

Evaluation of adverse cutaneous reactions to aminopenicillins with emphasis on those manifested by maculopapular rashes

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We assessed 195 subjects with histories of adverse reactions to aminopenicillins, using 1) skin tests with penicilloyl polylysine (PPL), minor determinant mixture (MDM), benzylpenicillin (PG), amoxicillin, and ampicillin (read after 20 min and 48 h); 2) patch tests with PG, amoxicillin, and ampicillin; and 3) RAST for penicilloyls G and V. Oral challenges with ampicillin, amoxicillin, and penicillin V were administered to 34/60 patients reporting maculopapular reactions. Immediate hypersensitivity (IH), in most cases for both penicillin and aminopenicillins, was diagnosed (based on skin tests, RAST, or both) in 35 subjects who had suffered anaphylactic shock, or urticaria, angioedema, or both urticaria and angioedema. Thirty-three of the 60 subjects reporting maculopapular reactions presented delayed intradermal and patch-test positivity, indicating delayed hypersensitivity (DH), for ampicillin and amoxicillin, and three were also positive for PG. Diagnoses were confirmed with oral challenges in 18/33. The remaining 27/60 were negative in all allergologic tests, with oral-challenge confirmation in 16. Our findings highlight the importance of the amino group in DH to aminopenicillins. Moreover, the mean time interval between the last reaction and our tests was significantly ($P < 0.01$) longer in DH subjects (54.96 months) than in those with IH (18.62 months), suggesting that the time of testing is less important in cases of DH.

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In recent years, reports of both immediate (3, 4, 13, 19) and delayed (2, 6, 16, 23, 26) reactions to aminopenicillins (APs) have become more frequent. Skin tests are widely recognized to be helpful in assessing type 1, IgE-mediated reactivity to APs and other penicillins (1, 4, 19, 20, 22, 25). This approach generally involves prick and intradermal testing with benzyl penicilloyl polylysine (PPL) and minor determinant mixture (MDM), but some reports (4, 19, 20, 25) have emphasized the importance of testing with APs as well. The AP side-chain structure has, in fact, been shown to play a role in both immediate and delayed hypersensitivity (DH) reactions to these drugs (4, 5, 19, 21, 23, 26). Patch tests have proven to be useful in diagnosing cases of allergic contact dermatitis caused by APs in factory workers in the pharmaceutical industry (14, 15, 18), and there is some evidence (2, 6, 16) that they can also be used to investigate other types of cutaneous reactions to these antibiotics, such as maculopapular rashes,

which seem to represent a substantial percentage of all adverse reactions to penicillins (and especially those provoked by ampicillin) (12). Recently, Gadde et al. (8) examined a large group of patients that were skin-test-negative in spite of histories of adverse reactions to β -lactams. In a small percentage of these subjects, oral challenges with β -lactams produced delayed reactions that generally consisted of non-urticarial cutaneous rashes. However, the presence of an amino group in the (D-) alpha position has been shown to be essential for a delayed-type allergic reaction to APs (27), and, for this reason, patch testing with benzylpenicillin alone may fail to reveal hypersensitivity to an AP. Tuberculin-like reactions to intradermal tests with β -lactams (including APs) have also been observed in patients with maculopapular or diffuse erythematous reactions caused by these drugs (2, 17, 23, 26, 28). In the study described here, we assessed patients who had reportedly experienced adverse reactions to APs. Our objective

was to determine the relative frequencies of immediate and delayed types of hypersensitivity to these drugs, and to evaluate the potential contributions of skin and patch testing to the diagnosis of the latter.

Material and methods

The study included all patients seen by our staff between 1987 and 1992 with histories of adverse cutaneous reactions to one or more APs. The protocol used included the following immunoallergologic tests.

