

Diagnosis of penicillin allergy by means of Phadebas RAST® penicilloyl G and V and skin tests

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Summary

Fifty patients with suspected allergy to penicillin were tested. Skin tests were done with Na-penicillin G and penicilloyl-polylysine.

Specific IgE antibody assays were done with penicilloyl G and V conjugates by means of RAST. The overall agreement between skin test and RAST results was 87%, borderline cases not included.

In one case, skin tests were positive to penicillamine only, while RAST for penicilloyl G and V both proved to be positive. One case of penicillin allergy could be diagnosed *in vitro* post mortem only. Two cases of Hoigné syndrome showed no evidence of allergy.

Patterns of skin manifestations varied but urticaria was the most commonly seen feature.

Twenty patients without adverse reactions to penicillin treatment and seven patients who had not received penicillin over the last 10 years served as controls. None of them were positive in either skin tests or RAST.

Two of our twenty control patients developed penicillin allergy during the study. Both showed positive RAST results.

Introduction

With the frequent use of penicillin, a high incidence of penicillin sensitivity in drug-related allergies is to be expected. Diagnosis of penicillin allergy is sometimes difficult due to the variety of other drugs that may be administered at the same time.

Skin manifestations are very variable (Kraft & Wide, 1976), and the most typical changes of anaphylactic sensitivity may be confused with the Hoigné syndrome. All four Gell & Coombs types of allergic response may be seen in penicillin allergy, though type II reactions are rare despite the occurrence of haemolytic antibodies related to high dosages of penicillin (Ackroyd, 1975).

The most common skin change is urticaria, associated with anaphylactic

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sensitivity; not unexpected as penicillin is a potent anaphylactic allergen and 75% of all fatal anaphylactic reactions are due to treatment with penicillin (Delage & Ivey, 1972). Urticaria due to anaphylactic responses, or to formation of immune complexes can be differentiated by detection of specific IgE antibody.

This paper reports the results of tests on seventy-seven patients, divided into three groups including a control group. The study was designed to evaluate the significance of circulating specific IgE antibody in relation to the case histories and skin tests. The patterns of cutaneous rash in the penicillin-sensitive patients were also observed.

Materials and methods

Patient serum samples

Serum samples were taken from fifty patients (group I) with a history of adverse reactions possibly due to penicillin. In most cases the sample was taken within 6 months of the reaction. The age range was 6–75 years (thirty females with mean age of 38 years, and twenty males with mean age of 34 years).

Control samples

Twenty serum samples from patients (group II) without adverse reactions upon penicillin treatment were also taken. Seven control subjects (six females and one male), age range 23–62 years, group III), none of whom had received penicillin treatment during the previous 10 years were also tested.

Skin tests

Skin tests were made on all patients except one, and in all control subjects. Usually, both PL (Benzylpenicilloyl-polylysine 500 nmol BPO/ml), kindly provided by Professor A. de Weck, and Na-penicillin G (Na-pen-G) were administered as prick tests in increasing concentrations from 1:20 to 1:2 and 10 u to 1000 u, respectively. Intracutaneous tests were done only if the prick tests were negative (PPL 1:20 and N-pen-G 10 to 1000 u). Only immediate skin reactions were considered in this study.

Total and specific IgE determinations

The serum samples were stored deep-frozen until examined. Specific IgE antibodies against penicillin antigenic determinants were measured by Phadebas RAST penicilloyl G and Phadebas RAST penicilloyl V*). The tests were run and results were evaluated, according to the standard Pharmacia procedures.

Total serum IgE determinations were simultaneously carried out on serum from all except two patients. The paper radio-immunosorbent tests (Phadebas IgE PRIST*) were made by standard procedures.

In two patients, blood was drawn on two different occasions and the *in vitro* analyses were done on each of the samples.

Results

A summary of results, and relation between results of skin test and RAST is presented in Table 1.

