

Allergy to penicillin unsuccessfully treated with a haptenic inhibitor (benzyl-penicilloyl-N₂-formil-lysine; BPO-Flys)

A case report

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Summary

In a patient with a past history of allergy to penicillin and requiring treatment, skin tests with penicillin and penicilloyl-polylysine (PPL) were positive, and a penicilloyl RAST was strongly positive, although the Prausnitz-Küstner test to penicillin and PPL were negative. The hapten BPO-Flys was administered together with penicillin to try to prevent reactions. An anaphylactic reaction occurred on the fifth day, and treatment was stopped. Serum total IgE values increased markedly after the reaction and PK titres to penicillin and PPL reached values of 1/256. The skin test reaction to PPL was negative the day after the clinical reaction, but became strongly positive again a few days later. The penicilloyl RAST remained strongly positive throughout. The authors consider that there was hypersensitivity to a penicillin metabolite other than the penicilloyl group, e.g. to minor determinants, and for this reason the hapten inhibitor failed.

Introduction

Hypersensitivity reactions to penicillin are due to different metabolites formed *in vivo* when the antibiotic is administered. Of these metabolites, the benzyl-penicilloyl group (BPO) is considered to be the major immunogen (De Weck & Eisen, 1960; Levine & Ovary, 1961). However, the importance of the minor metabolites as causative agents of the anaphylactic reactions has also been reported (Levine & Redmond, 1961).

By linking BPO with a monovalent lysine, Hoffman la Roche synthesized a haptenic non-immunogenic substance, the benzyl-penicilloyl-N₂-formil-lysine (BPO-Flys), which is incapable of inducing allergic reactions in patients sensitive to BPO; however, it is able to block the antibodies directed against the BPO determinants (De Weck & Schneider, 1972). This substance has been successfully used for blocking the allergic reactions to penicillin in hypersensitive patients (De Weck & Girard, 1972; Girard *et al.*, 1974).

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In this paper we present a case unsuccessfully treated with the said substance.

Patient and methods

The patient was a female, aged 72 years, suffering from cholecystitis. She had a past history of polyarticular rheumatism and at the age of 67 years had an immediate reaction with generalized urticaria and hypotension after administration of penicillin.

Penicillin was used to treat her cholecystitis, after the patient submitted to a study of her hypersensitivity to the antibiotic according to the plan described in this paper. Hypersensitivity was confirmed and penicillin was administered in the following way, together with BPO-Flys.

Treatment with penicillin G and BPO-Flys

According to the instructions of the Penicillin Allergy Study Group, created for the study of this hapten (De Weck, 1974), the patient received a dose of 400 mg of BPO-Flys, intravenously, twice during the first day. From the second day, the drug was administered intramuscularly in doses of 100 mg twice a day, and penicillin G (PNG) was administered under supervision. The total daily amount of PNG was divided into doses of 500,000 units every 8 hr.

Diagnosis of the hypersensitive state and complementary analyses

Before the treatment with PNG and BPO-Flys, and during and after it, the following tests were made.

Skin tests. The substances and concentrations were as follows: benzyl-penicilloyl-polylysine (PPL), 250 nmol BPO/ml; penicillin G (PNG), 10 u/ml; BPO-Flys, 1.0 mg/ml.

0.04 ml of each of these substances was injected intracutaneously into the forearm and the skin reactions were evaluated after 20 min and 24 hr as follows: a weal smaller than 5 mm, negative; 6–10 mm, +; 10–15 mm, ++; larger than 15 mm, +++.

Prausnitz-Küstner (PK) tests. Two series of successive dilutions in saline from 1/2 to 1/512 of all the serum samples obtained from the patient were injected into three recipient subjects, after negativity of the serum for Australia antigen was demonstrated. 24 hr later, 0.04 ml of PPL containing 500 nmol BPO/ml and 0.04 ml of PNG containing 1000 u/ml were injected intracutaneously into the sites previously sensitized.

PPL, PNG and BPO-Flys were supplied by the Roche Research Department.

RAST analysis. All the serum samples were analysed by means of the RAST against conjugates of phenoxymethyl-penicilloyl-human serum albumin (PMPO-HSA) and benzyl-penicilloyl-human serum albumin (BPO-HSA). The coupling procedure of PMPO-HSA and BPO-HSA to activated paper discs was essentially the same as that described by Ceska, Eriksson & Varga (1972) and Ceska & Lundkvist (1972). The background level (ct/min) of each serum sample tested was established by running discs to which HSA (human serum albumin) was coupled, in duplicate and in parallel with the penicilloyl-HSA RAST, and a RAST response greater than twice the HSA mean count level was considered positive (Basomba *et al.*, 1978).

Total IgE serum levels. Total IgE was measured in all serum samples by radioimmunoassay, using the Phadebas IgE kit (Pharmacia, Uppsala).

Complementary analysis. Complete haematological and urine studies were carried out before and after the treatment with BPO-Flys.

