

Cross-reactivity between penicillins and cephalosporins: Clinical and immunologic studies

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Nineteen well-characterized penicillin-allergic patients were investigated for their sensitivity to cephalosporins containing potentially cross-reactive side chains. All patients were administered cephmandole parenterally and, if this was tolerated, a course of oral cephaloridine was administered. Only two patients responded to the cephmandole; none of the remaining patients reacted to cephaloridine. Benzylpenicilloyl RAST-inhibition studies with sera from three subjects who had not reacted to the cephalosporins demonstrated that cephmandole linked to proteins was capable of recognizing benzylpenicilloyl-specific IgE antibody. It is concluded that consideration of side chain structures can help to predict possible cross-reactions between penicillins and cephalosporins, but carefully controlled challenge tests are advisable before penicillin-allergic patients are treated with cephalosporins. In relation to cross-reacting potential, in vitro experimental studies are difficult to interpret and may in some circumstances overestimate the risk. (J ALLERGY CLIN IMMUNOL 1989;83:381-5.)

The penicillins are a major and widely used group of antibiotics containing a β -lactam structure. With their extensive use and the high doses that can be administered, they can be considered relatively non-toxic. The major adverse effects noted are the development of allergic reactions. A widely quoted world survey¹ suggested that the incidence of such reactions varied from 0.7% to 10% of treated patients. Cephalosporins, which also contain a β -lactam structure, have also caused allergic reactions, but it is often difficult to establish if a primary reaction to the cephalosporins is occurring or whether a cross-reaction in a penicillin-allergic subject is involved.² Studies have demonstrated that penicillin-allergic subjects are at more risk for a reaction to a cephalosporin than non-penicillin allergic subjects,^{3,4} but the incidence varies depending on the stringency of the criteria applied to

Abbreviations used

BPO: Benzylpenicilloyl
PLL: Poly-L-lysine
HSA: Human serum albumin

define the penicillin-allergic group. Experimental studies with animal-raised antisera have demonstrated that cross-reactions between penicillins and cephalosporins are possible and can be rationalized on the basis of similarities in the respective side chain structures.⁵⁻⁷ In this study a group of well-characterized penicillin-allergic subjects were challenged with cephalosporins containing side chain structures that might be expected to lead to cross-reaction. The results are compared with data from in vitro cross-reactivity studies with anti-BPO-specific IgE antibody from patients and cephmandole protein conjugates.

MATERIAL AND METHODS

Subjects

During a period of 1 year, a group of penicillin-allergic patients were selected in a collaborative study involving two hospitals. Two criteria had to be fulfilled for a patient to be included: (1) The patient had to have a previous history of a type I allergic reaction to a penicillin with no history

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TABLE I. Clinical data of the patients studied

Pat	Age (yr)	Sex	Drugs involved	Clinical manifestations	Time
1	31	M	Amoxicillin (o)	Hypotension, generalized erythema, pruritus	2 mo
2	22	F	Penicillin (p)	Generalized erythema and	3 yr
			Ampicillin (o)	angioedema of mouth and eyes	
3	50	F	Amoxicillin (o)	Hypotension, wheezing	3 mo
4	60	M	Amoxicillin (o)	Hypotension, generalized erythema	2 mo
5	64	F	Penicillin (p)	Generalized maculopapular rash	1 yr
			Amoxicillin (o)	Generalized erythema and pruritus	8 mo
6	52	F	Amoxicillin (o)	Hypotension, generalized erythema and pruritus	3 mo
7	40	M	Penicillin (p)	Generalized maculopapular rash and angioedema	3 mo
			Bacampicillin (p)	Angioedema of tongue, facial angioedema	1 mo
8	62	M	Amoxicillin (o)	Pruritus and generalized erythema	4 mo
9	50	F	Penicillin (p)	Generalized maculopapular rash	1 yr
10	54	F	Penicillin (p)	Generalized erythema, breathing difficulties	16 yr
11	39	F	Penicillin (p)	Generalized pruritus and erythema	15 yr
12	40	M	Penicillin (p)	Hypotension, facial angioedema	2 yr
13	50	F	Amoxicillin (o)	Generalized maculopapular rash	6 mo
14	50	M	Amoxicillin (o)	Hypotension, generalized pruritus	4 mo
15	30	M	Penicillin (p)	Hypotension, difficulty breathing	4 mo
			Ampicillin (o)	Generalized pruritus	2 mo
16	50	F	Penicillin (p)	Hypotension, pruritus of lips, breathing difficulties	3 mo
17	41	F	Amoxicillin (o)	Generalized maculopapular rash	5 mo
18	47	F	Penicillin (p)	Generalized angioedema and pruritus	6 mo
19	74	F	Penicillin (o)	Generalized erythema, breathing difficulties	3 yr

