

Penicillin resensitization among hospitalized patients

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The purpose of this study was to determine the frequency of resensitization to penicillin after oral or intravenous treatment with β -lactam antibiotics in hospitalized patients with histories of penicillin allergy. Seventeen adults (aged 24 to 76 years) and one child (aged 10 years) were treated intravenously and/or orally with β -lactam antibiotics after negative skin tests were obtained with benzylpenicilloyl polylysine, potassium penicillin G, and alkaline hydrolysis products of penicillin G as minor determinant mixture. Repeat skin testing was performed 1 to 12 months after the therapy. Three patients (16%) became skin test positive after the treatment. Two patients reacted to potassium penicillin G alone, and the other patient reacted to benzylpenicilloyl polylysine and minor determinant mixture. These three patients were among the 15 patients who were treated with intravenous antibiotics. This study reveals a high percentage of skin test conversion after intravenously administered penicillin therapy and confirms the present practice of advising patients with a history of penicillin allergy who have successfully completed penicillin treatment to have a repeat skin test before future exposure to β -lactam antibiotics. (J ALLERGY CLIN IMMUNOL 1991;88:213-7.)

Key words: Penicillin allergy, resensitization, intravenous β -lactam antibiotics, skin testing

Approximately 10% of hospitalized patients claim to be allergic to penicillin.¹ However, many of these patients are mislabeled as such and could tolerate these antibiotics.¹⁻³ There are many studies demonstrating that skin testing with penicillin and its degradation products is the most nearly accurate method for identifying patients who are at risk to develop an immediate hypersensitivity reaction when they receive penicillin.⁴⁻⁶ Hypersensitivity to penicillin may be evanescent, and the rate of sensitivity can fall significantly without additional exposure between 1 to 10 years after the initial reaction.^{7,9} This study was performed to determine how frequently patients become resensitized after reexposure to β -lactam antibiotics.

In this study we report the result of our evaluation of 18 patients with histories of penicillin allergy who were treated with β -lactam antibiotics after negative skin tests.

Abbreviations used

BPO: Benzylpenicilloyl polylysine
KPG: Potassium penicillin G
MDM: Minor determinant mixture
AIDS: Acquired immunodeficiency syndrome

METHODS

Patients

All of our patients were hospitalized in Strong Memorial Hospital, Rochester, N. Y., and required antibiotics for the treatment of an infectious process.

This study was performed in two phases: phase 1 from April 1984 to June 1985, and phase 2 from July 1987 to February 1989. With the exception of one patient who was mentally retarded, the history was obtained from the patients and/or the parents. In the case of the mentally retarded patient, a history of penicillin allergy was noted in the hospital chart, but no details were recorded. All of our patients had a history of allergy to penicillin and/or its derivatives. The age range of the 17 adults was 24 to 76 years, and one patient was a 10-year-old child.

The history of penicillin allergy, the reason for antibiotic treatment, and the interval between the end of treatment and repeat skin testing are summarized in Table I.

Most of our patients (15 of 18) were treated with intravenous β -lactam antibiotics; the remaining three patients were treated orally.

The initial penicillin skin tests were negative in all of

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TABLE I. Brief clinical summaries*

