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Prevention of allergic reactions to penicillin

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Adverse reactions to medications are a significant cause of both morbidity and mortality in the United States. Penicillin and its multiple semisynthetic analogues are no exceptions. Between 1% and 10% of all patients undergoing treatment with these drugs develop reactions to them.¹ The majority of reactions are in the form of rashes. However shock, severe upper and lower respiratory obstruction, and fatal reactions have been documented. The mechanisms by which the reactions take place are multiple and may be divided into nonimmunologic, possibly immunologic and immunologic. This article is concerned with the immunologic reactions mediated by reaginic or IgE antibody. Manifestations of this type of reaction include urticaria, angioedema, laryngospasm, bronchospasm, and anaphylactic shock. The most effective means for eliminating allergic reactions to the penicillins, as with any other antigen, is avoidance. Ideally, the goal is to withhold therapy from those destined to have reactions and administer it only to those unlikely to have reactions. Ways of discriminating the two populations have been the focus of much research and a discussion of these risk factors ensues.

RISK FACTORS

Exposure to penicillin

Allergic reactions to penicillin can occur during the course of a first treatment with this medication; however, it is more common for a patient to tolerate penicillin during an initial course and develop a reaction during a subsequent exposure. Nontherapeutic exposures to environmental and occupational sources of penicillin may also account for sensitizing a patient. Some of these occult sources of penicillin include foods, in utero exposure, and occupational exposure.¹⁻⁴ The sensitizing potential of skin testing with penicillin determinants has never been studied directly. However, in a recent study involving 240 children with histories of previous reactions to penicillin who underwent skin testing followed by an oral course of penicillin, only two had positive skin tests on retesting.⁵

Age

Young and middle-aged adults are most likely to develop penicillin allergy.¹ Whether there are actual differences in the immune responses or differences in likelihood of exposure at the various ages remains a question.

Route of administration

Adverse reactions to penicillin including systemic anaphylaxis and even fatalities can occur after exposure by any route: intradermal, oral, or parenteral.^{1, 6, 7} However, reactions are less likely when penicillin is taken orally than when it is administered by the parenteral route. The relative safety of the oral route may be a function of differences in handling, absorption of antigen in the gastrointestinal tract, or dosage dependent.⁸

History of allergy

A history of allergy, in general, as shown by large scale prospective investigations, appears to have no bearing on a patient's likelihood of reacting positively to skin tests with penicillin reagents.⁹ A history specific for penicillin allergy, on the other hand, has some significance. The patient with a history of an earlier reaction to penicillin is at least 6 times more likely to experience a reaction on subsequent exposure as is a person with a negative history of earlier reaction.

SKIN TEST REACTIONS

The clinically relevant determinants of penicillin include the minor determinants, benzylpenicillin, benzylpenicilloylamine, and benzylpenicilloate (which is virtually totally cross-reactive with benzylpenicilloate), and the major determinant (so named because approximately 95% of tissue-bound penicillin is found in this form), the benzylpenicilloyl moiety.

Series of clinical trials examining the predictive value of penicillin skin test reagents have been carried out. Among the early studies of this type are two that used penicilloyl-polylysine, the major determinant alone. In one study, 993 adult men about to receive a course of penicillin G for routine prophylaxis underwent skin testing with the major determinant.¹⁰ Among those with previous histories of penicillin allergy, 35% had positive skin tests compared with 6.8% of those having had an uneventful course of penicillin. Those who knew of no previous course of penicillin reacted at a rate of 3%. History-negative patients, regardless of skin test results, underwent a course of penicillin; 5.2% of those with positive skin tests had reactions compared with 0.9% of the patients with negative skin tests.

Brown et al.¹¹ had similar findings. In their study, 16,239 patients underwent intradermal skin testing. Forty percent of those with positive histories reacted on the skin test compared with 6% who had previously received penicillin without reactions and 3.6% of those who recalled no previous penicillin administration. Of those who received therapeutic courses of penicillin subsequent to testing, the greatest number of reactions occurred among those who were 4+ positive on the skin test (10.2%). Those who were 2+ positive

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on the skin test reacted 4.2% of the time compared with 1.3% of those who had equivocally positive skin tests and 0.5% of those with negative skin tests.

It was subsequently shown that patients recently recovered from penicillin-induced anaphylaxis developed antibodies directed against minor determinants of penicillin. Thus, studies were carried out to evaluate the possible predictive value of skin tests with conjugates of these materials.¹²

Green and Rosenblum¹³ reported the results of a cooperative prospective study of the value of skin testing with penicilloyl-polylysine and penicillin G carried out by the Penicillin Study Group of the American Academy of Allergy. Almost 3000 patients were enrolled in the study. They were categorized as either history-positive or history-negative for penicillin allergy.

Those with previous histories of penicillin allergy had a 19% rate of positive skin tests while only 7% of those with negative histories reacted. A total of 355 patients underwent treatment with penicillin. Of these, nine had positive skin tests and 346 had negative skin tests. Among those with positive skin tests, 67% had reactions compared with 3% of those whose skin tests were negative. It is pertinent that of the 3% history-positive, skin test-negative patients who had reactions, only three (1%) of all those undergoing treatment were thought to have had IgE-mediated type reactions, thus representing test failures.

The reason for test failures with the combination of major and minor determinants was felt to be the absence of other clinically relevant minor determinants. Thus a series of studies was undertaken that used, in addition to the major determinant and penicillin G, penicilloate or penicilloic acid.¹⁴⁻¹⁶ These studies supported the usefulness of a complete battery of major and minor determinants in screening patients likely to react to subsequent penicillin administration.

Further studies were done in which both major and minor determinants of penicillin, as well as major and minor determinants of some of the penicillin analogues, were used.¹⁷⁻²⁰ Although investigators were not totally in agreement, it was not clear that the addition of determinants of the semisynthetic penicillins, beyond the penicillin reagents, added to the clinical usefulness of the test battery.

While these multiple studies attest to the efficacy of such skin tests for screening, no licensed minor determinants are yet available in the United States. For this reason, a collaborative trial of major and minor penicillin derivatives in hospitalized adults is being undertaken through the National Institute of Allergy and Infectious Diseases. Reagents have been supplied by Dr. Bernard Levine, who acted as a consultant to the Institute. The interim results of this collaborative trial involving eight centers, Cornell University, National Institute of Allergy and Infectious Diseases, Northwestern University, Rochester University, University of California at Los Angeles, University of Colorado, University of Washington, and Walter Reed Army Medical Center, were published as an abstract.²¹

The preliminary findings showed that 14% of history-positive patients were skin-test positive to a battery of major and minor determinants compared with 4% of history-negative

patients. Skin test-negative patients were treated regardless of their histories of previous penicillin allergy. The testing was efficacious in screening immediate and accelerated allergic reactions to penicillin and its analogues. The final results of this study are pending.

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