

Controlled administration of penicillin to patients with a positive history but negative skin and specific serum IgE tests

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Summary

Background Although subjects with a positive history of immediate allergy to penicillin and negative skin test are traditionally considered to tolerate penicillin, current evidence indicates that they may develop an immediate reaction despite negative skin and serum specific IgE tests. It is thought that these patients require additional tests to confirm the diagnosis.

Objective To assess in a large group of patients with a history of immediate allergy to penicillins but with both skin test and CAP-FEIA-negative to classical and side chain penicillin determinants, the role of controlled administration of betalactams as a diagnostic test.

Methods A group of 330 patients with a history of immediate allergic reactions to penicillins was studied by two evaluators from the same allergy unit using the following protocol: skin tests with major and minor determinants of benzylpenicillin (benzylpenicilloyl-poly L-lysine and minor determinant mixture), amoxicillin and ampicillin, and determination of specific IgE antibodies to penicillins, by CAP-FEIA, in serum. If both tests proved negative, a controlled administration of the drug was then carried out.

Results A total of 89 (27%) patients were skin test and CAP-FEIA-negative and therefore required controlled administration of the drug. Of these, 49 developed an immediate response and were therefore considered allergic, and the remainder had good tolerance after administration of both benzylpenicillin and amoxicillin. The clinical characteristics of this group were similar to the other allergic patients who were skin test or CAP-FEIA-positive, except that they were younger ($P < 0.01$). Twenty-two (45%) developed a response to benzylpenicillin and 27 (55%) had a selective response to amoxicillin. Although all reactions appeared within 1 h, a positive correlation was found between the dose inducing the response and the time elapsed from drug administration, for both benzylpenicillin and amoxicillin ($P < 0.001$).

Conclusion These data indicate that an important number of subjects are not correctly identified if only skin tests and/or CAP-FEIA are used and that this is particularly relevant for side chain-specific reactions and younger subjects. This suggests that new diagnostic tests are required so as to limit the use of controlled administration.

Keywords CAP-FEIA, controlled administration, immediate reactions, penicillins, skin tests

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Introduction

Skin testing is usually employed to evaluate subjects with immediate allergic reactions to penicillins [1] and the results are reported to be positive in more than 90% of truly allergic patients [2,3]. Furthermore, those patients who have a clear positive history but negative skin tests to the penicillin determinants benzylpenicilloyl (BPO) and minor determinant mixture (MDM) are thought to have a high chance of tolerating the drug [2]. However, it is now known that other determinants in addition to those mentioned above are required to obtain an optimal response. These include mainly amoxicillin (AX),

penicillin V and other betalactam derivatives such as cephalosporins [4,5].

Initial studies carried out in a small number of patients suggested that some subjects could be skin test-negative but RAST-positive to penicillin determinants [6,7]. Recent data, however, from a large group of subjects with immediate allergic reactions to penicillin derivatives, showed that up to 14% were RAST-positive but skin test-negative [8]. However, some evidence indicates that skin testing with the classical penicillin determinants mentioned above is not as effective as originally thought and that up to 20% of cases with a clear positive history can be skin test and RAST-negative but positive after controlled administration of a penicillin derivative [9–11].

We evaluated the role of controlled administration of several penicillin derivatives in a group of patients who presented a history compatible with an immediate allergic reaction to betalactams but who were skin test and CAP-FEIA-negative. In

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order to use well-defined cases and the same criteria for interpreting the clinical reports, all subjects came from the same allergy unit (Carlos Haya Hospital) and were evaluated by the same two members of the group (M. J. T. and M. B.). The results indicate that an appreciable percentage of patients require controlled administration to confirm the diagnosis after a positive history but negative skin test and negative CAP-FEIA.

Materials and methods

Patients

All subjects who were referred to our clinic from family practice or the hospital emergency department over a period of 10 years with a history of immediate allergic reaction to a penicillin derivative were eligible for inclusion in the study. Only those patients with negative skin test and CAP-FEIA and who required a controlled administration for confirmation of immediate allergy to penicillins were finally included in this study. Patients were classified into five categories based on the medical report or, failing that, their own description of the symptoms. (a) Those with maculopapular exanthema on different areas of the skin. (b) Those with skin weal and flare reactions on several parts of the body with or without angioedema. (c) Those with any of the symptoms reported above accompanied by dysphonia, difficulty in breathing, hoarseness, abdominal cramps or faintness. (d) Those with several of the symptoms mentioned above plus documented hypotension. (e) Those cases who, after having had skin manifestations, could not specify whether they were maculopapular or wheal and flare. In all five categories the symptoms had to appear within 1 h after drug administration.