Pat, Patient number; o, drug taken by oral route; p, drug taken by parenteral route.

Time is the period elapsed between the allergic reaction to the penicillin and the drug provocation carried out in this study.

of a previous reaction or exposure to any cephalosporins. (2) The patient had to have one or more positive skin tests to a panel of four penicillin-related material or a positive BPO RAST to their serum. If these criteria were negative, a positive challenge test to benzylpenicillin was required. With these criteria, 19 patients were finally selected, seven male and 12 female subjects. Full details are presented in Table I.

Intradermal tests

Four different skin test materials were used. BPO PLL at a final concentration of 5×10^{-5} mol/L (Stallergenes Laboratories, Fresnes, France), benzylpenicillin, 10,000 U/ml (Antibioticos SA, Leon, Spain), amoxicillin, 20 mg/ml, and ampicillin, 20 mg/ml (Beecham Pharmaceuticals, London, England). The skin test solutions were made and used immediately. The tests were carried out in the volar side of the forearm; 0.02 to 0.05 ml of solution was injected, and the reaction was read after 15 minutes. A wheal diameter 4 mm greater than the initial bleb in two perpendicular directions was considered positive. The nonspecific irritant capacity of each skin test solution was investigated in a control population of subjects with no history of penicillin sensitivity or other allergies. To avoid any serious reactions during the skin testing, initial tests were carried out with diluted solutions. These solutions were generally 100-fold lower for benzylpenicillin and tenfold lower for the remainder. However, in some extremely sensitive pa-

tients, still lower dilutions were used since there is a wide range over which patients can react.*

Specific IgE antibody measurement (BPO RAST)

Specific IgE antibody directed against the BPO hapten was measured with reagents purchased from Pharmacia Fine Chemicals (Uppsala, Sweden). The assay was carried out according to the manufacturer's instructions, and results $>0.8\%$ uptake of radiolabeled material were considered positive.

Penicillin and cephalosporin protein conjugates

Protein conjugates of benzylpenicillin, ampicillin, and cephamandole with HSA were prepared according to the method of Levine and Ovary,¹⁰ and the hapten density of the conjugates was determined per the method of Ebata et al.¹⁰

RAST inhibition

RAST inhibition was carried out by preincubating serum samples (50 μ l) with HSA conjugates (30 μ l) before a BPO RAST procedure according to the method of Yman et al.¹¹ The conjugates were used at a 5×10^{-3} , 5×10^{-4} , 5×10^{-5} , and 5×10^{-6} with respect to the hapten.

TABLE II. Immunologic parameters and provocation results in the group of patients studied

Pat	BPO RAST	Skin tests				Penicillin challenge	Cephalosporin challenge	
		BPO PPL	PG	AMP	AX		Parenteral	Oral
1	0.2	-	-	-	+	ND	GT	GT
2	2	-	+	-	-	ND	Positive	ND
3	0.7	-	+	-	-	ND	GT	GT
4	1.2	+	+	-	-	ND	GT	GT
5	1.1	+	+	-	-	ND	GT	GT
6	0.2	+	+	-	-	ND	GT	GT
7	0.2	-	-	-	-	ND	GT	GT
8	1.2	+	+	-	-	Positive	GT	GT
9	11	+	-	-	-	ND	GT	GT
10	0.5	+	-	-	-	ND	GT	GT
11	0.8	+	+	-	-	ND	GT	GT
12	0.4	-	-	-	-	Positive	GT	GT
13	0.3	-	-	-	-	Positive	GT	GT
14	0.4	-	-	-	+	ND	GT	GT
15	0.2	-	+	-	-	ND	GT	GT
16	0.4	-	+	-	-	ND	Positive	ND
17	0.2	+	+	-	+	ND	GT	GT
18	11	+	+	+	-	ND	GT	GT
19	5.6	+	+	+	-	ND	GT	GT

Pat, Patient number; PG, benzyl penicillin; AMP, ampicillin; AX, amoxicillin; ND, not done; GT, good tolerance.