Skin tests

Skin tests (prick and intradermal) used the following haptens:

- 1) PPL (Allergopen, Reinbek, Germany). The undiluted solution was obtained by reconstituting the lyophilized contents of a vial containing 0.175 mg of PPL plus 20 mg of mannitol in 5 ml buffer. A 1:10 dilution in 0.9% NaCl was initially used. When results were negative, the test was repeated with the undiluted solution.
- 2) MDM (Allergopen) containing 0.6 mg benzylpenicillin and 0.5 mg benzylpenicilloate per milliliter. Initial testing was done with a 1:10000 solution in 0.9% NaCl; tests were repeated with a 1:10 dilution when initial results were negative.
- 3) Penicillin G potassium (PG) (Bristol Italiana, Sermoneta, Italy) was used at increasing concentrations ranging from 0.2 IU/ml to 2000 IU/ml (diluted in 0.9% NaCl).
- 4) Ampicillin (AM) (Amplital, Farmitalia, Milan, Italy) and amoxicillin (AX) (Velamox, Zambelletti, Milan, Italy) were diluted in 0.9% NaCl and used at a concentration of 1 mg/ml.

All of the above haptens were initially tested on the volar forearm skin by the prick method. Reactions were considered to be positive when a wheal > 3 mm in diameter was present 15–20 min later. When prick tests were negative, 0.02 ml of the hapten solution was injected intradermally within the volar forearm skin. Readings were made 20 min and 48 h after injection; results were defined as positive when wheals > 5 mm were present. Positive controls for prick and intradermal tests were done with histamine (at 10 and 1 mg/ml, respectively). Normal (0.9%) saline was used as a negative control.

Patch tests

Patch tests were done with 1) PG (5000 IU/g in vaseline), 2) AM (5% in vaseline), and 3) AX (5% in vaseline). The patches were applied to the interscapular area of the back and read after 48 and 72 h. Results were defined according to the criteria of

Wilkinson et al. (30). Biopsies of the reactive skin were taken in four cases. Control patch tests in 20 healthy subjects, who had previously been treated with APs without any adverse effects, were all negative.

Radioallergosorbent test (RAST)

In vitro assays were done with the Phadebas RAST (Pharmacia, Uppsala, Sweden) for antigen-specific IgE against penicilloyls G and V.

Oral challenge with penicillin V (PV) and APs

Thirty-four of the patients who had described maculopapular reactions to APs agreed to submit to oral challenges with PV (Fenospen, Farmitalia), as well as with AM (Amplital, Farmitalia) or AX (Velamox, Zambelletti). These patients were admitted to the day hospital for 24 h. The APs were initially administered at a dose of 5 mg; if no reaction occurred, the challenge was repeated with 50 mg, and eventually with 500 mg. The PV challenge was initially administered at a dose of 1000 IU and repeated, when negative, at 10000 IU and eventually with 100000 IU. All repeat challenges were administered 1 week after the previous challenge.

Statistical analysis

The differences between percentages were assessed by the chi-square test, and those between means, by Student's *t*-test for unpaired data.

Results

We examined a total of 195 patients (147 females, 48 males; age range: 13–86 years; mean age: 37 ± 15.38 years) with histories of adverse reactions to APs. The mean period of time that had elapsed between the last known antigen exposure and our allergologic work-up was 40.50 ± 55.65 months. Fig. 1 shows the APs reported by these patients as causes of the adverse reactions they had experienced: the most frequently implicated antibiotic was AM, followed by AX and bacampicillin (BC). Fourteen patients had reportedly experienced reactions to two of the above APs, and 26 of the 195 described reactions to other β -lactam antibiotics as well (cephalosporins in 14 cases, PG in 11, and piperacillin in one).

The clinical manifestations described by the patients are listed in Table 1. In the vast majority of cases, the symptoms were exclusively cutaneous: systemic involvement was reported in less than 20%.

Thirty-five of the 195 patients (17.9%) were diagnosed, on the basis of positive prick or intradermal tests, RAST, or all three, as having had immediate

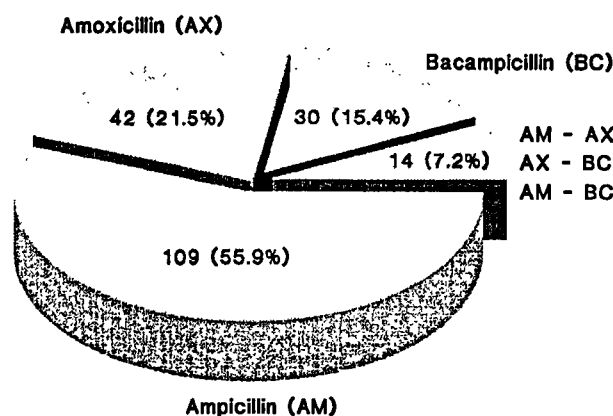


Fig. 1. Aminopenicillins reported as causes of adverse cutaneous reactions by 195 patients assessed.