For purposes of comparison we used two control groups from the other patients with a history of immediate allergic reaction to penicillin: those who were skin test-positive to at least one penicillin determinant and those who were skin test-negative but CAP-FEIA-positive.

The study was approved by the institutional review board, and informed consent was obtained from all the subjects before carrying out the study.

Skin test

The following determinants and the final concentrations used were: BPO 5×10^{-5} mmol/L, MDM 2×10^{-2} mmol/L (both provided by Allergopharma, Merck, Darmstadt, Germany), AX 20 mg/mL (Beecham, Toledo, Spain) and ampicillin (AMP) 20 mg/mL (Antibiotic SA, Leon, Spain). These were all carried out as previously described [9, 11]. Skin tests were made by prick, and if responses were negative, intradermal tests were carried out. Responses were classified as positive or negative as previously described [12]. Briefly, in the skin prick tests a weal larger than 2 mm with a negative response to the control saline was considered positive. In the intradermal tests the weal area was marked initially and 20 min after testing, and an increase in diameter greater than 3 mm was considered positive. The reason for including AX and AMP from the very beginning was based on previous evidence of side chain-specific reactions to AX [9]. Skin tests were performed at different times with a minimum interval of 1 week. At the first evaluation only determinants from benzylpenicillin (BP) were tested and AX and AMP at the

second evaluation, thus enabling identification of selective reactors.

Specific IgE antibody determination. Pharmacia CAP-FEIA System

Pharmacia CAP System FEIA (Uppsala, Sweden) is an *in vitro* test system based on ImmunoCAP technology for determination of circulating specific IgE antibodies. The drug of interest, c1 (BPO) and c6 (AXO), covalently coupled to ImmunoCAP, react with the specific IgE in the patient's serum specimen. After washing away non-specific IgE, enzyme-labelled antibodies against IgE are added to form a complex. After incubation, unbound enzyme anti-IgE is washed away and the bound complex is then incubated with a developing agent. After stopping the reaction, the fluorescence of the elute is measured in FluoroCount 96. To classify test results, fluorescence for patient samples is compared directly with FU for standards run in parallel. Pharmacia CAP-FEIA System-specific IgE measuring range: 0.35–100 kU_A/L, cut-off value ≥ 0.35 kU_A/L positive test results and <0.35 kU_A/L negative test results.

Controlled administration

Single blind placebo-controlled administration, performed in those cases with negative skin test and CAP-FEIA was carried out as described [9, 11] with some modifications. BP was administered intramuscularly at the following doses: 1 mL at 10^3 IU/mL, 1 mL at 10^4 IU/mL, 1 mL at 10^5 IU/mL and completing at 1 mL of 10^6 IU/mL if good tolerance was established at the previous doses. Similarly, AX or AMP was given by oral route at the following doses: 5 mg, 50 mg, 100 mg, 250 mg and 500 mg. Tests were all made with a minimum 30-min interval between each. According to the symptoms developing after controlled administration, the patients were reclassified in their respective groups.

Criteria for establishing classical or selective reactions

Tests were performed at different times with at least 1 week between evaluations. Those subjects reporting an immediate reaction to a penicillin derivative who were skin test-negative to BPO and MDM, CAP-FEIA-negative to BPO and tolerated the maximum concentration of BP by the intramuscular route, were considered as having good tolerance to common determinants of BP. If a positive result was seen after any of the tests the subjects were considered to be allergic. The next evaluation was with AX and AMP; if all results were negative, subjects were classified as non-allergic, but if at least one of the tests proved positive they were classified as selective reactors.

Statistical studies

The comparison between groups was made by chi-square analysis for the variables sex, drug involved and type of reaction and by one-way ANOVA for the variables age and time interval. The association between the time from controlled administration to appearance of the symptoms and the dose inducing the reaction was made by Spearman correlation coefficient.

