

Penicillin allergy: a practical approach to management

Gordon L. Sussman, MD, FRCPC, FACP
Kathleen Davis, MD
Peter F. Kohler, MD

Although penicillin is nontoxic, it is highly immunogenic and is the most common drug that causes allergic reactions. A previous reaction to penicillin has been shown to be unreliable in predicting sensitivity in 75% to 90% of patients. To more accurately test for penicillin allergy, diagnostic skin test reagents have been developed; these include the major determinant (benzylpenicilloyl-polylysine) and the minor determinant mixture (penicillin G potassium, benzylpenicilloate sodium and benzylpenicilloyl-*N*-propylamine). Penicillin skin testing has been shown to be safe and useful in predicting immediate IgE-mediated reactions (overall predictive value 99%). Reactions that occur when patients are challenged with penicillin are mild or accelerated urticarial reactions. We outline a practical and rational therapeutic approach based on the current understanding of penicillin allergy.

Si elles sont peu toxiques, les pénicillines occupent le premier rang parmi les médicaments allergisants. Une réaction précédente à la pénicilline ne prédit pas la sensibilité chez 75% à 90% des sujets. Il est plus précis de recourir aux cuti-réactions à l'allergène dit majeur (la benzylpénicilloyl-polylysine) et à un mélange d'allergènes dits mineurs (pénicillin G de potassium,

Dr. Sussman is head of the Allergy Section, Division of Immunology, Wellesley Hospital, Toronto, and a lecturer at the University of Toronto; Dr. Davis is a clinical immunologist in Denver; and Dr. Kohler is professor of medicine at Tulane Medical School, New Orleans.

Reprint requests to: Dr. Gordon L. Sussman, 202 St. Clair Ave. W, Toronto, Ont. M4V 1R2

benzylpénicilloate de sodium et benzylpénicilloyl-*N*-propylamine), qui permettent de prédire de façon sécuritaire et fiable (à 99%) les réactions allergiques immédiats par IgE. Les effets allergiques qui surviennent lors d'une provocation par pénicilline sont des urticaires dites légères ou accélérées. Les auteurs décrivent une conduite rationnelle et pratique fondée sur les connaissances actuelles en ce domaine.

Natural and semisynthetic penicillins are relatively nontoxic; however, they are highly allergenic. The prevalence of penicillin allergy in the general population varies between 1% and 10%.¹ In the United States approximately 300 to 1000 deaths per year are attributed to penicillin-induced anaphylactic reactions.¹ The morbidity related to nonfatal IgE-mediated reactions (urticaria and anaphylaxis) is an even greater problem. For this reason and because penicillin is often the indicated antibiotic, physicians have long sought a safe, simple and inexpensive method of detecting sensitivity. When properly performed with appropriate reagents, penicillin skin testing can fulfil such a need.

Skin test reagents

Penicillin is a hapten that combines rapidly with proteins; the resulting immunogens stimulate an immune response.^{2,3} Most people have an immune response when exposed to penicillin. Patients who are allergic to penicillin have an IgE antibody response; this and other immunologic and nonimmunologic factors render them sensitive to subsequent exposure.

In the 1950s penicillin skin tests often gave

false-negative results because the penicilloyl derivative was not being formed fast enough at the test site to produce a positive response. This problem was solved by conjugating benzylpenicilloyl to polylysine. The resulting "major determinant" is one of the test reagents used in penicillin skin testing.⁴ It is the major metabolite of penicillin and is commercially available (Pre-Pen, Kremers-Urban Co., Milwaukee, Wisconsin). Later it was found that all reactions could not be predicted with one reagent alone. Subsequently a mixture of minor metabolites of penicillin consisting of penicillin G potassium, benzylpenicilloate sodium and benzylpenicilloyl-*N*-propylamine was developed.⁵ Of the components of this "minor determinant" mixture penicillin G produced most positive reactions. This is important because the mixture is not yet commercially available, and penicillin G alone is only a slightly less satisfactory reagent.⁶

Originally the major determinant was described as predictive of urticarial reactions and the minor determinant of anaphylactic reactions. However, Parker¹ has shown quantitatively that reactions to the major determinant are more often associated with anaphylactic reactions.