Table 1. Clinical manifestations described by subjects studied and results of allergologic tests

Symptoms	No. patients studied	No. IH* patients	No. DH** patients
Urticaria	46	6	—
Angioedema	19	1	—
Urticaria/angioedema	18	6	—
Maculopapular rash	60	—	33
Erythema	16	—	—
Bullous eruption	4	—	—
Anaphylactic shock	21	18	—
Urticaria/angioedema and respiratory symptoms	10	3	—
Urticaria/angioedema and gastrointestinal symptoms	1	1	—

* Immediate hypersensitivity diagnosed on basis of skin tests or RAST.

** Delayed hypersensitivity diagnosed on basis of delayed intradermal reactivity and patch tests (and oral challenges in 18).

hypersensitivity (IH) reactions. Eighteen of these patients had reportedly experienced anaphylactic shock; the other 17 had developed urticaria, angioedema, or both, accompanied by respiratory disturbances (dyspnea, rhinitis, asthma) in three cases and by gastrointestinal disturbances in one. In 31 of the 35 (88.6%), onset of symptoms occurred within 1 h of administration of the drug; in the remaining four (11.4%), symptoms first appeared 2 h after oral administration (BC in three cases, AM in one).

The patterns of reactivity for these 35 IH patients are shown in Table 2. Five showed skin-test positivity only for APs, while 13 others were also positive for PPL, MDM, PG, or for two or all of these. Three of these latter 13 had, in fact, reported adverse reactions to PG as well as APs. Sixteen reacted positively to PPL, MDM, PG, or to two or all of these but showed no reaction to any of the APs tested. The remaining patient responded negatively to all skin tests, although he showed positivity for

Table 2. Patterns of skin-test reactivity in 34/35 patients with immediate hypersensitivity

PPL	MDM	PG	AM	AX	No. patients
—	—	—	+	+	4
—	—	—	+	—	1
+	—	—	+	+	5
—	+	+	+	+	5
+	+	+	+	+	2
—	+	—	+	+	1
+	—	—	—	—	11
—	+	—	—	—	4
—	+	+	—	—	1

penicilloyl G and V in RAST. RAST results were positive for penicilloyl G and V in 13/35 IH patients, including the one mentioned above.

Sixty of the 195 patients we examined had reportedly experienced maculopapular reactions. Thirty-three of these patients were diagnosed as having DH, as reflected by positive patch-test results and delayed positivity in the intradermal tests. The clinical manifestations experienced by these patients consisted of maculopapular skin eruptions accompanied by angioedema in 12 cases. In 10 patients, the maculopapular eruption had gradually assumed an urticarial aspect after confluence of the original lesions. According to patients' reports, all of these symptoms had appeared 24 h or more after initiation of AP treatment, and had persisted for several days after the drugs had been discontinued and corticosteroid therapy had been started. In 8/33 cases, the involved skin underwent a desquamative phase before healing. In 3/33 patients, the cutaneous symptoms had been accompanied by high fever.

All 33 patients presented patch-test positivity and delayed intradermal reactions to both AM and AX; three were also positive (patch and delayed intradermal reactions) for PG. There were no delayed reactions to PPL or MDM. Biopsies of patch-tested skin in four of these 33 patients showed perivascular lymphocyte-eosinophil infiltrates and epidermal spongiosis (Fig. 2).

