cephalosporin or β -lactam antibiotic.

None of the 33 patients had documentation or exam findings consistent with an IgE-mediated reaction. Aside from one patient with end-stage renal disease who devel-

oped pruritus without an eruption (see below), we found 3 patients (9.1%) who developed skin eruptions with the β -lactam antibiotics. The first patient was tested in our allergy clinic and tolerated an initial course of amoxicillin/clavulanate. Two years later, she again took amoxicillin/clavulanate, but this time she developed a fever of 101°F and erythematous pruritic eruption on her arms and legs on the 6th day of treatment. She denied any blisters or vesicular lesions. All of her medications including β -adrenergic antagonist were stopped. The eruption spontaneously resolved without requiring steroids. She was retested to penicillin determinants again, and her testing remained negative. The second patient also was seen in the allergy clinic. This patient developed a sparse, erythematous papular eruption on the 3rd day of her first subsequent course of amoxicillin, but 2.5 years later, she took a course of amoxicillin without difficulty. She had another course of amoxicillin 5 weeks later, and, again, she appears to have tolerated it without any untoward effects.

The third patient who developed a skin eruption with β -lactam antibiotics had a prolonged hospitalization of 10 months, and the allergy service examined her on multiple occasions. She was seen initially after she had developed an eruption to meropenem. She had negative penicillin skin testing and was started on piperacillin/tazobactam. After her third dose of piperacillin/tazobactam, she developed a morbilliform eruption. All antibiotics were stopped and she was treated with methylprednisolone. She received ceftazidime 3 months later, but this antibiotic was stopped after 6 days because fever but no skin eruption. The allergy service retested her to the penicillin major and minor determinants 5 months after the initial testing because she required high-dose ampicillin/sulbactam for vancomycin-resistant *Enterococcus* meningitis and bacteremia. Again, her skin tests were negative. She was treated with intrathecal ampicillin/sulbactam and high-dose i.v. ampicillin/sulbactam (30 g daily). She developed some self-limited erythema with this initial course of antibiotics, which did not require any systemic steroids. The erythema did not progress and eventually resolved, without the antibiotics being discontinued. The following month she was treated with a course of ampicillin/sulbactam and a course of oxacillin and she tolerated both of these antibiotics without difficulty. Two weeks later she was given seven doses of piperacillin and again developed a nonblistering, nonpruritic, erythematous papular skin eruption, which became petechial in appearance. She was receiving both piperacillin and levofloxacin at the time of the eruption, and both agents were discontinued. She did not require any corticosteroids for this eruption. Despite the multiple courses of β -lactam antibiotics, she never exhibited any evidence of an IgE-mediated reaction. Also, there was never any blistering lesions or evidence of Stevens-Johnson syndrome.

Six of the 33 patients (18.2%) were receiving oral steroids for other disease processes when they received the subsequent doses of β -lactams. The first of these six pa-

tients suffered from chronic idiopathic urticaria requiring hydroxyzine, 40 mg of prednisone (initially daily and then it was changed to every other day), and doxepin before and during one of her subsequent courses of ampicillin/sulbactam. This patient also complained of pruritus during another admission when she was given a dose of piperacillin, but no rash was documented. According to the progress notes, the house staff attributed the pruritus to her end-stage renal disease. This patient received a total of three subsequent courses of penicillins and one subsequent course of cephalosporin. The second patient was suffering from graft versus host disease requiring him to take varying doses of prednisone and diphenhydramine. He had four subsequent courses of penicillin derivatives and was taking corticosteroids and diphenhydramine with all of them. He had no evidence of any IgE-mediated reactions with any of these antibiotics. The third patient received one subsequent course of penicillin but also required hydrocortisone for adrenal insufficiency. The fourth patient was taking low-dose prednisone for her rheumatoid arthritis with both subsequent courses of cefazolin, but she tolerated the antibiotics without difficulty.

