

Anaphylaxis to amoxycillin but good tolerance for benzyl penicillin

In vivo and *in vitro* studies of specific IgE antibodies

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Three patients are reported on who suffered anaphylactic reactions after amoxycillin (AX) treatment and challenge but tolerated benzylpenicillin (BP) parenterally and orally. Two of the three patients had positive skin tests and RAST to AX reagents but negative responses to benzyl penicilloyl (BPO) specific skin tests and RAST and the minor determinant mixture (MDM) skin test reagent. The third case was negative to all skin tests and RAST. RAST and RAST inhibition on the two positive sera suggest that the response is related to the acyl side chain of AX.

Key words: amoxycillin; anaphylaxis; IgE antibodies.

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The BPO hapten is the major allergenic and antigenic determinant derived from benzyl penicillin. It is formed spontaneously *in vivo* and *in vitro* by coupling to the epsilon amino group of lysine in proteins (2). The other haptens involved in allergic reactions to penicillins are: penicillenate, penicillamine, penamaldate, penicoyl and penicillanyl (3), collectively called the minor determinants. Although many allergic reactions have been proved to be of penicilloyl specificity, in others IgE antibodies to BPO cannot be found and the minor determinants are implicated (3). The importance of the acyl side chain in determining the specificity of the responses has also been studied. Atsumi et al. (1) reported that antibodies raised in rabbits against benzylpenicillin react with many different parts of the molecule structure including the side chain. Other authors have also presented evidence of IgE antibodies directed to the acyl side chain of the penicillin molecule (3).

In this paper the specificity of the responses of three patients who experienced anaphylactic

reaction after oral amoxycillin have been studied clinically and immunologically.

MATERIAL AND METHODS

The clinical characteristics of the patients studied were as follows:

Case 1: A 37-year-old male with hypotension, generalised erythema and pruritus on two consecutive occasions after taking oral AX 6 months prior to the study.

Case 2: A 39-year-old male with hypotension, wheezing, breathing difficulties and generalised erythema after taking one capsule of AX.

Case 3: A 20-year-old female with generalised pruritus after taking AX orally and on another occasion generalised pruritus and erythema with hypotension after oral intake of AX with acetylsalicylic acid.

Intradermal skin tests were carried out using the following materials: BPO 5×10^{-5} M (Stallergens lab), MDM 10^{-2} U (Stallergens lab), AX 20 mg/ml (Beecham Pharmaceuticals). The

AX concentration was previously shown to be non-irritant in a group of 30 normal subjects who were not allergic to penicillins. Skin tests were read 20 min after injection and expressed as a percentage increase over the wheal area produced by histamine alone (0.01 %). A 20 % increase in the area was considered negative, values between 20 and 50 % increase as dubious and values over 50 % as positive. The AX skin test was carried out separately to the BPO and MDM tests. Saline diluent was used as the negative control.

In vitro measurement of specific IgE to the BPO hapten was carried out using commercial reagents (Pharmacia). For the AX RAST, AX was coupled to polylysine and the conjugate coupled to cellulose discs following the method of Juhlin et al. (5). Sera from 23 subjects who were not allergic to penicillins and had different total IgE values were tested in order to determine the mean and standard deviation of a negative control group with this assay. All determinations were made in duplicate and discs coupled to polylysine were used in parallel. Results were expressed as percentage of maximum counts added after subtracting the value of the polylysine discs. The mean of the negative control group was 0.27 and the SD 0.17. A value in the AX RAST higher than the mean plus 2 SD was considered positive.

RAST inhibitions were carried out by preincubating test sera with AX (800 mM) before conducting the AX RAST.

For BP challenge 1 million units of BP were given parenterally and if tolerated satisfactorily,

phenoxymethylpenicillin was given after an interval of 3 days in a dosage of 600 000 units every 8 h for 3 further days. During this period the patients were carefully monitored for symptoms compatible with an IgE-mediated allergic reaction. AX challenge was carried out by the oral route as follows: a capsule of AX (5 mg) was administered and if tolerated over a 2-h period the dose was increased to 50 mg and then to 500 mg after a further 2 h.