Eighteen of these 33 patients had received oral challenges with AM or AX and PV. All 18 reacted positively to the APs (13 to AM, five to AX; 12 of the 18 reacted to the 5-mg challenge, and six to the 50-mg challenge) with diffuse maculopapular eruptions; 10 also developed angioedema of the face, hands, and feet. The PV challenge (up to 1000000 IU) was well tolerated by all but one: this patient, who had reacted to PG in the patch and intradermal tests as well, developed a mild diffuse maculopapular eruption 6 h after the 1000-IU challenge. All of the positive reactions to the oral challenge occurred between 6 and 24 h after administration: 13 patients began to manifest symptoms 6–12 h after the challenge (seven during the sixth hour) and



Fig. 2. Biopsy of patch-tested skin from patient who reacted positively to AM. In epidermis, there is diffuse spongiosis with numerous vesicles and lymphocytic exocytosis. Papillary dermis is edematous and lymphocytic infiltrate is present around superficial and deep vascular plexi. Follicular involvement is evident with spongiosis and lymphocytic exocytosis. Scattered eosinophils are also present throughout specimen.

in the remaining five, symptoms appeared 13–24 h after provocation.

Twenty-seven other patients who had described maculopapular rashes during AP therapy had negative results in all of the allergologic tests. Sixteen of these agreed to submit to challenges (11 with PV and AM, five with PV and AX), which failed to provoke any symptoms.

All allergologic tests were negative in the 20 patients noted in Table 1 whose reactions had shown erythema or bullous eruptions.

Table 3 shows the length of time that had elapsed between the most recent adverse reaction and our allergologic work-up for the IH and DH subgroups. Over half of the patients whose test results indicated IH had been tested within 12 months of their last known antigen exposure. This finding represented a significant difference ($\chi^2 = 9.01$; $P < 0.01$) with respect to the group found to have DH, in which only seven (21%) of the 33 had been assessed within 1

year of the most recent reaction. The mean intervals between the most recent reaction and testing for the two subgroups (IH: 18.62 ± 31.63 months; DH: 54.96 ± 70.59 months) were also significantly different ($t = 2.63$; $P < 0.01$).

Discussion

The protocol used to examine the 195 patients described here, all of whom reported adverse reactions during AP therapy, indicated that only 68 (34.8%) had actually experienced allergic reactions, and nearly half of these (48.5%) were delayed, non-IgE-mediated reactions.

Our findings confirm those of other investigators (6, 23, 26) who have noted that maculopapular eruptions seem to be typical of delayed reactions to APs. In contrast, all of the patients with IH had developed urticarial, angioedematous, or both manifestations, and 18 had experienced anaphylaxis, which was not reported by any of those with delayed reactions.

Within our study population, there were also 27 patients with histories of maculopapular reactions and negative results in all of the tests (including patch tests). It is also probable that the cutaneous symptoms described by these patients were "coincidental reactions"; i.e., manifestations of the underlying infection itself rather than allergic reactions to the drugs prescribed to treat it (24). This interpretation is supported by the negative responses observed in 16 of these 27 patients to oral challenges with AM or AX and PV. It is also possible that some of these 27 patients were suffering from infectious mononucleosis when their reactions occurred. This disease appears to provoke biologic alterations in the immune system that can increase the risk of reactions to AM, although the mechanisms involved in the Epstein-Barr virus/AM interaction are still unclear (9). Kluge et al. have reported delayed intradermal reactions to AM in patients with mononucleosis, but patch tests and oral challenges with this drug were not done in these subjects (10). In any case, the reappearance of symptoms provoked by the oral challenges in 18 other patients with positive skin test results indicates that a specific immunologic mechanism is involved in many of the maculopapular eruptions associated with AP use. Similar findings have been reported by others (23, 26).

One of the most striking findings to emerge from this study is that nearly half of the allergic reactions diagnosed involved delayed, non-IgE-mediated hypersensitivity. The relatively high number of patients with DH reactions in this series may be partially due to the timing of the allergologic evaluation: on the average, these 195 patients were tested by our staff more than 3 years after their most recent adverse reaction. When we analyzed the positive cases in

Table 3. Relationship between positive results in allergologic tests and time elapsed since last adverse reaction

Time interval (years)	No. patients with positive results	
	Immediate hypersensitivity	Delayed hypersensitivity
<1	21	7
1–2	8	6
3–4	2	9
5–6	2	3
>6	2	8
	35	33

light of this factor (Table 3), we discovered that 21 (60%) of the 35 patients found to have IH had been tested within 1 year of their reaction; as the reaction-testing interval increased, the number of positive results decreased. A very different trend emerged from the same analysis of patients diagnosed with DH: 60.6% of these 33 patients were diagnosed more than 2 years after their most recent reaction. In addition, the mean reaction-testing interval for those diagnosed with IH (less than 2 years) was markedly shorter than that seen for the DH subgroup (more than 4 years).

