

Anaphylaxis to penicillins after non-therapeutic exposure: an immunological investigation

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Summary

Background There are instances where individuals may come into contact with penicillins without being aware of it. This non-therapeutic exposure from different sources may cause sensitization and even clinical manifestations in subjects allergic to penicillins.

Objective To determine the capacity that inadvertent contact with penicillins may have in inducing resensitization and symptoms in patients diagnosed as allergic to penicillins who were followed over a long period of time after their initial evaluation.

Methods A follow-up study of penicillin-allergic subjects who agreed to be regularly tested for *in vitro* and *in vivo* control of their sensitivity. Skin tests were carried out with major and minor determinants of benzylpenicillin (BPO and MDM), amoxicillin (AX), and ampicillin (AMP), and specific IgE antibodies were determined by radioallergo-sorbent test (RAST). A questionnaire was sent to and answered by the subjects in order to see if they experienced symptoms at any time during the follow-up period. In addition, if any unexplained symptoms occurred, a bleeper system was used to contact the allergy centre.

Results Seven subjects experienced anaphylactic reactions with no obvious cause. At the time of their initial allergic reaction, which was caused by exposure to prescribed penicillin, the subjects had one or more positive skin tests and/or RAST results to penicillin related reagents. However, over the following 2–4 years all their tests became negative. After reporting their unexplained reaction all seven had one or more positive skin tests and/or RAST results again and when retested 1 week later RAST measurements showed that levels of penicillin-specific IgE were maintained or increased. None of the subjects had knowingly received penicillin but the questionnaire showed that six had been exposed to it and in the seventh case exposure was likely. In two cases contact was by sexual intercourse with a partner who was receiving penicillin, three subjects had handled penicillin formulations and one had drunk from a glass previously used for giving penicillin. In the seventh case exposure could have occurred whilst in hospital for surgery, although this was not proven.

Conclusions these results show that non-therapeutic exposure to penicillin can cause severe symptoms and that *in vitro* and *in vivo* testing can help in the diagnosis of such cases.

Keywords: anaphylaxis, exposure, inadvertent, penicillins, RAST, skin test

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Introduction

There is no doubt that the penicillins are an extremely useful class of antibiotics with a very low level of toxicity. However, it is also true that a small proportion of patients become sensitized when treated and can then develop allergic reactions on subsequent exposure, which in a small number of cases can be anaphylactic with life-threatening consequences [1].

The penicillins, in common with most other drugs, are low molecular weight compounds and would not be expected to cause allergic responses. A number of studies, though, have shown that small molecules can stimulate immune responses if they are chemically coupled to larger molecules such as proteins. This can be achieved by chemical synthesis, but penicillins react spontaneously, if slowly, with proteins under physiological conditions and can then elicit penicillin specific allergic responses. In considering any allergic response it is important to appreciate the differences between the sensitization and challenge phases. During the sensitization phase the immune system responds to the allergen but the subject does not experience any symptoms. Sensitization is related to the allergen to which the subject is exposed, the number of exposures and most importantly, the subjects themselves, via genetic factors [1–3]. The majority of penicillin allergic individuals become sensitized through therapeutic exposure but there are other routes such as inhalation [4] or dermatological contact in an occupational environment [5]. It has also been suggested that sensitization can occur through ingestion of penicillin contaminated food or drinks [6,7] or other inadvertent exposures [8–10]. However, attempts to calculate the amount of penicillin in a low exposure situation able to sensitize an individual should be viewed with caution, as discussed by Dewdney and Edwards [11] in the case of allergy caused by penicillin in milk.

The second phase, challenge, occurs when a sensitized individual reacts with symptoms to a relatively small amount of the material which may previously have caused no problems. Several reports have drawn attention to the low levels of penicillin which can trigger an allergic reaction [6,8–10,12,13], but whereas some are supported by careful investigations [13–15] others are anecdotal [7,10].

It is common practice to deny penicillin allergic individuals further treatment with penicillins but they can still be at risk from non-therapeutic exposure. Some follow-up studies on penicillin allergic subjects have been published [16,17] and provide useful information about the natural progression of a patient's response and capacity for resensitization. It was during our own extensive follow-up programme on a large cohort of

penicillin allergic patients that seven developed anaphylactic reactions of initially unknown cause. These previously sensitized patients form the basis of the present investigation.

Materials and methods

All patients who were diagnosed as allergic to penicillin in our out-patient clinic and were willing to give 6-monthly blood samples and be skin tested annually were eligible for inclusion in the follow-up study. All the patients were advised to avoid contact with penicillins and report any allergic symptoms to the unit as soon as possible.

