

Skin tests in the diagnosis of eruptions caused by betalactams

P. LISI, V. LAPOMARDA, L. STINGENI, D. ASSALVE, K. HANSEL, S. CARAFFINI AND D. AGOSTINELLI

Allergologic and Environmental Dermatology Unit, Department of Medical and Surgical Specialities, University of Perugia, Policlinico Montelucente, I 06100 Perugia, Italy

The aetiological evaluation of adverse cutaneous reactions to penicillins is still not an easy problem to solve. Skin testing is usually carried out intradermally with benzylpenicilloyl polylysine (BPO-PPL) and minor determinant mixture (MDM), but these are often unsuitable for the detection of sensitivity to betalactam antibiotics. 101 selected subjects, with different cutaneous reactions to betalactams and with a clinical history of positive challenge, were skin tested (patch test, prick test, intradermal test) with a standard betalactam series (amoxycillin, sodium penicillin G, ampicillin, bacampicillin, aztreonam, ceftriazone, BPO-PPL, MDM). 1 or more positive reactions to skin tests, mainly to intradermal tests, were observed in 47.5% of the subjects studied, especially in those with maculopapular eruptions, urticaria/angioedema and drug reactions caused by ampicillin and amoxycillin. Cross-sensitivity was demonstrated in 22.8% of cases and was due almost solely to the semisynthetic penicillins. Finally, to increase the yield in detecting positive patients, it is necessary that ampicillin and amoxycillin be tested in addition to major and minor determinants.

Key words: drug reactions; betalactams; antibiotics; skin tests; patch test; intradermal test; cross-sensitivity. © Munksgaard, 1997.

Accepted for publication 1 May 1997

The aetiological evaluation of cutaneous and mucous reactions to systemic drugs is still not an easy problem to solve (1-3), and no easier when immunologic mechanisms are involved. It is well-known that *in vitro* tests are not dangerous but not very reliable (4-6), while those *in vivo* are sometimes hazardous and provide contrasting results (3, 5).

The radioallergosorbent test (RAST) is suitable in some drug reactions and mainly in those caused by penicillins (7), but positive results are obtained only in patients with anaphylactic shock, urticaria and serum sickness-like reactions. In these disorders, and especially in exanthematic, eczematous and erythrodermic eruptions, fixed eruptions and anticonvulsant-induced rashes, skin tests are very useful, even if the safe patch test is still thought to be less helpful in comparison to the risky intradermal test.

Skin tests are widely used for the diagnosis of allergic reactions to penicillins, but the classical reagents benzylpenicilloyl polylysine (BPO-PPL) and minor determinant mixture (MDM) are often unsuitable for the detection of sensitivity to betalactams (1, 8).

For all these reasons and to study cross-reactivity among these drugs, we have carried out skin tests in a group of patients with different cutaneous reactions to semisynthetic penicillins using a standard betalactam series.

Materials and Methods

In the last 3 years, 101 selected subjects (66 female, 35 male) aged from 15 to 87 years (average age, 46.1 years), with a history of cutaneous drug reactions (urticaria/angioedema, 44; maculopapular eruptions, 32; anaphylactic shock, 13; other disorders, 12), were investigated. The undesired effects were caused by betalactam antibiotics (amoxycillin, 46; sodium penicillin G, 19; ampicillin, 13; bacampicillin, 3; cephalosporins, 20), as suggested by personal history of relapse of the clinical picture after inadvertent re-administration of the drug or a chemically-related compound.

All subjects were evaluated by a diagnostic protocol planned to include, in chronological order, patch tests, prick tests and intradermal tests with the causative drug and the substances reported in Table 1. Some of these were chosen in order to investigate possible allergic cross-reactivity among

Table 1. Betalactam series used for skin tests

	Patch tests ^o (%)	Prick tests ^{oo} (mg/ml)	Intradermal tests [†] (mg/ml)
amoxycillin	25	5	5
sodium penicillin G	5	5 ^a	5 ^a
ampicillin	25	5	5
bacampicillin	25	5	5
aztreonam	20	20	5
ceftriazone	20	20	5
BPO-PPL*	—	0.035	0.035
MDM**	—	0.6+0.5	0.6+0.5
saline solution	—	as is	as is
histamine hydrochloride	—	10	0.1

^o In petrolatum; ^{oo} in hydroglyceric solution (1:1); [†] in phosphate-buffered saline solution.