Results

A total of 330 subjects were initially considered as having had a clinical history compatible with an immediate allergic reaction

Table 1. The table shows the time interval between the reaction and the study (Interval), the clinical symptoms as defined in Methods (Group), the drug involved in the original reaction (Historic drug) and the drug inducing a positive response by provocation (Present drug) in the group of patients with positive controlled administration

Patient	Age	Sex	Interval (days)	Group	Historical drug	Present drug
1	41	F	3650	E	Amoxicillin	Amoxicillin
2	28	F	30	D	Amoxicillin	Benzylpenicillin
3	37	M	5250	A	Amoxicillin	Amoxicillin
4	37	F	3240	E	Amoxicillin	Amoxicillin
5	54	F	1080	E	Amoxicillin	Amoxicillin
6	31	F	60	D	Amoxicillin	Amoxicillin
7	31	M	5	C	Amoxicillin	Amoxicillin
8	52	F	720	E	Benzylpenicillin	Benzylpenicillin
9	33	F	30	D	Penicillin	Benzylpenicillin
10	39	M	750	C	Penicillin	Benzylpenicillin
11	70	F	2300	A	Penicillin	Amoxicillin
12	42	M	180	C	Amoxicillin	Amoxicillin
13	18	F	8	D	Amoxicillin	Amoxicillin
14	48	F	240	C	Amoxicillin	Amoxicillin
15	25	F	60	B	Amoxicillin	Amoxicillin
16	17	F	365	C	Amoxicillin	Amoxicillin
17	49	M	4	C	Amoxicillin	Benzylpenicillin
18	33	F	30	C	Amoxicillin	Benzylpenicillin
19	49	M	2520	E	Amoxicillin	Amoxicillin
20	37	M	640	C	Amoxicillin	Amoxicillin
21	53	F	780	E	Amoxicillin	Benzylpenicillin
22	42	F	180	B	Amoxicillin	Amoxicillin
23	25	M	150	B	Amoxicillin	Benzylpenicillin
24	26	F	7	C	Penicillin	Amoxicillin
25	55	F	30	D	Penicillin	Benzylpenicillin
26	32	M	90	C	Penicillin	Benzylpenicillin
27	45	M	90	C	Cloxacillin	Benzylpenicillin
28	21	F	540	B	Amoxicillin	Amoxicillin
29	43	M	60	D	Amoxicillin	Amoxicillin
30	19	F	60	C	Amoxicillin	Amoxicillin
31	28	F	30	C	Penicillin	Benzylpenicillin
32	14	F	210	B	Cloxacillin	Benzylpenicillin
33	62	M	60	B	Penicillin	Benzylpenicillin
34	49	M	20	C	Amoxicillin	Amoxicillin
35	44	M	7	D	Amoxicillin	Amoxicillin
36	36	M	210	D	Amoxicillin	Amoxicillin
37	33	F	365	B	Amoxicillin	Amoxicillin
38	18	F	250	B	Amoxicillin	Benzylpenicillin
39	54	F	36	C	Amoxicillin	Amoxicillin
40	35	M	161	B	Amoxicillin	Benzylpenicillin
41	27	M	33	C	Amoxicillin	Amoxicillin
42	18	F	620	D	Amoxicillin	Amoxicillin
43	48	M	773	C	Amoxicillin	Amoxicillin
44	37	F	1020	E	Ampicillin	Benzylpenicillin
45	55	F	895	D	Penicillin	Benzylpenicillin
46	28	F	78	B	Penicillin	Benzylpenicillin
47	64	M	950	B	Benzylpenicillin	Benzylpenicillin
48	33	M	55	B	Penicillin	Benzylpenicillin
49	18	F	2050	E	Benzylpenicillin	Benzylpenicillin

to a penicillin derivative. According to the patients' descriptions, the drugs involved in the reaction were AX in 64.8% of cases, AMP in 13%, BP in 2.8%, other penicillins in 3.8% and in 15.6% the specific penicillin inducing the reaction could not be established. From the whole group, 203 (61.5%) were skin test-positive, 38 (11.5%) were skin test-negative and

CAP-FEIA-positive and 89 (27%) were skin test and CAP-FEIA-negative and therefore required a controlled administration to confirm the diagnosis, and these 89 formed our study group. Of these, 49 developed an immediate response after controlled administration of BP or AX and were therefore considered allergic, and the remaining 40 had good tolerance

Table 2. The table shows the time interval between the reaction and the study (Interval), the clinical symptoms as defined in Methods (Group) and the drug involved in the original reaction (Historic drug), in the group of patients with good tolerance to benzylpenicillin and amoxicillin after controlled administration

