

Frequency of systematic reactions to penicillin skin tests

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Background: Penicillin skin testing is generally considered to be safe when performed sequentially with puncture and intradermal testing although fatalities have been reported.

Objective: We analyzed the rate of systemic reactions to penicillin skin tests for a period of seven and two-thirds years.

Method: This retrospective study used a computerized database at the Mayo Clinic. Altogether 1710 patients were skin-tested to penicillin from January 1992 to September 1999. All patients tested had a history of penicillin allergy. Patients were tested with benzylpenicilloyl polylysine (Pre-Pen) (6.0×10^{-5} M), freshly prepared penicillin G (10,000 units/ml), and penicilloate (0.01M). Prick tests were done first and if negative then intradermal tests. Systemic reactions were evaluated and treated by physicians.

Results: Eighty-six patients had positive penicillin skin tests of which two had systemic reactions. Our systemic reaction rate for all patients tested was 0.12%; and 2.3% for the penicillin skin test-positive group, with no fatalities.

Conclusion: The incidence of systemic reaction to penicillin skin tests is low. Skin prick tests should always be done first. If there is a history of a previous serious reaction, the skin tests—if done—should be diluted to start with. Those doing penicillin skin tests should be prepared to treat a systemic reaction.

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Introduction

Skin testing is a generally accepted method for determining allergic hypersensitivity to penicillin. Skin tests can be done rapidly and both their safety and efficacy have been established. Negative skin tests to penicillin, when both the major determinant and minor determinants are used, confer a low risk of subsequent serious allergic reaction when these patients are given a therapeutic course of penicillin or cephalosporins. Saxon et al reported no IgE-mediated reactions after giving penicillin in any patients who had negative penicillin skin tests.¹ In this study, more than 1000 skin tests were performed during a 10-year period. Penicillin skin testing is generally considered to be safe when performed se-

quentially with scratch or puncture followed by intradermal testing if the scratch or puncture tests are negative. A review by Ressler and Mendelson suggested that a sequential epicutaneous (eg, scratch or prick) and intradermal test are generally safe with a systemic reaction rate of probably 1% or less.² Valyasevi et al reported a systemic reaction rate of 0.072 % to penicillin and other antibiotic skin tests in a review of systemic reaction rates to all skin tests over a 5-year 6-month period.³ In this study, we report the systemic reaction rate to penicillin skin tests over 7 years 8 months, a follow up of the previous study with a longer time period focusing on penicillin skin tests.

Objective

In this study, we present 2 patients who had systemic reactions to penicillin allergy skin tests. We describe the systemic reactions, identify the time of onset, and determine the response to

therapy. We review the systemic reaction rate to penicillin skin tests at the Mayo Clinic (Rochester) from January 1992 to September 1999.

Materials and Methods

Patients

In this retrospective study, we used a computerized database at the Mayo Clinic to identify patients who developed systemic reactions to skin tests. As shown in Table 1 we performed penicillin skin tests in 1,710 patients from January 1992 to September 1999. All patients were referred for testing because of histories of penicillin allergy. The Institutional Review Board approved this study.

Skin Test Methods

For skin puncture tests, the reagent was applied on the volar surface of the forearm in droplets 1 inch apart by one of nine nurses. A bifurcated needle (Allergy Labs of Ohio, but for the past 2 years Duotip-test, Lincoln Diagnostics, Inc.) then punctured the skin at a perpendicular angle through the droplets down into the skin. The intradermal tests were performed by injecting the testing reagent intracutaneously using a sterile plastic disposable 1-mL tuberculin syringe through a 26-gauge or 27-gauge needle. Approximately 0.01 to 0.02 mL of testing reagent was injected to create a 2 x 2 millimeter superficial bleb. The wheal-and-flare reaction was measured and recorded 15 minutes after the application of the testing reagent. The patients would report any systemic reactions to the nurses, and physicians evaluated all systemic reactions. The physicians initiated treatment of the systemic reactions and made the clinical decision to dismiss the patients after recovery.

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Table 1. Penicillin Skin Test and Sr *Rates

Patients Tested	Patients with Positive Tests	Patients with SR	SR rate for Patients with Positive Tests(%)	Overall SR Rate (%)
1710	86	2	2.3%	0.12%

* SR = systemic reaction.

Extracts

We used a freshly prepared penicillin G (10,000 units/mL) (Apothecon, Princeton, NJ), benzylpenicilloyl polylysine (Pre-Pen) (Schwarz Pharma, Inc, Milwaukee, WI) (6.0×10^{-5} M), and, penicilloate (0.01 M) (made locally in the Mayo allergic research laboratory). Positive (histamine) and negative controls were used. The reagents were stored at 4°C.

Interpretation of Skin Test Results

With the skin puncture test, we considered both a wheal diameter larger than 3 mm surrounded by erythema (a flare) to be positive. Pseudopods, irregular extensions of the wheal, were indicative of a strongly positive test. For an intradermal skin test, we considered a wheal of at least 3 mm in diameter with a surrounding flare to be positive.

Systemic Reactions

The symptoms and signs of a possible systemic reaction were observed and recorded by nurses and physicians. These subjective and objective manifestations included the following symptoms: pruritus, flushing, urticaria and angioedema in the skin; cough, chest tightness, wheezing, and dyspnea in the respiratory system; eye itching and conjunctival redness in the eyes; and congestion, and sneezing in the nose.