BPO RAST result expressed as percent of uptake or radiolabel on the solid phase. A result of >0.8% uptake is taken to be positive. For concentrations used, see Material and Methods.

Provocation tests

As part of the selection procedure, some patients were challenged by administering benzylpenicillin (10 units) intramuscularly, and if this did not provoke a reaction, an oral course of amoxicillin was initiated 3 days later (500 mg three times a day for 4 days). This procedure was used to establish a definite diagnosis.

Patients selected for the study were all challenged with cephalosporins. Cephmandole (0.2 ml of 100 mg/ml) was administered subcutaneously, and if this was tolerated, a further injection of 500 mg intramuscularly was administered after 30 minutes. If no reaction was observed to cephmandole, then cephaloridine was administered orally (500 mg three times a day for 3 days). Any adverse effect was noted.

All these provocation tests were carried out with careful monitoring of the patients, and full emergency cover was provided. Informed consent was given by each patient, and the study was approved by the committees for research of both hospitals.

RESULTS

Patients

Clinical details of the patients selected are presented in Table I. Results of skin tests, RAST, and challenge tests are presented in Table II. Three subjects (patients 7, 12, and 13) were negative to the skin tests and RAST but were selected on the results of penicillin

provocation tests. Patient 7 experienced generalized pruritus and facial angioedema, patient 12 experienced transient hypotension, and patient 13 experienced generalized maculopapular rash. Only two patients demonstrated a positive response to cephalosporin challenge. Patient 2 experienced a profound and sustained hypotension that required treatment with saline and Dopamine (Astra Pharmaceutical Products, Westboro, Mass.) after injection of cephmandole (500 mg intramuscularly). Patient 16 reacted to cephmandole (0.2 ml of 100 mg/ml subcutaneously) with transitory hypotension, dysphonia, generalized pruritus, and upper airway breathing difficulties.

Protein conjugates

Analysis of the three protein conjugates demonstrated that the benzylpenicillin conjugate had 14 groups per molecule; the ampicillin conjugate had 12 groups per molecule of protein; and the cephmandole conjugate had 10 groups per molecule of protein.

RAST inhibitions

Results of RAST-inhibition studies are illustrated in Fig. 1 with a pool of the sera from subjects 9, 18, and 19 (Table II). All the conjugates could inhibit the positive serum pool, but cephmandole demonstrated the poorest inhibition, 42% at 5×10 mol/L. The

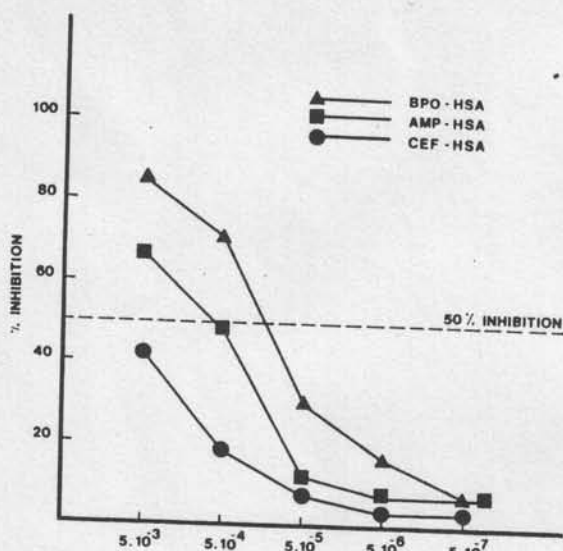


FIG. 1. RAST inhibition with a pool of three sera from patients 9, 18, and 19. Inhibition with each individual sera elicited similar results. BPO-HSA, benzylpenicilloyl human serum albumin conjugate; AMP-HSA, ampicillin human serum albumin conjugate; CEF-HSA, cefamandole human serum albumin conjugate.

three individual sera elicited similar results (data not presented).