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Table 1. Agreement between skin test and RAST results ($n=70$ patients, groups I and II)

		Skin test PPL/pen G			Total
		Negative	Questionable	Positive	
RAST (pen G + V)	—	50 (98%)	1	4 (23%)	55
	+/-	0	0	2 (12%)	2
	+	1*	1	11 (65%)	13
Total		51 (100%)	2	17 (100%)	70

If +/— cases are excluded: RAST result agreement with positive skin tests, 73%; RAST result agreement with negative skin tests, 98%; average agreement RAST *vs* skin test results, 92%.

* Skin tests positive to penicillamine only.

Penicilloyl G vs penicilloyl V RAST results

Thirteen patients had circulating IgE antibodies against one or both allergens. There was a good agreement between the two sets of results. Three patients with adverse symptoms had detectable IgE antibodies against penicilloyl V alone and one patient with urticaria was RAST-test positive only to penicilloyl G. Two patients showed borderline values to penicilloyl V but were negative for penicilloyl G. One patient, borderline positive for penicilloyl G, was RAST-test positive for penicilloyl V.

No IgE antibodies to penicillin were detected in any serum from the control individuals.

RAST vs skin test results

Ninety-eight per cent (50/51) of the skin-test negative patients were also RAST negative to both allergen preparations (Table 1). The only patient with positive RAST in this group, however, developed a positive skin test when a penicillamine preparation was applied.

Sixty-five per cent (11/17) of the skin test positive cases also gave positive RAST results. Of the six remaining skin-test positive patients, four were RAST-negative, though two of these were skin test positive only upon intradermal testing. Two other prick test positive patients showed a borderline RAST result.

The overall agreement between skin test and RAST results was 92% (the borderline cases not included) in the patient group with adverse reactions possibly due to penicillin therapy (Table 1).

Anaphylaxis

One patient, a 6-year-old child with sepsis, died of a generalized anaphylactic reaction 15 min after injection of penicillin. Specific IgE antibodies against both penicillin antigen conjugates were detected in samples of blood taken post mortem. No skin tests were made.

Another patient had a non-fatal generalized anaphylactic reaction, or a Hoigné syndrome response. There was no skin test reaction to either penicillin antigen, and no specific IgE antibody in a blood sample taken 6 weeks after the reaction.

Table 2. Patients (serum samples) with adverse reactions after penicillin treatment distributed on negative and positive skin test and RAST results

Reaction upon drug treatment	Skin tests				RAST			
	-	+/-	+	Total	-	+/-	+	Total
Anaphylaxis	1	0	0	1	1	0	1	2
Urticaria	8	1	14	23	12	3	8	23
Maculo-papular exanthema	15	1	1	17	15	0	2	17
Macular exanthema	3	0	0	3	1	0	2	3
Other reactions	6	0	0	6	6	0	0	6
Total				50				51

Urticaria

Eight of the 23 (35%) patients with urticarial reactions as a possible consequence of penicillin treatment, had circulating IgE antibodies against one or both conjugates used (Table 2). All of them exhibited positive skin test reactions. Weal and flare reactions upon skin testing occurred in six patients in whom circulating IgE antibodies could not be detected by the RAST technique (Table 2).

Exanthema

The RAST was positive in four of twenty patients who developed exanthema after the drug administration. The skin test was positive only in one patient with maculo-papular exanthema and pruritus, and gave a borderline response in another patient with maculo-papular exanthema (Table 2).

None of the patients without any adverse reaction after penicillin treatment had positive skin tests and RAST results. One patient was receiving penicillin therapy without adverse effects when the blood sample was taken. RAST showed IgE antibodies to penicillin and therapy was discontinued. Later, skin tests were made during which the patient showed asthma-like reactions.

Another patient had both negative skin test and RAST results at the initial test. However, 4 days later there was an urticarial eruption and a second blood sample was taken which was shown to contain IgE antibodies against penicilloyl V. The total serum IgE level had increased from 10 to 170 u/ml.

Table 3. Test results compared with onset of reaction-relative start of penicillin treatment (borderline test results not included)

	Period of time between start of penicillin treatment and onset of adverse symptoms		
	≤ 1 day	2 days-2 weeks	> 2 weeks
RAST positive	1	9	2
Skin test positive RAST negative	0	4	0
Skin test and RAST negative	3	20	4

Test results vs onset of reactions after penicillin administration

There was no apparent discrepancy between test-negative and test-positive patient groups as regards the onset of the adverse reactions relative to the start of treatment (Table 3).