Whereas the interval between the reaction and testing may influence test results in cases of IH (7, 11, 22, 29), our findings indicate that the time of testing is less important in cases of DH. Although further study will be necessary to confirm our suspicion, it would appear that negative patch and skin tests with APs in a patient with a maculopapular reaction are a fairly reliable indicator that the eruption was not an immune phenomenon triggered by the antibiotic, but rather a manifestation of the disease process itself. In contrast, negative results in a patient with an immediate reaction must be interpreted in light of the time that testing is performed.

In the series described here, 77 patients who complained of urticarial, angioedematous, or both reactions (which appear to be characteristic of IH) had negative results in all of the allergologic tests. Over half of these (39/77) were first seen by our staff more than 1 year after the most recent adverse reaction. The negative findings in three of the 21 patients who had experienced anaphylactic reactions to an AP are undoubtedly related to the fact that these patients were tested, respectively, 10, 18, and 21 years after their adverse reaction.

Another significant aspect that emerges from this study is the importance of the amino group in the side-chain of the AP molecule in provoking delayed reactions. In 30 (90.9%) of the 33 patients with this type of hypersensitivity, skin and patch test findings were positive for AM and AX, but negative for PG. Oral challenge responses also indicated good tolerance of penicillin in the vast majority of these patients. The remaining three patients of this subgroup showed positive reactions to PG, as well as to AM or AX, but there were no cases of positivity to PG, PPL, or MDM alone. An identical picture has been described by de Haan et al. (6) in a patch-test study of patients suffering maculopapular reactions to APs. Stejskal et al. (21) have provided *in vitro* data which further confirm the importance of the amino group in the side-chain in these reactions: in lymphocyte-stimulation studies of patients with contact dermatitis caused by APs, PG was consistently incapable of inducing a positive response. The amino group in the side-chain seems to be less important

in specific IgE-mediated reactions: only 14% of the IH patients in our series presented skin test positivity for the APs alone.

The above findings show the importance of skin tests with APs themselves in patients reporting adverse reactions to these antibiotics. Skin tests with PPL and MDM may fail to detect side-chain-specific reactions to individual APs. In the previously cited study by Gadde et al. (8), penicillin challenges were administered to 649 patients with histories of adverse reactions to penicillin or other β -lactams (more detailed descriptions of the culprit drugs were not provided) and negative skin tests with PPL and MDM. Only 17 (2.9%) experienced probable IgE-mediated reactions, prompting the authors to conclude that the vast majority of patients with previous penicillin allergies can tolerate full-dose treatment, if penicillin skin tests are negative. It is difficult to predict the implications of these findings for patients like those in our study, all of whom had reported reactions during treatment with APs. In light of the severity of the reactions experienced by our IH patients (urticaria, angioedema, both urticaria and angioedema, anaphylactic shock), we did not do oral challenges in any of these cases. For this reason, we cannot comment on the predictive value of negative skin tests with PPL and MDM in this type of patient.

Patch testing also proved to be a useful tool in evaluating adverse reactions to APs, particularly those manifested by maculopapular eruptions, although the significance of patch-test positivity is similar to that that can be attached to tuberculin-like reactions that appear 12–24 h after intradermal injections of these drugs. All of the DH patients in this study presented positive reactions to both types of test. However, our experience, as well as that of others (2), indicates that there are cases characterized by delayed intradermal-test positivity and patch-test negativity. The significance of these patterns of reactivity has yet to be fully defined. However, the results of this study confirm that the presence of both patch-test and delayed intradermal positivity in patients reporting maculopapular reactions during AP therapy is a clear indication of delayed hypersensitivity to these drugs.

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