Pt	Age (yr)	Sex	Diagnosis	History of pen allergy	Treatment	Interval†	Skin test results
1	36	M	Cellulitis SLE	Large local reaction to IM injection of pen as a child	Pen VK PO for 2 wk	1 mo	Neg
2	76	M	Pneumonia Mentally re- tarded	Noted in chart	Ampicillin IV for 10 days, then PO for 10 days	2 mo	Neg
3	54	M	Vasculitis FUO	Rash as a child with IM pen G 25 to 30 yr previously	Ticarcillin IV for 5 days	1 mo	Neg
4	54	F	Lung abscess Asthma Diabetes mel- litus	Difficulty breathing with IM pen 30 yr previously	Pen VK PO 3 days, then stopped because of worsening of asthma	1 mo	Neg
5	39	M	Chronic si- nusitis	Hives and fever 5 to 6 hr after IM pen as a child	Pen VK PO 2 mo later, pen VK PO for 3 wk 1 mo later, ampicillin PO for 9 days	7 mo	Neg
6	31	F	Pelvic abscess	Periorbital edema, cough, and difficulty breathing after pen treatment 8 yr previously	Ampicillin IV for 3 wk	3 mo	Pos BPO and MDM
7	56	F	Pneumonia Alcoholic cir- rhosis	Generalized urticaria and local swelling after IM pen 20 yr previously	Pen IV for 5 wk Nafcillin IV for 3 days	2 mo	Pos KPG
8	65	M	Pneumonia Multiple myeloma	Flushing and angio- edema 2 hr after IM pen injection 5 to 10 yr previously	Pen IM for 2 wk Cefoperazone for 2 wk	1 mo	Neg

Pt, Patient; PO, orally; IV, intravenously; IM, intramuscularly; pen, penicillin; Pen VK, potassium penicillin V; SLE, systemic lupus erythematosus; UTI, urinary tract infection; CLL, chronic lymphocytic leukemia; SBE, subacute bacterial endocarditis; *E. coli*, *Escherichia coli*; Rx, treatment; FUO, fever of unknown origin; neg, negative; pos, positive.

*Patients 1 to 10 were studied between April 1984 to June 1985, and patients 11 to 18 were studied between July 1987 to February 1989.

†Interval between end of treatment and follow-up skin test.

these patients. They were treated with different β -lactam antibiotics according to their underlying infections within 48 hours after the skin tests. Repeat skin tests were performed generally between 1 and 8 months after the treatment, with one exception, a patient with AIDS who was retested 12 months after his treatment (Table I).

Reagents for skin testing

Three penicillin reagents were used in our study for each patient. BPO solution, at a concentration of 6×10^{-5}

mol/L (Pre-Pen, Kremers-Urban Co., Milwaukee, Wis.), was used for both prick and intradermal tests. KPG was purchased from Sigma Chemical Co., (St. Louis, Mo.) and used at a concentration of 10,000 U/ml for prick tests and 1000 U/ml followed by 10,000 U/ml for intradermal tests. MDM was prepared by alkaline hydrolysis of penicillin G¹⁰ and used at a concentration of 1×10^{-2} mol/L for both prick and intradermal tests. In addition to the above skin test reagents, many of our patients were skin tested with the specific β -lactam antibiotics considered for their treat-

TABLE I. Cont'd

Pt	Age (yr)	Sex	Diagnosis	History of pen allergy	Treatment	Interval†	Skin test results
9	69	F	Osteomyelitis Diabetes mellitus	Generalized rash-? hives <1 hr after IM pen 25 yr previously	Ampicillin IV for 4 wk Ampicillin PO for 2 wk	2 mo	Neg
10	60	M	Pneumonia Coronary artery disease	Immediate angioedema of the feet after IM pen 30 yr previously	Nafcillin IV for 3 wk Ampicillin IV for 10 days	1 mo	Neg
11	24	M	H-flu pneumonia AIDS (homosexual)	Generalized hives with pen Rx for skin abscess 2 yr previously	Ampicillin IV for 9 days	12 mo	Neg
12	64	M	Pneumococcal pneumonia	Generalized hives, swelling of lips after pen treatment 30 yr previously	Cefazolin IV for 14 days	5 mo	Pos KPG
13	62	F	<i>E. coli</i> UTI CLL	Generalized pruritic rash 45 min after pen Rx 4 yr previously	Cefazolin IV for 10 days and then PO for 4 days	8 mo	Neg
14	10	M	<i>Pseudomonas</i> pneumonia Cystic fibrosis	Generalized hives with β -lactam antibiotics	Ceftazidime IV for 10 days	3 mo	Neg (borderline BPO)
15	49	F	Malignant otitis media	Skin rash as a child with pen Rx	Mezlocillin IV for 12 days Ceftazidime IV for 4 wk	8 mo	Neg
16	71	M	<i>Streptococcus</i> SBE	Large local swelling after pen 20 yr previously	Pen G IV	3 mo	Neg
17	36	F	Pelvic infection	Skin rash as a child	Ampicillin IV for 10 days	1 mo	Neg
18	34	M	SBE	Morbilloform skin rash after 2 wk of oral pen 14 yr previously	Pen IV for 3 wk	3 mo	Neg