* Benzylpenicilloyl polylysine (Bracco, Milano), tested in 81/101 subjects.

** Minor determinant mixture: benzylpenicillin+benzylpenicilloate sodium salts (Bracco, Milano), tested in 81/101 subjects.

^a Equal to 3010 IU.

penicillins and between penicillins and 2 betalactams, 1 of the monobactam group (aztreonam) and the other of the 3rd generation cephalosporins. Concentrations and vehicles used were deduced from data in the literature (9, 10) and from our previous experience (3).

Patch tests were performed on the back according to ICDRG criteria, while prick tests and intra-

dermal tests were performed on the volar forearm using 0.05 ml of the various solutions. Wheal reactions were read at 10 and 20 min and judged positive when the test side was equal to or greater than the histamine reaction. Subjects were reassessed 1 and 2 days after skin testing to evaluate possible delayed reactions (tuberculin or eczematous type).

In order to insure the safety of patients who suffered from angioedema and anaphylactic shock, prick tests and intradermal tests were carried out in an environment suitable for resuscitation. Written informed consent was obtained from all subjects.

Results

1 or more positive reactions to skin tests were observed in 48 (47.5%) of the 101 subjects studied and especially in those who suffered from maculopapular eruptions or urticaria/angioedema (Table 2). The intradermal tests were positive in 41/48 subjects (Table 2), but in 20 of these, there was an overlap in positivity of the different tests and, in particular, between patch tests and intradermal tests in 5, between prick tests and intradermal tests in 4, and between all 3 tests in 11. In the remaining 7 patients, 5 showed positive reactions only to patch tests and 2 only to prick tests.

The results of skin tests with the causative drugs are shown in Table 3. The most commonly positive

Table 2. Positive skin test reactions and clinical manifestations in 101 patients with a history of betalactam adverse reactions

Clinical manifestations	Positive reactions							
	total		patch tests		prick tests		intradermal tests	
	no.	(%)	no.	(%)	no.	(%)	no.	(%)
urticaria/angioedema	24/44	54.5	9	20.5	7 (0)	15.9	22 (0)	50.0
maculopapular eruptions	20/32	62.5	10	31.2	10 (8)	31.2	16 (12)	50.0
anaphylactic shock	0/13	0.0	0	0.0	0	0.0	0	0.0
other disorders	4/12	33.3	2	16.7	0	0.0	3 (0)	25.0
total	48/101	47.5	21	20.8	17 (8)	16.8	41 (12)	40.6

In parentheses, positive delayed reactions.

Table 3. Positive skin test reactions and causative drugs in 101 patients with a positive history of betalactam adverse reactions

Clinical manifestations	Positive reactions							
	total		patch tests		prick tests		intradermal tests	
	no.	(%)	no.	(%)	no.	%	no.	(%)
amoxycillin	24/46	52.2	8	17.4	8 (5)	17.4	22 (9)	47.8
sodium penicillin G	7/19	36.8	4	21.1	2 (0)	10.5	6 (0)	31.6
ampicillin	7/13	53.8	5	38.5	4 (3)	30.8	6 (3)	46.2
bacampicillin	2/3	66.7	1	33.3	1 (0)	33.3	2 (0)	66.7
cephalosporins	8*/20**	40.0	3	15.0	2 (0)	10.0	5 (0)	25.0
total	48/101	47.5	21	20.8	17 (8)	16.8	41 (12)	40.6

* Cephalixin 4; cephaloridine 2; ceftriazone 2.

** Cephalixin 9; cephaloridine 5; ceftriazone 3; cefatrizine 1; cefaclor 1; cefonicid 1.

In parentheses: positive delayed reactions.