DISCUSSION

The problem of cross-reactivity between penicillins and cephalosporins in allergic patients is a complex problem involving many factors. However, studies with animal-raised antisera suggest that consideration of the side chain structure of β -lactam-containing drugs may yield important clues to their cross-reacting potential. Anti-BPO antibodies cross-react well with some cephalosporins, such as cephalexin, cephalothin, and cephaloridine, which have identical or very similar side chain to benzylpenicillin,⁵⁻⁷ but react poorly with other cephalosporins, such as cefuroxime and cefotaxime, which have very different side chains.¹² Even cross-reactivity among penicillins, or the lack of it, can be rationalized in terms of side chain-structure considerations. For example, we have previously described some patients who are allergic to amoxicillin but can tolerate benzylpenicillin,^{13, 14} and there is evidence from antibody studies that these two penicillins are poorly cross-reactive.¹⁵

In the present study,¹⁹ well-characterized penicillin-allergic patients were assessed for their ability to cross-react with two cephalosporins, cephalexin and cephaloridine. Both of these cephalosporins have side chain structures similar to the penicillins to which the patients responded and might have been expected

to give reactions. We found that only two of the 19 subjects (10.5%) reacted to the cephalexin challenge; the remaining subjects tolerated both cephalosporins with no adverse effects. Both of the reacting patients (Nos. 2 and 16) had experienced allergic reactions to parenteral benzylpenicillin in the past and gave a skin test response only to benzylpenicillin in this study. However, one other subject also satisfied these criteria (No. 15) but did not respond to either cephalosporin. Overall, among the measurements made on the subjects or on their sera, no pattern of responses singled out the reacting subjects from the nonreactors. In particular, the BPO RAST was positive in sera from seven patients (>0.8% uptake of radiolabeled material), but only one of these patients responded to cephalexin (patient 2). In spite of this, sera from three of these subjects who had not reacted could be inhibited with a cephalexin protein conjugate with RAST inhibition.

In this study there is a clear discrepancy between the results of the challenge tests and the *in vitro* antibody inhibition data, but the reasons for this are not clear. There are obvious differences in the relative amounts or concentrations of drug which can be used for *in vitro* and *in vivo* studies, and these differences may influence the hapten density of any protein conjugates formed or prepared. We used protein conjugates with hapten densities unlikely to be achieved *in vivo* and thus may have been able to demonstrate *in vitro* inhibition, even though the antibody was poorly cross-reactive. It is also possible that *in vivo* chemical reactions unrelated to those occurring during *in vitro* couplings may occur, leading to, in the case of cephalexin, different haptenic groupings. In this context it is perhaps significant that, whereas RAST systems have been developed and used to diagnose penicillin-related allergies, no corresponding cephalosporin systems have been reported.

From these and other studies, it is clear that treatment of some penicillin-allergic patients with cephalosporins can result in allergic symptoms caused by cross-reactions. When a detailed clinical history, including skin tests and antibody measurements, is able to pinpoint the offending penicillin, it may be possible to predict whether a cephalosporin will cross-react. In our study, two subjects with sensitivity to benzylpenicillin confirmed by skin tests, reacted to a cephalosporin, cephalexin, with a structurally similar side chain, but 17 other subjects with similar histories did not. RAST-inhibition studies also overestimated the risk.

This low incidence of reactions in a "favorable cross-reacting situation" does not, in our view, suggest that clinicians should be complacent about treating

penicillin-allergic patients with cephalosporins. It is seldom necessary to administer cephalosporins to penicillin-allergic patients, but our study suggests that, if this is required, then a controlled challenge test will elicit a useful guide to patient reactivity. If the cephalosporin is tolerated, then further treatment can be administered, but the patient should be carefully monitored during and after therapy.

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