RESULTS

Results of skin tests and RAST to the different haptens are shown in Table 1. All three patients were skin test negative to both BPO and MDM and their sera were negative in the BPO RAST. When challenged with penicillin by parenteral and oral routes they experienced no reaction. In Case 1, a skin test with 20 mg/ml AX gave a wheal area 500 % larger than the histamine control and the subject experienced moderate systemic pruritus. The AX RAST gave 4.9 % of label uptake and oral challenge was not considered necessary. Case 2 was skin test positive to AX (100 % > histamine value) and the RAST was 4.3 % label uptake. When given 5 mg AX the subject experienced generalised pruritus and erythema that required the administration of adrenaline. Case 3 was skin test negative to AX and after 5 mg of AX, orally, experienced hypotension and generalised erythema that required treatment. The specificity of the RAST response for sera from subjects 1 and 2 was studied by RAST inhibition. Both sera were completely

Table 1

Results of skin tests, RAST and oral challenge to AX in three AX allergic subjects

Patient	Skin tests*			RAST†		Oral challenge
	BPO	MDM	AX	BPO	AX	
1	-	-	+	0.24	4.9	ND
2	-	-	+	0.55	4.3	generalised pruritus, erythema, hypotension,
3	-	-	-	0.3	0.4	hypotension, dyspnea, generalised pruritus.

* - = negative, + = positive; for detail see Results section.

†RAST score is presented as % of uptake label. Results > 1 % are considered positive for BPO RAST. Results > 0.6 % are considered positive for the AX RAST.

ND = Not done, patient responded systemically to skin test.

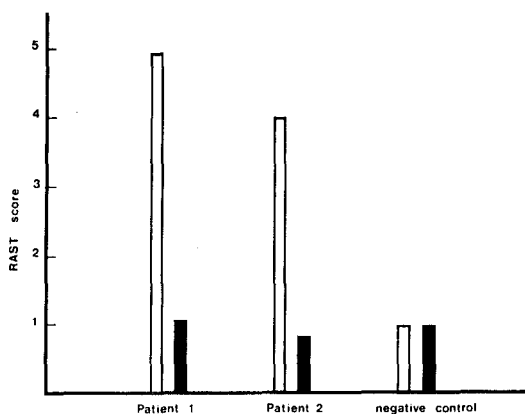


Fig. 1. AX RAST inhibition on sera from two patients compared to a negative serum.

□ uninhibited serum

■ serum preincubated with 800 mM AX

inhibited to background values using AX at 800 mM concentration (Fig. 1).

DISCUSSION

These results show that the three patients were clinically sensitised to AX, but could tolerate BP without experiencing adverse reactions. The only differences between the chemical structure of amoxycillin and benzyl penicillin are in the acyl side chain where amoxycillin has an additional p-OH group and α -amino function. RAST inhibition studies on sera from two of our patients suggest that the IgE antibody recognises the side chain. Other authors (1, 3) have also stressed the importance of the side chain specific antibody, and particularly de Haan et al. (4) have shown, using monoclonal antibodies, that the side chain can be a unique epitope. Some authors have suggested that skin testing with BPO and MDM is an efficient way of diagnosing allergic reactions to penicillins (7, 8), but the introduction of structurally diverse semisynthetic penicillins could result in sensitised patients who do not respond to these reagents. Moos et al. (6) studied cystic fibrosis patients who received only semisynthetic penicillins and found a higher frequency of positive

skin tests with the treatment drugs than with benzylpenicillin-related reagents. In Spain the major prescribed penicillin is amoxycillin, and our studies suggest that it may not be advisable to rely on benzylpenicillin-related diagnostic reagents (BPO and MDM) only to aid diagnosis.

We are currently extending our studies relating to side chain specific IgE antibody using a large population of allergic patients who received various penicillin antibiotics.

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