Table 1. Clinical reactions and test results

Day:	(Anaphylactic reaction)																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Penicillin G	(500,000 u daily)																				
BPO-Flys	(800 mg) (2 × 100 mg daily)																				
Skin tests																					
PNG	+						++				+++	+++	+++						+++	+++	+++
PPL	++						-				++	++	++						+++	+++	+++
BPO-Flys	-						-				-				-						-
PK (serum titres)																					
PNG	-						1/8				1/256	1/256								1/64	
PPL	-						1/2				1/256	1/256								1/16	
RAST																					
BPO-HSA	++						++				++	++	++						++	++	++
PMPO-HSA	++						++				++	++	++						++	++	++
Total serum IgE (u/ml)	173						224				4700	9800								7600	

Results

Penicillin G plus BPO-Flys was well tolerated by the patient for the first 4 days, apart from slight skin irritation a few min after the injection (see Table 1). On day 5, after the injection of 500,000 u of PNG, an immediate severe reaction occurred, consisting of urticaria, angioneurotic oedema, dyspnoea, nausea and abdominal pain. The blood pressure, initially 120–90 mmHg fell to undetectable levels. Therefore, emergency treatment with 200 mg of cortisol, adrenaline and antihistamines was initiated. Clinical recovery followed, although the urticaria persisted for more than 12 hr. Thereafter the treatment with penicillin G was stopped, although BPO-Flys was still administered for 9 more days.

As shown in Table 1, the skin test with PPL, which was positive before the treatment with PNG and BPO-Flys was initiated, became negative the day after the clinical reaction and then positive again later. The skin test to PNG, however, became more positive.

Prausnitz-Küstner tests with PPL and PNG were negative before the treatment began, and became positive after treatment, reaching serum titres of 1/256. RAST tests were strongly positive in all the serum samples against both PMPO-HSA and BPO-HSA. Serum IgE increased from a level of 174 u/ml before treatment with PNG and BPO-Flys up to a value as high as 9000 u/ml on the eighth day after the clinical reaction. BPO-Flys was well tolerated and no changes related to the administration of this substance were observed. The skin test to this substance was always negative.

Discussion

Benzyl-penicilloyl-N₂-formil-lysine has been successfully used as an inhibitor of allergic reactions to penicillin. In some cases, a decrease in the skin reaction to PPL and PNG, and in the haemagglutinating antibody titres, have been observed after its use (De Weck & Girard, 1972; Girard *et al.*, 1974). However, because of the way the studies were carried out, it is difficult to say in how many cases the tolerance to penicillin was due to BPO-Flys rather than to other factors.

In this patient, the need for penicillin therapy and the past history of penicillin allergy justified the clinical use of the inhibitor. However, because of the anaphylactic reaction which occurred on the fifth day, the treatment with penicillin had to be stopped. Although the clinical reaction may have occurred because of an insufficient dose of BPO-Flys or other factors, hypersensitivity to an antigen other than the penicilloyl group must be considered. Thus, in our opinion, an isolated test for detecting anti-BPO antibodies appears to be insufficient as a criterion for treatment with penicillin under the protection of the inhibitor.

The tolerance to penicillin during the first days of treatment cannot be attributed, we believe, to the inhibitor, but rather to the low level of the specific antibodies which were undetectable by the PK test. After the anaphylactic reaction, a great increase in the total serum IgE was observed in our patient, reaching values twenty times higher than that of the initial test. The skin sensitivity to PNG and the titres reached by the PK test paralleled the former increase. This confirms some of the observations carried out on the behaviour of the reaginic system after anaphylactic shock (Couteaux-Dumont, Poncelet-Maton & Radermecker, 1974).

Since only the skin reaction to PPL became negative on the day after the anaphylactic reaction, a specific blockage of the skin-sensitizing anti-BPO antibodies by BPO-Flys could be one reason, while the lack of blockage of the anti-minor determinant antibodies could be the cause for the persistent positive reaction to PNG. We suggest that a previous inhibition by BPO-Flys of the cutaneous reaction to PNG could provide a better criterion for the administration of the inhibitor.

RAST analysis has proved in previous studies to be a good technique for the detection of IgE-specific antibodies against penicilloyl group determinants (Wide & Juhlin, 1971; Juhlin & Wide, 1972; Kraft & Wide, 1976; Basomba *et al.*, 1978). In the present case the RAST result was strongly positive before starting the treatment with penicillin and the inhibitor, while the PK test was negative. This lack of concordance between the result of the RAST and that of the PK test is not easy to explain, since both techniques detect serum reaginic antibodies. It seems, therefore, that RAST could be considered a more accurate test in detecting hypersensitivity to penicillin.

De Weck & Girard (1972) reported that about 10% of penicillin-allergic patients spontaneously present a positive skin test with BPO-Flys, and this fact has been confirmed in other studies (Girard *et al.*, 1974), whereas in our series of patients with a reaginic type of hypersensitivity, the number of those sensitive to BPO-Flys rose to 38% (unpublished observations), which leads us to think either of the possible immunogenicity of BPO-Flys or the presence of impurities of the minor determinant type. Nevertheless, in our present patient, no cutaneous hypersensitivity could be detected to this substance. The above data, plus the clinical events mentioned, make us reject the hypothesis that a hypersensitivity to BPO-Flys could have been the cause of the anaphylactic crisis. We think that the BPO-Flys was, despite its lack of effect, well tolerated at all times.

We wish to draw attention to the need for immunological studies of the dynamics of drug allergic reactions, to the significance of antigenic determinants other than the BPO group and to the importance of studying more precisely the clinical states in which the use of BPO-Flys as an inhibitor of the allergic reactions to penicillin is advisable.

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