Specific immunoglobulin (Ig) E antibodies were determined by radioallergosorbent test (RAST) using benzyl penicilloyl polylysine (BPO-PLL), amoxicilloyl polylysine (AX-PLL) and ampicilloyl polylysine (AMP-PLL) based reagents [18]. Skin tests were carried out as previously described [19] using the following reagents: BPO-PLL, minor determinant mixture of benzyl penicillin (MDM), amoxicillin (AX) and ampicillin (AMP).

Results

During the course of our follow-up study seven subjects reported systemic allergic reactions with no apparent cause. Table 1 details the clinical data for these patients at the time of their original allergic episode. Oral AX was the causative agent for cases 1,2,5 and 6, the association amoxicillin clavulanic acid (AX-CL), also by oral route, for case 3, and the other two patients responded to parenteral benzyl penicillin. The diagnosis in four patients (cases 1,3,4 and 6) was anaphylactic shock and in three urticaria. According to the patients' descriptions, the time interval between the causative event and onset of symptoms varied between 15 and 90 min, and in general was shorter in those cases developing symptoms compatible with anaphylactic shock (cases 1,3,4, and 6). Case 1 reported developing similar symptoms in the past after taking 500 mg of AX orally, and on another occasion hoarseness and throat itching after eating strawberries. She was confirmed by challenge to be allergic to strawberries as well. The time interval elapsed between the occurrence of the allergic episode and evaluation is shown in Table 1. The shortest interval was 2 months and the longest was 18 months. The results of the immunological tests carried out at the time of their initial allergic episode are given in Table 2. Patients 1 and 4 were skin-test positive to MDM, AX, and AMP; patients 2, 3, 5, and 6 were skin-test positive to AX and patient 7 to BPO. Patients 1 and 4 developed systemic symptoms

Table 1. Clinical data of the penicillin-allergic subjects included in the study. The interval evaluation is the time elapsed between the occurrence of the allergic episode and the evaluation. Time interval is the period of time elapsed between the drug administration and the appearance of the symptoms

Subject	Age	Sex	Reaction	Drug involved	Route*	Time interval	Interval evaluation
1	59	F	Systemic pruritus, throat itching, dysphonia, dyspnoea, maculopapulae	AX	O	30 min	2 months
2	34	F	Maculopapulae on trunk, legs and lips angioedema	AX	O	1 h	14 months
3	31	F	Generalized erythema, pruritus, nausea, abdominal cramps, hypotension	AX-CL	O	15 min	16 months
4	45	M	Nausea, vomiting, tongue angioedema, systemic pruritus, hypotension, loss of consciousness	BP	P	20 min	1 year
5	38	F	Maculopapulae on abdomen, trunk and legs	AX	O	1 h	18 months
6	32	F	Hypotension, generalized erythema, pruritus in palms and lips angioedema	AX	O	20 min	11 months
7	42	M	Maculopapulae and pruritus in arms, abdomen and legs	BP	P	90 min	8 months

* O = drug taken by oral route or P = parenteral route.

during these tests. Patients 1, 2, 3, and 6 were positive to AX-PLL RAST and patient 7 to the BPO-PLL RAST.

Table 3 details the symptoms reported by the subjects after suspected inadvertent contact with a penicillin derivative. Those patients who experienced symptoms compatible with anaphylactic shock (cases 1, 3, 4, and 6) developed a more severe reaction and with a shorter time interval than those who developed urticaria (see also Table 1 for comparison). The most moderate symptoms were reported by those who had had sexual contact. Only two cases (3 and 6) suspected that the reaction was due to contact with a formulation containing AX and used the bleeper. Case 1 also used the bleeper although she did not know the cause of the reaction. In the other cases the

patients failed to relate the appearance of the symptoms with the possible contact with a penicillin derivative.

A careful examination of the car in which case 1 had been travelling at the time of the reaction disclosed several capsules of AX in the glove compartment, where she had been looking for cigarettes. Case 2 developed mild erythema on the legs, abdomen and face of unexplained cause which her family doctor evaluated as urticaria. When she came for allergological evaluation she associated the appearance of the urticaria with sexual intercourse with a partner who had been taking oral AX for a lung infection. Case 3 developed immediate systemic pruritus, followed by hoarseness, facial angioedema, maculopapulae on the abdomen and legs, and called the evaluator with the bleeper. She was clearly developing the symptoms after administering a syrup with AX to her son. Case 4 reported that he had drunk milk from a glass that had previously been used by his son for taking a formulation with AX. Case 5 developed urticaria of unexplained cause and took antihistamines without consulting. She reported that her husband was taking AX 500 mg qid, prescribed for maxillary sinusitis. She denied prior episodes of urticaria or any other event after sexual contact. Case 6 developed erythema, faintness, hypotension and dysphonia, and did not suspect any link between the episode and previous contact with penicillins. When she came to the unit she recalled that she had handled a syrup with AX just before the reaction occurred.