CASE 1

History of Present Illness

A 9-year-old boy had anoxic encephalopathy at the time of birth and a seizure disorder. He was mentally retarded. He had a history of asthma, primarily exacerbated by respiratory tract infections, which has required multiple hospitalizations. His asthma was complicated by a history of recurrent aspiration and required gastro-

tomy tube placement for nutritional support. He was evaluated at our allergy clinic for his history of a skin rash after treatment with penicillin and amoxicillin as well as urticaria caused by cefpodoxime. He also had history of rhinitis and chronic renal failure requiring hemodialysis.

Medications

The patient was treated with phenobarbital 60 mg orally once a day; Flonase, 2 sprays in each nostril once a day; Zantac, Ventolin and Intal nebulization as needed.

Physical Examination

The patient had normal vital signs. The patient had microcephaly, lumbar scoliosis, and spastic quadriplegia; he was wheelchair bound with a gastrostomy tube. His respiratory examination was normal.

Clinical Course

The patient had a positive skin test to penicillin (positive after intradermal injections which were 4 x 4, 4 x 4, and 3 x 3 millimeters of wheal diameters and 10 x 12, 12 x 10, and 6 x 6 millimeters of flare diameters for freshly mixed penicillin G, Pre-Pen, and penicilloate). Ten minutes later, the patient complained of dyspnea and developed urticaria. He was evaluated by a physician and was given 0.1 mL of epinephrine (1:1000) subcutaneously. The systemic reaction resolved after 30 minutes and the patient was dismissed from the clinic.

CASE 2

History of Present Illness

A 68-year-old man had a history of skin rash to oral penicillin 20 years ago. He was scheduled to have a right shoulder rotator cuff repair and was being sent to our allergy clinic for pen-

icillin skin testing. He had history of paroxysmal atrial fibrillation.

Medications

Amiodarone 200 mg orally once a day and aspirin one tablet once a day.

Physical Examination

The patient had normal vital signs. There was mild subacromial crepitus in both shoulders. There was a slight reduction of motion of the shoulder and slight weakness in abduction. The respiratory examination was normal.

Clinical Course

The patient had a positive skin test to penicillin (positive after intradermal injection, which was 10 x 9 millimeters of wheal diameter, 15 x 12 millimeters of flare diameter for benzylpenicilloyl (Pre-Pen). Twenty minutes later, he developed diffuse urticaria about 1 cm in diameter over his chest and axillary areas. His vital signs were stable; blood pressure was 116/81 mmHg, heart rate was 64 beats per minute, respiratory rate was 16 per minute. He was treated successfully with chlortrimeton 8 mg and prednisone 20 mg orally. The patient was not given epinephrine subcutaneously because of his cardiac arrhythmia history.

DISCUSSION

Penicillins are the most common cause of allergic drug reactions. A negative penicillin skin test in a patient with a history of penicillin allergy will help to reassure the physician and the patient. In the event that penicillin is needed and administered, they will know that serious life threatening IgE-mediated reactions will be rare. Macy reported an adverse reaction rate to therapeutic courses of penicillin class antibiotics during the year after a negative penicillin skin test of 3.2% (3 of 93).⁴

In the past, Van Dellen found three fatalities reported in the literature after both scratch and intradermal skin tests to penicillin.^{5,6} One of us (RVD) knows of two additional fatalities not reported in the literature from penicillin skin tests. Green et al described 412 patients who had positive skin test re-

sults (scratch followed by intradermal testing) of which 3 of these patients had systemic reactions (2 urticaria/angioedema and 1 anaphylaxis) to skin testing (0.7% of those tested with positive skin tests).⁷ Sullivan et al observed positive skin reactions in 740 patients of which 4 mild systemic reactions (generalized pruritic rashes, 3 of which were urticaria) to skin testing were observed (0.5% of all those tested).⁸ Gadde et al reported 12 systemic reactions and 1 large local reaction to penicillin skin testing in 5063 patients tested, the systemic reaction rate of 0.26% of all patients tested with both positive and negative skin tests.⁹

In this study, the allergic systemic reaction rate to penicillin skin tests (sequential skin puncture and intradermal tests) was 0.12% (2 of 1710). For the skin test positive patients the systemic reaction rate was 2.3% (2 of 86) and there were no fatalities. The allergic systemic reaction in these two reported cases consisted of symptomatic complaints of dyspnea and urticaria. A majority of the systemic reactions (11 out of 13) in Gadde et al study were skin manifestations of pruritus, urticaria, and local swelling.⁹ Our patients were successfully treated with a subcutaneous injection of epinephrine in one patient and prednisone and oral antihistamine in the second patient. Valyasevi et al reported all six patients who had

systemic reactions to allergy skin tests had asthma.³ In this report, one patient had no history of asthma and overall, 86 of 1710 (5.0%) patients were skin test positive.

CONCLUSION

Penicillin skin tests, when performed by sequential puncture and then intradermal in a patient with a history of penicillin allergy, were safe. In general, our case review study found that IgE-mediated systemic reactions, if they occurred, were mild and responded to treatment. There were no fatalities, however, we know of rare fatalities. In a situation where treatment with penicillin is necessary in spite of a history of IgE mediated allergy, the skin puncture test should be performed first followed by intradermal tests if the puncture test is negative. If extreme sensitivity is suspected by history, a diluted concentration should be used for skin testing. Thus a careful history should always be taken before skin testing.

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