

Onset of Penicillin Rashes: Relation between Type of Penicillin Administered and Type of Immune Reactivity

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In 90 patients with clinical symptoms of penicillin allergy, the onset of the skin reaction was related to the type of penicillin administered (small- or broad-spectrum) and to the type of immune reactivity. Early onset reactions (urticaria, Quincke's edema, Arthus reactions) were frequently seen after the use of benzylpenicillin, while late onset reactions, mostly macular papular rashes, were mainly seen after the use of aminopenicillins. The clinical symptoms of penicillin hypersensitivity were not related to one single type of immunological (cellular or humoral) reactivity.

Key words: aminopenicillins; benzylpenicillin; delayed type hypersensitivity; ELISA; immediate type hypersensitivity; penicillin hypersensitivity.

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Allergic reactions are well known to occur during or after therapy with small- or broad-spectrum penicillins. Most of this knowledge (onset and immunological type) has concerned the reactions caused by benzylpenicillin (4, 7). Only little is known about the onset of hypersensitivity reactions due to semi-synthetic, broad-spectrum penicillins (aminopenicillins). In general, the humoral immune reactivity has been investigated, and the delayed-type reactions ignored. To obtain greater insight into these immunological reactions we studied the relationship between:

- 1) the onset of a clinical hypersensitivity reaction and the penicillin derivative administered,
- 2) the onset of a clinical penicillin hypersensitivity reaction and the type of immune reactivity.

MATERIAL AND METHODS

Ninety patients with a history of skin reactions to penicillin were investigated by *in vivo* and *in vitro* tests. Early onset reactions (Table 1) were

defined as reactions beginning within 24 h of the start of penicillin therapy. Skin eruptions or symptoms of late onset (Table 1) were defined as reactions beginning after 24 h, or sometimes more than 2 weeks, after the start of penicillin therapy.

The type of immunological reactions was determined *in vivo* by patch tests (delayed type) and intracutaneous tests (immediate type). Patch tests were performed according to Bruynzeel & van Ketel (1) with benzylpenicillin (Gist-Brocades, The Netherlands), ampicillin (Beecham, The Netherlands), and amoxicillin (Beecham). The skin reactions were read after 48 h. The reactions were graded according to Freget (6). Intracutaneous tests with penicilloyl polylysine (PPL-6, Sigma, Missouri, USA) and benzylpenicillin solution were done on patients with negative patch tests, and were performed according to De Haan et al. (3).

The enzyme-linked immunosorbent assay (ELISA) was performed as described by De Haan et al. (4). The conjugates prepared (8) were: (Benzylpenicilloyl)₄₉-Trans, (Ampicilloyl)₄₉-Trans, (Amoxicilloyl)₄₉-Trans.

The passive hemagglutination test was performed according to Thiel et al. (9). Discrimination between IgM and IgG was made by preincubation with β mercaptoethanol (11).

Relation between reaction onset and use of penicillins

Early onset reactions often occurred after injections of benzylpenicillin (Table 1). Late onset

Table 1

Relation between clinical pattern/symptoms and the penicillin derivative administered

Onset of reaction	Clinical pattern/symptoms	Use of	
		Aminopenicillins	Benzylpenicillin
Early	urticaria	5	4
	Quincke's edema	4	2
	anaphylactic reaction		6
	Arthus-like reaction*		5
Late	maculopapular rashes	47	3
	erythrodermia	1	-
	pruritus	8	-
	erythema multiforme	-	-
	exsudativum like eruptions	6	-
	bullous eruptions	2	-

* Redness at the injection site was regarded as an Arthus reaction.

reactions were found in 64 of the 67 patients who had been treated with aminopenicillins (Table 1). The difference between the use of benzylpenicillin and aminopenicillins in relation to the onset of the hypersensitivity reactions is statistically significant ($P < 0.005$) (chi-square test).

Relation between onset of the hypersensitivity reactions and immune reactivity

Patients with early onset of symptoms (Table 2) had no delayed type immune reactivity *in vivo*, whereas skin tests with PPL and/or benzylpenicillin were positive in 16 of 23 patients. In patients with late onset reactions, cellular and/or humoral immune reactivity was demonstrated in 44 of 67 patients. Circulating antibodies (Abs) were found in 28 of these 67 patients.