In case 7 the only possible association that could explain the appearance of the symptoms was that he had had a knee operation with local anaesthetic and

Table 2. Skin-test and RAST data on penicillin-allergic subjects at the time of their initial evaluation

Subject	Skin tests				RAST values	
	BPO	MDM	AX	AMP	BPO-PLL	AXO-PLL
1	—	+	+	+	0.2	6.3
2	—	—	+	—	0.2	5.2
3	—	—	+	—	0.4	6.2
4	—	+	+	+	0.3	0.2
5	—	—	+	—	0.2	0.4
6	—	—	+	—	0.2	4.3
7	+	—	—	—	12.2	0.7

RAST values over 1.6 were considered positive to BPO-PLL and 1.8 positive to AX-PLL.

Table 3. Symptoms reported by the patients after inadvertent contact with a penicillin derivative. Time interval was the time elapsed between the administration of the drug and the appearance of the symptoms. Interval evaluation is the time elapsed between the appearance of the symptoms and the time when the subject was evaluated

Subject	Symptoms developed	Event	Drug involved	Time interval	Interval evaluation
1	Generalized erythema, hypotension, dyspnoea and lips and eye angioedema	Manipulation of capsule	AX	10 min	3 days
2	Systemic pruritus, erythema in legs, abdomen and face	Sexual contact	AX	90 min	3 months
3	Generalized maculopapulae, facial angioedema, systemic pruritus	Manipulation of a syrup	AX	15 min	5 days
4	Generalized erythema, systemic pruritus tongue angioedema	Contamination of a glass	AX	30 min	14 days
5	Maculopapulae on abdomen and trunk	Sexual contact	AX	2 h	1 month
6	Generalized erythema, hypotension dysphonia	Contact manipulation	AX	30 min	20 days
7	Maculopapulae on trunk, abdomen, legs	Surgical operation	Unk.	2 h	6 months

Table 4. Sequential follow-up of the skin-test results before and after developing the reaction. In cases 1,2,3 and 6 specific IgE was determined to AXO-PLL and in case 7 to BPO-PLL. -4, -3, -2 and -1 are the years previous to the occurrence of the reaction after non-therapeutic exposure. Day of evaluation is the time when the subjects were studied

Skin tests		Patients						
		1	2	3	4	5	6	7
-4 year	BPO	-			-			+
	MDM	+			+			-
	AX	+			+			-
	AMP	+			+			-
-3 year	BPO	+	-	-	-	-	-	+
	MDM	+	-	-	+	-	-	-
	AX	+	+	+	+	+	+	-
	AMP	+	-	-	+	-	+	-
-2 year	BPO	-	-	-	-	-	-	+
	MDM	-	-	-	-	-	-	-
	AX	+	+	-	-	-	+	-
	AMP	-	-	-	-	-	-	-
-1 year	BPO	-	-	-	-	-	-	-
	MDM	-	-	-	-	-	-	-
	AX	-	-	-	-	-	-	-
	AMP	-	-	-	-	-	-	-
Day of evaluation	BPO	-	-	-	-	-	-	+
	MDM	+	-	-	+	-	-	-
	AX	+	+	+	+	+	+	-
	AMP	+	+	+	+	+	-	-

developed urticaria while still in hospital. Good tolerance to local anaesthetic agents was confirmed.

The follow-up period with sequential determinations of skin tests is presented in Table 4, and *in vitro* specific IgE antibodies in Fig. 1. Patients 1, 4, and 7 had been followed up for 4 years prior to the occurrence of the episode, and the others for 3 years.

Results of skin tests (Table 4) show that cases 1 and 7 remained positive during 3 years and became negative during the fourth year of follow up, cases 2, 4, and 6 became negative during the third year of evaluation, and cases 3 and 5 during the second year. When the skin test became positive after the latest allergic episode, cases 1, 4, and 7 had the same pattern of positivity as at the initial

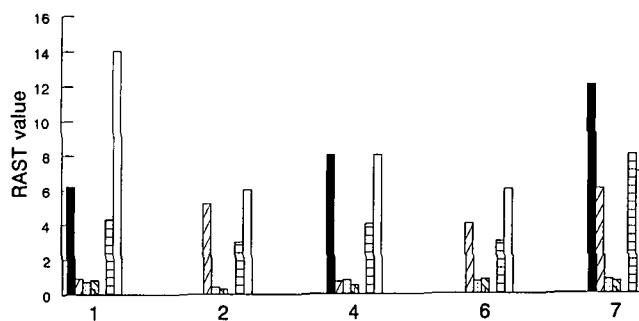


Fig. 1. Sequential follow-up of specific IgE values in the subjects before and after developing the reaction. In cases 1, 2, 3 and 6 specific IgE was determined to AXO-PLL and in case 7 to BPO-PLL. -4,-3,-2 and -1 are the years prior to the occurrence of the reaction after non-therapeutic exposure. 1. RAST carried out at the day of the evaluation (see Table 4). 2. Seven days after the evaluation.

evaluation, cases 2, 3, and 5 were positive to AMP in addition to AX, and case 6 was positive to AX only. Seven days after these evaluations the pattern of positivity was similar.