Patient	Age	Sex	Interval (days)	Group	Historical drug
1	37	F	1100	C	Ampicillin
2	42	F	1200	B	Amoxicillin
3	21	M	174	C	Amoxicillin
4	28	F	5200	D	Amoxicillin
5	33	F	1520	E	Penicillin
6	36	M	730	B	Amoxicillin
7	35	F	365	C	Penicillin
8	17	F	620	C	Amoxicillin
9	49	M	30	A	Amoxicillin
10	53	F	365	B	Amoxicillin
11	18	M	1074	E	Penicillin
12	31	M	2800	D	Amoxicillin
13	47	F	122	A	Penicillin
14	55	F	840	A	Amoxicillin
15	66	F	320	E	Amoxicillin
16	63	M	1000	C	Benzylpenicillin
17	19	F	30	E	Amoxicillin
18	37	M	620	E	Amoxicillin
19	23	F	1020	D	Penicillin
20	39	F	90	E	Amoxicillin
21	54	M	3650	A	Amoxicillin
22	40	F	250	B	Penicillin
23	19	F	161	B	Amoxicillin
24	48	F	365	E	Penicillin
25	26	F	755	D	Amoxicillin
26	35	F	90	A	Benzylpenicillin
27	28	M	180	A	Amoxicillin
28	32	M	1150	E	Amoxicillin
29	54	F	365	C	Penicillin
30	42	M	400	E	Amoxicillin
31	51	M	530	E	Penicillin
32	30	F	278	B	Amoxicillin
33	49	F	814	C	Amoxicillin
34	38	F	185	A	Penicillin
35	44	F	90	A	Amoxicillin
36	31	M	170	E	Amoxicillin
37	49	F	950	B	Penicillin
38	61	M	890	E	Amoxicillin
39	38	F	225	E	Amoxicillin
40	57	F	60	E	Penicillin

after controlled administration of BP and AX. Thus, after all the tests 290 patients were finally considered as allergic. According to the medical report ($n=92$) or their own description of the symptoms ($n=198$), 20 patients (6.9%) were classified into group A, 84 (29%) into group B, 95 (32.8%) into group C, 59 (20.3%) into group D and 32 (11%) into group E.

Comparison of the clinical characteristics of the patients who were skin test and CAP-FEIA-negative but positive after controlled administration with the two control groups showed no significant differences in sex, drug involved, type of reaction or time interval. However, the group requiring controlled administration was younger than the other two groups ($P<0.01$).

The clinical characteristics of the study group are described in Table 1 (those with a positive controlled administration) and

Table 2 (those with good tolerance). In the first group the mean age was 37.4 ± 13.6 years and in the second it was 39.4 ± 13.1 years. The mean time interval between the reaction and the study was 632 ± 1075 days in the first group and 769.4 ± 1017.7 days in the second. The comparisons between subjects with a positive and negative controlled administration for age, sex, drug involved, time interval and symptom categories showed no statistical differences.

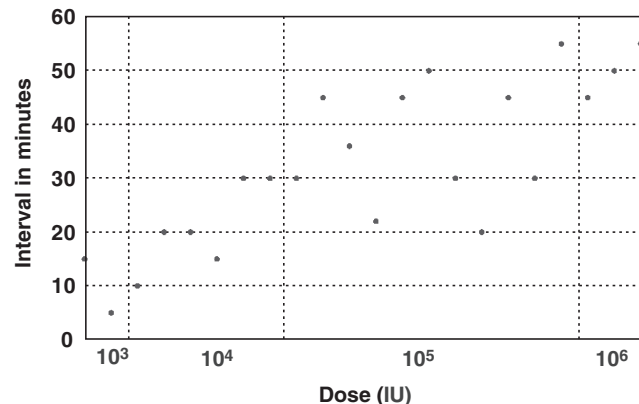
In the controlled administration, 22 (45%) patients responded to intramuscular BP, so they were non-selective reactors (Table 1). Most of the reactions were mild to moderate and well controlled with antihistamines, though some required adrenaline. The dose of BP that triggered the response and the type of symptoms can be seen in Table 3. One (4.5%) case had a

Table 3. Patients positive after controlled administration with intramuscular benzylpenicillin, classified into groups and dose inducing the reaction

Doses	Clinical categories				
	Group A	Group B	Group C	Group D	Total
10 ³ IU	0	0	1	1	2
10 ⁴ IU	0	2	2	2	6
10 ⁵ IU	0	7	4	0	11
10 ⁶ IU	1	2	0	0	3
Total	1	11	7	3	22