ment. Semisynthetic penicillins and cephalosporins for skin testing were prepared at a concentration of 1 mg/ml.

Histamine phosphate (0.001 mg/ml) and buffered saline containing human serum albumin (Hollister-Stier Laboratories, Spokane, Wash.) were used in every patient as a positive and negative control, respectively.

Skin testing procedures

Patients were first skin tested on the volar aspect of the forearm by the prick technique. If there was erythema >5 mm and a wheal >3 mm diameter after 15 to 20 minutes, the prick test was considered positive. If the prick test was negative, the intradermal skin tests were applied on the skin of the forearm or upper arm with 0.02 ml of the above

reagents. After 15 to 20 minutes, the intradermal skin test was read, and a wheal >5 mm was considered to be positive if a definite flare was also present.

RESULTS

Penicillin skin testing is a usual practice in Strong Memorial Hospital for patients who have a history of penicillin allergy and require β -lactam antibiotics for their underlying infections. Between July 1987 and May 1989, at least 35 hospitalized patients with history of penicillin allergy were skin tested. All of our patients with negative skin tests tolerated β -lactam antibiotics without any immediate or accelerated re-

actions. Of the hospitalized patients who had a history of penicillin allergy in Strong Memorial Hospital and received β -lactam antibiotics after negative skin testing, 18 were available for repeat skin test.

The first patient who converted her skin test from negative to positive (patient No. 6, Table I) was a 31-year-old white female patient who had a history of penicillin allergy since 1976 when she was treated with penicillin for tonsillitis and reacted with periorbital edema and shortness of breath. She apparently took ampicillin later without a problem. The patient was treated in hospital for a pelvic abscess with a 3-week course of intravenous ampicillin, clindamycin, and gentamicin after negative skin tests with penicillin and ampicillin. The patient tolerated the treatment well. Repeat skin tests were positive with the intradermal BPO and MDM 3 months after the end of her antibiotic treatment.

The second patient whose skin test became positive (patient No. 7) was a 56-year-old female patient who had reacted to intramuscular penicillin with local swelling and generalized hives about 20 years earlier. She had a history of alcoholic cirrhosis and was treated for pneumonia with intravenous penicillin for 5 weeks and intravenous nafcillin for 3 days after negative skin tests for penicillin. A repeat skin test was positive 1½ months later with the intradermal KPG only.

The third patient who became resensitized (patient No. 12) was a 64-year-old white male patient who had developed severe skin erythema, hives, and angioedema of the lips after treatment with penicillin in the 1950s. This patient completed a course of intravenous cefazolin for left upper lobe infiltration and pleural effusion caused by pneumococcal infection (after negative skin test). Five months later, he had a positive prick test with KPG only.

Patient No. 11, who had AIDS, developed generalized pruritic maculopapular rash on day 9 of ampicillin treatment. He did not develop any other complications, such as wheezing, syncope, or angioedema. Repeat skin testing in this patient after 12 months was negative.

Patient No. 14 was a 10-year-old male patient with cystic fibrosis who had at least two negative skin tests in the past and had been treated with ceftazidime with urticaria occurring late in both antibiotic courses. Three months later he was admitted for another course of ceftazidime treatment. This time his skin test revealed a 3 mm wheal and a 15 mm flare with the intradermal BPO. The test was repeated after an hour, and he developed a wheal of 1 to 2 mm with a flare of 20 mm. Although this result did not meet our criteria for a positive test, it represented a suspicious change from his previous completely negative skin

tests (which had been followed by late urticarial reactions 7 to 9 days after ceftazidime treatment was started). Therefore, because of the new changes in his skin test, we decided to apply a seven-step desensitization with intravenous ceftazidime, which was uneventful. Again, on day 8 of the ceftazidime course, he developed itching and hives over his upper lip. Hydroxyzine was started, ceftazidime was continued, and hives disappeared. This patient was not counted as one of the skin test converters because his skin test did not meet our criteria for positivity.