Figure 1 presents the RAST data from the time of the original allergic episode to the reaction in question for the five patients whose serum had initially been RAST positive. Four of the five became negative within 12 months, and the fifth within 24 months. All reverted to positive after their latest reaction. Furthermore, samples taken 1 week later showed similar or increased RAST results, confirming the recent challenge (Fig. 1). In all cases the RAST became negative before the skin tests, although there were variations in time from case to case.

Discussion

Antibiotics present in foods [11, 20], in the environment [4,12,13], or excreted by animals or humans [21] can be a source of exposure and therefore sensitize individuals or challenge those who are already sensitized [11]. The potential of penicillin in milk to cause these problems has been reviewed [11]. The writers concluded that sensitization was unlikely and that there were very few documented cases to support the claim that penicillin contaminated milk represented a significant hazard to individuals whether they were allergic or not. These theoretical considerations provided a scientific input to debates on acceptable levels of penicillin contaminants in food and on risk assessment. They also highlighted the lack of objective immunological data for the majority of allergy cases involving non-therapeutic exposure.

Our study provided an opportunity to monitor proven penicillin allergic subjects by objective immunological measurements and determine the evolution of their condition as they went about their daily lives.

During the study seven subjects reported allergic reactions with no apparent cause and were examined in more detail. Clinical histories taken at the time of their first allergic episode suggested that five had reacted to amoxicillin and two to benzyl penicillin and this was confirmed by skin tests and/or RAST measurements. These subjects were then monitored for 2–4 years during which time all their initially positive results/responses became negative, with the *in vitro* test becoming negative. In all cases the skin tests became negative over a period that ranged from 2 to 4 years after initial evaluation, but the specific IgE values all became negative by the second year evaluation, except case 7, positive to BPO, who became negative by the third year. In all instances the RAST became negative before the skin tests. The evolution of skin tests and RAST has been

studied by different authors. Sullivan *et al.* reported that the duration of skin-test positivity varied after the last known exposure to the drug. The prevalence was 73% within 1 year and declined to 57% after 10 years [22]. However, the decline in specific IgE antibodies in serum, although variable, seems to be faster and some studies have reported that the half life can be 10 days and the RAST can be negative in a period of months [23], although in some cases it may persist for years [1].

Careful evaluation of the patients suggested that they had developed symptoms after inadvertent contact with penicillin and the subsequent positive skin-test and/or RAST results confirmed the diagnosis. In five cases the reported allergic reaction followed what was believed to be the first penicillin exposure since their initial episode but in two cases subjects may have had several exposures before exhibiting symptoms. This suggests that at least these latter patients went through a resensitization phase before reacting as has been investigated by others [17]. These two cases received the penicillin by the vaginal route following sexual intercourse. Cases of postcoital urticaria have been reported [21] but confirmatory evidence of the cause has been lacking. Our cases were confirmed by objective diagnostic tests.

The fact that five of our seven subjects had initially reacted to amoxicillin could imply that it has higher inherent allergenicity than other penicillins. We believe, however, that our excess of amoxicillin-allergic subjects probably relates more to its widespread use in ambulatory practice [24–26], although other studies do suggest that amoxicillin is capable of eliciting very specific responses [27]. It has also been suggested that commercial amoxicillin and other alpha-amino penicillins contain immunogenic polymers which may induce sensitization. Recent studies carried out by our group do not confirm this and indicate that various different commercial alpha-amino penicillins are free of polymers and other contaminants [28].

The appearance of subjects with anaphylactic reactions caused by non-therapeutic exposure to penicillins indicates that inadvertent exposure is relevant [15]. The risk of primary sensitization by non-therapeutic exposure is very small but our carefully monitored cases provide evidence that sensitized individuals are vulnerable and that non-therapeutic resensitization of previously sensitized individuals may occur. Our studies have also demonstrated the usefulness of objective diagnostic tests. The penicillin related skin tests and RASTs provided crucial diagnostic evidence for the patients' initial allergic reactions caused by therapeutic penicillin exposure and more importantly enabled us to pinpoint the cause of their subsequent reactions when penicillin exposure was initially not suspected.

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