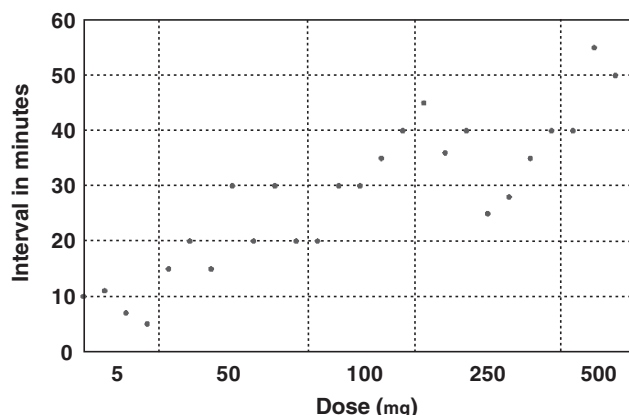
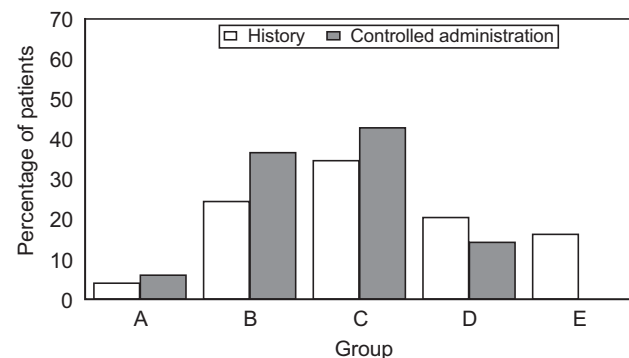
Table 4. Patients positive after controlled administration of oral amoxicillin but having good tolerance to intramuscular benzylpenicillin, classified into groups and dose inducing the reaction

Doses	Clinical categories				
	Group A	Group B	Group C	Group D	Total
5 mg	0	0	2	2	4
50 mg	0	0	6	1	7
100 mg	0	1	4	0	5
250 mg	0	4	2	1	7
500 mg	2	2	0	0	4
Total	2	7	14	4	27

**Fig. 1.** Correlation between the dose inducing the reaction and the time elapsed between drug administration and reaction in those patients responding after controlled administration of intramuscular benzylpenicillin.

maculopapular rash induced after a dose of 10⁶ IU and was included in group A, 11 (50%) cases belonged to group B and nine of them reacted with 10⁵ or 10⁶ IU of BP, seven (31.8%) cases were in group C and three of them reacted to concentrations below 10⁵ IU, and finally three (13.6%) cases were in group D and all responded to concentrations below 10⁵ IU. In summary, the more severe the reaction the lower the dose required to induce the symptoms.

Twenty-seven (55%) patients had good tolerance to BP but developed a reaction after the oral administration of AX, so they had selective reactions (Table 1). Two (7.4%) cases

**Fig. 2.** Correlation between the dose inducing the reaction and the time elapsed between drug administration and reaction in those patients responding after controlled administration of oral amoxicillin.**Fig. 3.** Percentage of patients included in the five different symptom categories according to the initial diagnosis based on clinical history and the final diagnosis after controlled administration.

developed a maculopapular reaction after the intake of 500 mg of AX by the oral route and were included in group A; seven (25.9%) patients developed mild urticaria without systemic symptoms and therefore were categorized in group B, six of these developed symptoms at the dose of 250 mg or greater; 14 (51.8%) cases were included in group C and 12 of them developed the response with doses below 250 mg; four (14.8%) cases were included in group D, two of whom developed the reaction with 5 mg. Results can be seen in Table 4.

The relationship between the dose of BP at which the patient developed the positive response and the time of appearance of symptoms is shown in Fig. 1. It can be seen that the lower the dose needed to induce the reaction the shorter the time interval between the dose and the reaction. Figure 2 shows the results in patients who developed a selective response to AX. A similar relation was found between dose and time interval. Most of the patients who reacted to AX at 100 mg or 250 mg did so after 30 min. There was a statistically significant correlation between dose and time interval for both BP and AX (Spearman correlation coefficient $P < 0.001$).