Total serum IgE

Out of twenty-nine serum samples with total IgE levels below 100 u/ml, 26% were found to have specific IgE antibodies against penicilloyl conjugates. The corresponding figure for samples with IgE levels of 100–500 and > 500 u/ml were 17 and 20%, respectively.

The arithmetic mean value of total serum IgE in patients with adverse reactions ($n = 50$) was 199 IgE u/ml and in the patients with no adverse reactions and in the controls ($n = 27$) the arithmetic mean value was 55 IgE u/ml.

Discussion

Diagnosis of penicillin allergy still remains difficult since the relationship between drug administration and occurrence of drug exanthema is not always obvious when other drugs are used concomitantly. There is no typical skin manifestation for penicillin allergy and skin tests should not be done while exanthemas are present. *In vitro* tests are therefore an important step towards easier diagnosis.

Although variable skin reactions occur in penicillin allergy, urticarial lesions are of particular interest since penicillin accounts for about 75% of all fatal anaphylactic reactions (Delage & Ivey, 1972).

In two patients with signs of anaphylactic shock that we examined, one non-fatal case had no allergy detectable by skin test and no specific antibody by RAST. The other, a child with sepsis who died of anaphylaxis within 15 min of an injection of penicillin, had specific IgE antibody detected in a post mortem sample of blood. As in fatal bee or wasp sting, the RAST offers a possible post mortem diagnosis after fatal shock due to penicillin.

Of the twenty-three patients with urticaria, fourteen showed positive skin tests, but only eight had a positive RAST. In three of the skin-test positive but RAST-negative cases, the serum sample was taken within a day of reaction. In two other cases the RAST was at a borderline level. These findings emphasize the necessity of a second blood sample one week later, in cases of a negative RAST when the blood has been taken early after the onset of the exanthema.

Positive skin tests and RAST were seen in two of fifteen cases with maculopapular exanthema, one of which showed a doubtful skin test. In no other case with skin manifestations could a positive *in vivo* or *in vitro* test be demonstrated.

These findings indicate that the more a skin lesion resembles an urticarial eruption, the more likely a specific IgE antibody could be involved; the more macular the lesions, the less evidence of a type I allergy. It is worth noting that the serum in one case of penicillin allergy, obviously due to a minor determinant, was positive by both RAST procedures but skin tests were positive to penicillamine only.

In a study of thirty individuals allergic to penicillin, Juhlin *et al.* (1977) found that skin tests with several penicillin derivatives seemed to give no more information than the RAST method using penicilloyl determinants.

The Hoigné syndrome is another sudden response, but not allergic being possibly a toxic-embolic reaction with symptoms which have been attributed to the concentra-

tions of procaine in serum (Green *et al.*, 1974; Kraus & Green, 1976). Two of our patients on clinical evidence were diagnosed as cases of Hoigné syndrome, and subsequent examination by skin test and RAST showed no evidence of penicillin allergy. Assays for procaine were not made.

In two cases we were able to follow the sensitization to penicillin. These cases give some information about the rapid development of specific IgE antibody. The first case tolerated penicillin well for 3 days. Upon skin testing, a positive reaction was seen and penicillin treatment was discontinued, RAST analysis was positive and confirmed the result of skin tests upon which 'asthmatic' symptoms were noticed. The second case was negative in skin tests and RAST to penicilloyl G and V, and tolerated penicillin infusions without any side effects for a week. On day 8 he developed urticaria and was found to be RAST penicilloyl V-positive. Total IgE levels increased from 10 to 170 units within 4 days.

Total IgE levels, taken as an arithmetic mean differed significantly between allergic and non-allergic persons. These findings however do not help us to identify potential penicillin-hypersensitivity subjects.

Our test results on penicillin-allergic, and on penicillin-treated but not allergic, normal patients, indicate good correlation between skin tests, Phadebas RAST and case history. As a routine practice we therefore prefer to do the RAST first, which allows us to predict results of skin tests in many instances. This, however, does not make skin tests unnecessary. They remain an important *in vivo* control of case history and RAST results.

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