DISCUSSION

This study was performed to determine the frequency of resensitization to penicillin in patients who had a history of allergy to penicillin and were treated with β -lactam antibiotics after negative skin tests.

Many studies have demonstrated that penicillin allergy is evanescent; therefore, patients can lose their sensitivity and receive a subsequent course of penicillin without experiencing an adverse reaction.^{7,9} However, the frequency of resensitization after the tolerated course of antibiotic has not been previously determined in adult hospitalized patients.

A previous study regarding resensitization was done by Mendelson et al.² on 219 healthy children with histories of penicillin allergy (4 months to 20 years of age) who were challenged with a 10-day course of oral penicillin after negative skin test. On repeat skin testing 1 month later, only two patients (<1%) became positive.

In our study we evaluated 18 (17 adults and one child) hospitalized patients who were ill and mostly required large doses of intravenous antibiotics for their illness. Three (16%) of 18 patients became resensitized and one additional patient developed a borderline skin test reaction that we did not consider as positive. However, the percentage of resensitization would have been higher if the borderline skin reaction had been counted as a positive skin test.

There might be several explanations for the high degree of resensitization among our patients versus the group of Mendelson et al.² First, we studied an older population of patients. In general, the highest frequency of penicillin sensitization occurs at ages 20 to 49 years and in chronically ill hospitalized patients who receive multiple courses of high-dose intravenous penicillin.¹ In our population, 10 of the 18 patients studied were older than 50 years and two of the three patients who became resensitized were older than 50 years. Both of these individuals had had their initial penicillin reactions in their third or fourth decade. Second, the frequency and the severity of allergic reactions to penicillin have been demonstrated to be

much less with oral administration than with parenteral routes. There have been only six reported deaths from anaphylaxis after oral administration, and the frequency of nonfatal reactions after oral administration was less than one half of that observed after parenteral administration of these antibiotics.⁸ Finally, the nature of the initial presentation of the allergic reaction may affect the frequency of resensitization. If there is a high frequency of IgE-mediated reactions as the initial presentation, then a higher frequency of resensitization might be expected. Concomitant exanthems produced by viral infections (which occur more frequently in the pediatric population) can be mistakenly interpreted as penicillin allergy by concerned parents.

The cross-reactivity between cephalosporins and penicillins has been attributed to the production of similar major metabolic determinants. This may explain the new skin test finding in patient No. 14 who developed a borderline reaction to BPO after treatment with Ceftazidime only. Although the production of minor determinant metabolites of cephalosporin similar to those of penicillins has not been established, it can be postulated that the resensitization of patient No. 12 to penicillin G, which is a minor determinant, was due to the existence of these metabolites. Presumably, our penicillin G skin test reagent contained more of the relevant determinant than did the cephalosporin solution, which elicited a negative skin test. The original sensitization in this patient had been with penicillin.

Although the number of patients studied was relatively small, our results indicate that the risk of resensitization is significant and must be seriously considered among patients with a history of penicillin allergy who are treated with β -lactam antibiotics after a negative skin test. This study confirms the practice of repeat skin testing in these patients before future

exposure to β -lactam antibiotics. It is worthwhile to note that we did not study the rate of initial sensitization by parenteral β -lactam antibiotics, which would be useful to determine in a future study. If the rate of skin test conversion in nonallergic patients is as high as it was in our study of previously allergic patients, then one would need to consider testing all patients who had received parenteral β -lactam antibiotics within a certain interval before a proposed repeat course.

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