The comparison between the initial classification based on history and the reaction the patient had in the controlled administration is shown in Fig. 3. There was an increase in the number of patients included in the first three groups (A, B and

C) after controlled administration compared with the classification made based on the clinical history, with the highest increase in patients with a wheal and flare reaction (group B) (36.7% vs. 24.5%) and a decrease of 6% in those with a more severe reaction (group D). These data indicate that after controlled administration the reactions are less severe than first thought.

Discussion

Amongst the factors that may contribute to the detection of patients with confirmed allergy but negative skin tests are: having a selective IgE response to a betalactam not tested; being skin test negative but RAST positive; and the loss of skin test sensitivity due to the natural evolution of penicillin allergy. Regarding the first, an important percentage of subjects, up to 50%, can be positive to side chain specific determinants [4,9,10]. In fact, different studies using semi-synthetic penicillins, either free [4,13,14] or conjugated to PLL [15], gave positive results, providing evidence that such specific responses may exist. However, some controversy remains [16], possibly due to the fact that different populations are involved, with presumably different patterns of drug use and therefore unique specificities in the IgE response. In our study, patients with selective reactions to AX ($n=27$) required provocation for diagnosis more often than patients with non-selective reactions ($n=22$), suggesting that the diagnostic efficiency of skin testing and/or CAP-FEIA is lower in selective reactions to side chain structures. These results are supported by previous studies [9,11].

Although not frequent, the possibility of finding negative skin tests but detecting specific IgE in serum of patients with immediate allergic reactions to penicillins has been reported [6,7]. Later evidence indicated that in subjects with immediate allergic reactions to penicillins, up to 13.1% could be RAST positive and skin test negative [8], these figures being higher than those reported previously [6,7,17]. Bearing this in mind, the 38 (11.5%) patients who were skin test negative but CAP-FEIA positive were expressly excluded from the study, since they could be diagnosed by conventional *in vitro* methods.

The third explanation for the requirement of controlled administration in this study group was the possibility of a long time interval between occurrence of the reaction and the performance of the skin tests, because skin test sensitivity is known to decrease over time [18,19]. Allergic subjects whose skin tests have become negative with time may still respond after drug administration and re-sensitize, becoming skin test positive again [20,21]. However, in our study this was not the case as no differences were observed in the time interval between this group of patients and those who were skin test positive or those who were skin test negative but CAP-FEIA positive. The only difference between groups was that the patients who were both skin test and CAP-FEIA negative were younger than those with either skin test or CAP-FEIA positive.

Of note was the direct and significant association between the dose of the drug to which the subject responded and the moment of the reaction (Figs 1 and 2); the greater the dose the longer the interval before the response, and in those cases where this interval was longer, urticaria was more frequent. Accelerated urticaria [22,23] has been described as one of the clinical entities that can be induced in penicillin-allergic patients, having a

variable time interval between drug administration and onset that can be as short as 2 h [1,23]. In a previous study of subjects who had had an immediate reaction to a penicillin derivative but were skin test and RAST negative we found subjects who developed a reaction after an interval varying from hours to days after drug intake [9]. Similar results have been reported by Gadde et al. [3], who found that in 649 subjects with a positive history and negative skin tests eight developed an accelerated reaction within 1–72 h. Although this entity has been claimed to be IgE mediated this has never been sufficiently proven [1,23]. The possibility of finding patients with accelerated urticaria not IgE mediated, and with both immediate skin test and specific IgE determination in serum negative, should not be confused with those patients having immediate IgE-mediated urticaria. Studies are required for the better definition of this accelerated type of reaction and therefore we propose to further monitor patients at the moment of the reaction, in parallel in peripheral blood and skin, measuring different regulatory cytokines and markers [24].

It is also worth mentioning that the patients appear to perceive, and therefore describe, their symptoms as more severe than later testing shows, as after controlled administration there was an increase in the number of patients with minor reactions, whereas there was a decrease in those with more severe reactions (Fig. 3). This variation in severity could also be explained by the lower dose of penicillins inducing the reaction at the controlled administration than the dose inducing the historic reaction, or to a decrease in the levels of specific IgE antibodies over time. Thus, further studies of this phenomenon are required.

Summarizing, this study emphasizes that in subjects with immediate allergic reactions to penicillins, a considerable proportion may be both skin test and CAP-FEIA negative to classical and side chain specific determinants, thus requiring a controlled administration to confirm the diagnosis. This was particularly relevant for side chain specific reactions and younger subjects. Consequently, new, less harmful and easily performed, diagnostic tests are required in order to limit the use of controlled administration.

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