The fifth patient of this subset is a 30-year-old woman suffering from cystic fibrosis. She had a history of urticaria with ampicillin/sulbactam ~8 years before being penicillin skin tested. One year before penicillin testing, she was given meropenem and developed a single hive while the antibiotic was infusing. The infusion was stopped and she was given diphenhydramine without progression of the reaction. Initially, she was penicillin skin tested in October 1998 and had a positive intradermal reaction to the minor determinant sodium benzylpenicilloate. She subsequently became colonized with bacteria, which was sensitive to only β -lactams antibiotics; therefore, she was desensitized to piperacillin/tazobactam in April 1999. This initial antibiotic was changed to meropenem without a break in the dosing and she continued the antibiotic for 6 weeks in total. Since her desensitization in April 1999, she has had five more exacerbations requiring 4- to 6-week courses of meropenem/imipenem along with 2- to 3-week tapered courses of oral corticosteroids. She does not take daily β -lactam antibiotics between her courses of meropenem/imipenem and she has not had any evidence of resensitization despite having known IgE antibodies to penicillin.

The sixth patient received a liver transplant in February 1998. He tolerated the first subsequent course of piperacillin/tazobactam without difficulty. His second subsequent course of piperacillin/tazobactam (which was changed to meropenem without a break in the dosing) occurred shortly after his liver transplant. He was taking 30 mg of methylprednisolone daily and cyclosporin at this time. With his third subsequent course, he was still receiving methylprednisolone (20 mg daily) and cyclosporin, and he also was given one dose of i.v. γ -globulin for possible hemolysis. This patient was evaluated by the hematology service for possible hemolysis, but the penicillin was not implicated as a cause. He also received a fourth course of dicloxacillin as

an outpatient while he was taking prednisone, 10 mg daily, and, again, he tolerated the medication without any evidence of an allergy. In summary, of these six patients who were receiving systemic corticosteroids, there appeared to be no evidence of any IgE-mediated reactions or "masking" of an allergic reaction.

DISCUSSION

To our knowledge, this report is the largest series investigating penicillin resensitization in penicillin-allergic patients previously skin tested for penicillin allergy who received parenteral antibiotics. There was no evidence of IgE-mediated reactions with the subsequent readministration of β -lactam antibiotics. Thirty of the 33 patients (90.9%) received at least one course of antibiotic treatment *via* parenteral administration. Over 55% of our patients received multiple courses of penicillin antibiotics. One patient has had 15 subsequent courses of penicillins and cephalosporins (12 penicillin and 3 cephalosporins) without any allergic signs or symptoms. One patient had positive penicillin skin testing, underwent desensitization, and had five subsequent courses of meropenem/imipenem without any evidence of resensitization. Although it is difficult to draw conclusions from one patient, one could suspect she would be the most likely person to become resensitized because she already has IgE antibodies toward penicillin.

Of the three patients who developed skin eruptions with subsequent courses of penicillins, two patients were able to tolerate subsequent administration of penicillins without difficulty, and the third patient had repeat penicillin testing, which remained negative, suggesting that these eruptions were non-IgE mediated. There was no evidence of Stevens-Johnson syndrome in the three patients who developed skin eruptions.

Unlike a previous report,¹⁴ we did not find any increase in resensitization with *i.v.* administration of the antibiotics. In fact, two of the three skin eruptions occurred in patients who received oral antibiotics as both the initial and the subsequent courses of penicillin. One of the two patients was seen in the Internal Medicine Clinic at our institution and a physician evaluated the eruption. There is no physician documentation of the other patient's eruption.

Included in this study were seven patients who had been given cephalosporins as the initial or subsequent course of antibiotics. Although this is an area of great debate, it generally is accepted that there is some low-degree cross-reactivity of cephalosporins with penicillin antibiotics. One study indicates that penicillin-allergic patients are at no greater risk than the general population to suffer a reaction,¹⁵ while an article from the United Kingdom reported that four of six fatal anaphylactic reactions to cephalosporins occurred in patients with a history of penicillin allergy.¹⁶ For our analyses, we separated those patients who received only cephalosporin antibiotics from the patients who received β -lactam antibiotics.

The findings of this study do not support the notion that patients allergic to penicillin are at a high likelihood of

penicillin resensitization. The data suggest that once a course of parenteral (or oral) β -lactam antibiotic has been tolerated, subsequent generation of anti-penicillin IgE antibodies must be uncommon. None of the 26 patients who received one or more subsequent courses of penicillin (totaling 77 courses of penicillins) had any evidence of an IgE-mediated reaction. This is consistent with a 95% confidence interval of 0–11.1%. The results of this study in which patients received parenteral β -lactam or cephalosporins are similar to outpatients challenged with oral penicillins or cephalosporins.^{9–13} After an uneventful course of a β -lactam antibiotic, it would seem advisable to remove the designation of penicillin allergy from the medical records.

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