Relation between immune reactivity and use of penicillin

Positive intracutaneous tests reactions were seen in 15 of the 20 patients who had been treated with benzylpenicillin. However, some patients who had been given aminopenicillins also showed positive immediate type reactions (Table 3).

Table 2

Relation between onset of the clinical hypersensitivity reaction and results of the skin tests and tests *in vivo*

Onset of hypersensitivity reaction	Positive patch test (intracutaneous test not done)			Negative patch test/positive intracutaneous test			Negative patch test/negative intracutaneous test		
	IgE	IgG/IgM		IgE	IgG/IgM		IgE	IgG/IgM	
Early ($n = 23$)	-	-	-	3	3	5	2	2	3
Late ($n = 67$)	2	9	19	3	4	7	2	8	13

Table 3

Relation between use of the penicillin derivative and results of the test *in vivo* and *in vitro*

Penicillin derivative	Positive patch test (intracutaneous test not done)			Negative patch test/positive intracutaneous test with PPL and/or benzylpenicillin			Negative patch test/negative intracutaneous test		
	IgE	IgG/IgM		IgE	IgG/IgM	-	IgE	IgG/IgM	
Aminopenicillins	2	8	19	5	3	7	2	3	16
Benzylpenicillin		1		1	9	5	2	2	-

Twenty-nine of 30 patients with positive patch tests had been treated with aminopenicillins. These 29 patients showed positive patch tests to both aminopenicillins, and in six of them cross reactivity between aminopenicillins and benzylpenicillin was found.

DISCUSSION

In the event of hypersensitivity reactions during penicillin administration it is necessary to confirm that they are penicillin-evoked. Therefore any reliable test for diagnosing penicillin allergy is helpful. The tests used are reliable for the confirmation of penicillin allergy (1, 3, 4, 7).

Late onset reactions, mostly macular papular eruptions, were seen after the use of aminopenicillins (Table 1). In addition, we also recorded erythrodermia, erythema multiforme exsudativum and bullous eruptions. An unexpected finding was that in eight patients pruritus, mostly caused by the use of aminopenicillin, was the only symptom (Table 1). Early onset reactions were frequently seen after injection of benzylpenicillin.

It would thus appear that aminopenicillins cause late-onset reactions, while early-onset reactions are mainly observed after injection of benzylpenicillin. As seen in Table 2, clinical penicillin hypersensitivity reactions are not necessarily bound to one single type of immunological reaction (2). This means that the reaction in a patient with clinical penicillin hypersensitivity must be confirmed by both *in vivo* and *in vitro* tests based on humoral and cellular immune reactivity.

Patch tests with penicillins have been shown (10) to have good specificity, as patch tests with L-(+)- α -Ampicillin, the stereo isomer of D(-)- α -Ampicillin, are negative. D(-)- α -Ampicillin is used clinically, and we used this derivative in the patch tests. The patch test is therefore a valuable *in vivo* test system for confirming a clinical hypersensitivity reaction. Most positive patch tests were found after the use of aminopenicillins (Table 3). There was a 100% correlation between the use of aminopenicillins and the positive patch tests with these aminopenicillins. Positive intracutaneous tests with PPI,

and/or benzylpenicillin were often found after the use of benzylpenicillin (Table 3).

This humoral immune response is in agreement with the results of our investigation on the immune response after treatment with benzylpenicillin (5). Anti-penicilloyl specific antibodies were found in a few patients with a positive intracutaneous test with benzylpenicillin only. Thus, the intracutaneous test with benzylpenicillin demonstrates not only major determinants, but also minor determinants. In summary, the results of this investigation show that both cellular and humoral immune reactivity can be found in penicillin-allergic patients. Therefore, skin testing in patients with a history of penicillin hypersensitivity must be done, not only intracutaneously, but also epicutaneously. Moreover, for the confirmation of a penicillin hypersensitivity reaction *in vitro* tests are supplementary to *in vivo* tests.

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