Skin test technique

A rigorous method of penicillin skin testing must be used because generalized reactions due to the skin test procedure have been reported.^{1,7} It is important to begin with an appropriate concentration of reagents (6×10^{-5} M of the major determinant and 10^{-2} M of the components of the minor determinant mixture). Prick skin testing is done first, with the major determinant and the minor determinant mixture (currently penicillin G, 10 000 U/ml). If there is a history of penicillin allergy these reagents are further diluted 100 times. If no reaction to prick testing occurs, an intradermal skin test is done. It is important to use a positive control (histamine phosphate, 0.1 mg/ml given intradermally) and a negative control (phosphorylated normal saline in phenol, given by the prick method and intradermally). This method of penicillin skin testing is safe and without side effects.^{1,5,6-10} Only one death from penicillin skin testing has been documented;⁷ a large dose was used.

Predictive value of history and skin test results

Several studies have shown that a history of penicillin allergy is unreliable in predicting penicillin sensitivity.^{5,6,8,9,11} Overall, 10% to 25% of patients with such a history have positive results of penicillin skin tests (Table I).^{5,6,8,9,11} Sullivan and colleagues¹⁰ recently reported that 60% of patients with a history of penicillin allergy had positive skin test results; the reason for this discrepancy is not clear.

However, several specific aspects of the histo-

ry have been shown to be more predictive of penicillin sensitivity. The first is the type of reaction. In a study of patients with a detailed history of penicillin allergy, positive skin test results were noted in 46% of those with a history of anaphylaxis, 17% of those with a history of urticaria and 7% of those with a history of maculopapular eruptions.⁶ The prevalence of positive skin test results is not greater in patients with a history of maculopapular eruptions than in patients with no such history. Also, the sooner the test is performed after a penicillin reaction occurs, the more likely there is to be demonstrable penicillin-specific IgE antibody.¹²

Another important factor is the predictive value of skin tests. Patients with negative test results have a low rate of reactions (1.1%) when challenged with penicillin (Table II).^{5,6,8,9,11} The allergic reactions that do occur then are usually accelerated urticarial reactions. Presumably these reactions are due to rapidly formed IgE antibody that was not present in high enough concentrations at the test site.

We took part in a multicentre study coordinated by the US National Institutes of Health to document the safety and efficacy of a standardized protocol for penicillin skin testing. The preliminary results have been published in abstract form.¹¹ Our overall results are summarized in Table III. Of 110 patients with a history of penicillin allergy, 31 (28%) had a positive skin test result. Therefore, 72% could receive penicillin despite a history of allergy. However, one patient with a history of

Table I — Results of penicillin skin testing, by history of penicillin allergy

History	Skin test result, %	
	+	-
+	10-25	75-90
-	3-7	93-97

Table II — Results of penicillin challenge testing, by penicillin skin test result

Skin test result	Penicillin challenge test result, %	
	+	-
+	70	30
-	1	99

Table III — Results of penicillin skin testing, by history of penicillin allergy, in 110 patients at the University of Colorado, Denver, 1980-84

History	Skin test result, no.		
	+	-	Not interpretable
+	31	78	1
-	2	57	2
Unknown	0	2	0

penicillin allergy who had a negative skin test result had a local reaction when challenged with a test dose of penicillin. Thus, a negative skin test result in a patient with a history of penicillin allergy was more than 98% predictive of no immediate reaction. One other patient with a history of penicillin allergy had an accelerated urticarial reaction 48 hours after administration of ampicillin.

The preliminary conclusions from the multicentre study can be summarized as follows: skin testing with major and minor determinants is safe and is highly efficacious in screening for immediate and accelerated allergic reactions to penicillin.

Usefulness of penicillin skin testing

Penicillin skin testing is clearly useful in evaluating the current risk of immediate or accelerated IgE-mediated reactions, the most serious being life-threatening anaphylaxis. It is of some use in evaluating drug-induced urticaria or anaphylaxis. However, penicillin skin testing is not useful in evaluating reactions that are not IgE mediated.

Penicillin skin testing is currently recommended within 24 hours before penicillin administration because there is a small but unknown risk of interim sensitization, perhaps from exposure to penicillin in food products such as milk. Testing should be repeated before every course of penicillin in patients with a history of penicillin allergy. Resensitization has been documented.¹⁰

Results of a recent study suggested that routine skin testing any time before penicillin administration is safe.¹³ Such a study would have to be done in truly allergic people, a small subset of those tested. Since large numbers of patients have

not been tested, routine skin testing cannot be recommended.

Penicillin skin testing is predictive only of immediate or IgE-mediated reactions. It will not help in the evaluation of other hypersensitivity reactions to penicillin such as maculopapular eruptions, hemolytic anemia and interstitial nephritis. Also, the results of penicillin skin testing may be suppressed for weeks after a severe urticarial or anaphylactic reaction.

Finally, penicillin skin testing may be useful for routine screening purposes. Between 3% and 7% of patients with no history of penicillin allergy have been shown to have positive skin test results.^{5,6,8,9,11} Theoretically, these patients are at risk for penicillin reactions. Adkinson and associates¹⁴ showed that screening skin tests could prevent IgE-mediated reactions. Of the small number of patients with a positive skin test result who have been challenged with penicillin, about 67% have had an immediate reaction.^{3,6} However, these patients all had a history of penicillin allergy. Reactions in patients without such a history may be less frequent. The cost-effectiveness of routine screening has not been determined. Presently, routine penicillin skin testing for screening purposes cannot be recommended.

Penicillin skin testing is also predictive of sensitivity to semisynthetic penicillins.^{1,5,6,8-10} The tests differ from those with benzylpenicillin with respect to the side chain only. Penicillin skin testing is not predictive of sensitivity to cephalosporin, which cross-reacts via the common β -lactam ring. A rate of cross-reactivity of 20% to 30% has been cited but may be incorrect.¹⁵⁻¹⁸ Solley and colleagues¹⁷ recently reported no reactions in 27 patients with positive penicillin skin test results who were challenged with cephalosporin. This area requires further study.

A maculopapular rash occasionally occurs 3 to 8 days after administration of ampicillin. It is commonly seen in patients with infectious mononucleosis, hyperuricemia or lymphatic leukemia. The rash is not an allergic reaction, and there is no contraindication to continuing ampicillin therapy and no reason to avoid ampicillin or penicillin after such a reaction.¹⁹ The rash differs from urticarial eruptions and maculopapular eruptions due to penicillin. Although the mechanism of these eruptions is not totally understood, they are likely immunologically mediated and therefore may recur on rechallenge.²⁰

Future perspectives

Presently, the management of penicillin allergy in patients with positive skin test results depends on the severity of the infection and the absolute need for penicillin. Avoidance is usually the safest and easiest method. If penicillin is absolutely indicated, desensitization can be done (Table IV).^{21,22} Epidemiologic evidence supports the

Table IV — Penicillin desensitization protocol*

Dose no.	Penicillin dosage, U
1	100
2	200
3	400
4	800
5	1 600
6	3 200
7	6 400
8	12 800
9	25 000
10	50 000
11	100 000
12	200 000
13	400 000
14†	200 000
15†	400 000
16†	800 000
17‡	1 000 000

* Adapted from Sullivan.²¹

† Administered subcutaneously.

‡ Administered intravenously.

safety of desensitization with oral penicillin compared with parenteral penicillin. Only six deaths from anaphylaxis induced by oral penicillin have been reported.²³⁻²⁶ While this number is only a reported index, death resulting from the oral use of penicillin appears to be rare. Also, nonfatal allergic reactions are less frequent after oral administration than after parenteral administration.²⁷

Today, penicillin desensitization is done by administering penicillin orally, then subcutaneously and finally intravenously; the doses are increased by small increments. Sullivan and collaborators²² described successful desensitization in more than 50 patients. Side effects from oral desensitization are mild (usually urticaria), and no fatal anaphylactic reactions have occurred. This is in sharp contrast to parenteral desensitization: 58% of patients have been reported to have experienced acute allergic reactions, 16% of which were serious anaphylactic reactions; one patient (4.5%) died.^{22,28}

The mechanism of desensitization is not entirely understood. Desensitization renders the patient tolerant specifically to penicillin, but treatment must not be interrupted. A recent study showed suppression of penicillin skin test results but not of histamine, compound 48-80 (a mast-cell degranulator) or pollen skin test results.²⁹ This indicates that penicillin-specific desensitization of mast cells likely occurred, with no specific suppression of general mast-cell release or end-organ response. Another possible method of administering penicillin in patients who are allergic is specific inhibition of immunologic reactions by monovalent haptens.³⁰ However, this approach is still experimental.

In summary, penicillin is often the indicated antibiotic. If used appropriately, it can be given to people from whom it often has been unjustifiably withheld. Suitable reagents are available for skin testing that are predictive of immediate IgE-mediated reactions in patients with penicillin allergy. Clinical practitioners should take advantage of the current understanding of the mechanisms of penicillin allergy.

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