Table 4. Cross-reactions among betalactam antibiotics

Causative drugs	Subjects (no.) with cross-reactions	Cross reactions					
		A	SPG	Am	B	Az	C
A	12/24		—	10	3	—	1
SPG	1/7	1		1	—	—	—
Am	7/7	4	4		4	—	—
B	2/2	2	2	1		—	—
Ce	1/4	—	1	—	—	—	—

A: amoxycillin; SPG: sodium penicillin G; Am: ampicillin; B: bacampicillin; Az: aztreonam; C: ceftriazone; Ce: cephalixin.

reactions were observed in subjects who reported cutaneous eruptions to ampicillin (7/13) and amoxycillin (24/46). Only 2 of these were positive to BPO-PPL or MDM.

Cross-reactions among betalactams can be seen in Table 4. These were documented in 23 patients (22.8%) and were more frequent in patients sensitized to ampicillin (7/7) and to amoxycillin (12/24). Skin testing was well tolerated in 99 patients. In the remaining 2, intradermal testing provoked a relapse of the skin manifestations: angioedema of the lips in one, morbilliform rash of the trunk in the other.

Discussion

In about half the cases studied (47.5%), sensitivity to 1 or more betalactam antibiotics was revealed by skin tests and mainly by intradermal tests. These and prick tests, however, must be re-evaluated after 1 and 2 days because delayed positive reactions are frequent (12/41 and 8/17, respectively) (Table 3). It is interesting to underline the positiveness of patch tests in 21 subjects (20.8%), 10 of whom suffered from maculopapular eruption and 9 from urticaria/angioedema, probably mediated by immune complexes.

The clinical pattern seems to influence the frequency of positive skin test reactions, which was higher in maculopapular eruptions and urticaria/angioedema than in anaphylactic shock. In the latter disorder, the negative reactions were likely in relation either to the fact that specific IgE antibodies have often been found only in the first days and/or weeks of eruptions (11), or to the symptoms not being immunomediated.

Among the betalactams investigated, positive skin tests to amoxycillin and ampicillin were the most common. As these were practically never associated with sensitivity to major and minor breakdown products of penicillin, it is probable that side-chains, besides the nuclear portion (betalactam and thiazolidine rings), are involved in the sensitization. In fact, the side-chain of amoxycillin and ampicillin differs from that of benzylpenicillin as it has an α amino group. The remaining phenyl

(ampicillin) or *p*-hydroxy phenyl (amoxycillin) groups are not unlike many other penicillins (12).

The importance of the side-chain structure seems highlighted by cross-sensitivity between betalactam antibiotics. This was demonstrated in 22.8% of our patients and was due almost solely to the semisynthetic penicillins (ampicillin, amoxycillin, bacampicillin), which are one of the major classes of betalactams (penicillins, cephalosporins). Cross-reaction between amoxycillin and ceftriazone was observed in only 1 case, while skin tests with aztreonam were always negative. Therefore, cephalosporins (and in particular those of the 3rd generation), monobactams and betalactams of the other 3 minor classes (carbapenems, oxacephems, clavams) can be administered to the patients allergic to penicillins (13–15), but only after having tested these compounds.

In conclusion, a careful history and the easy performance of skin tests are very useful in the diagnosis of undesirable cutaneous and mucous reactions from systemic betalactams, as well as in the study of cross-reactivity. As intradermal testing bears a definite risk of generalized reactions (2, 5), it is advisable to carry this out only when patch tests and prick tests are negative. Nevertheless, patients with a history of Stevens-Johnson or Lyell syndrome, anaphylactic shock or serious angioedema, should not be evaluated by skin tests. Finally, to increase the yield for detecting positive patients, it is necessary that several semisynthetic penicillins (i.e., ampicillin, amoxycillin) be tested in addition to major and minor determinants.

References

1. Blanca M, Vega J M, Garcia J, Carmona M J, Terrados J, Avila M J, Miranda A, Juarez C. Allergy to penicillin with good tolerance to other penicillins; study of incidence in subjects allergic to betalactams. *Clin Exp Allergy* 1990; 20: 475–481.
2. Shear N H. Diagnosing cutaneous adverse reactions to drugs. *Arch Dermatol* 1990; 126: 94–97.
3. Mencacci A, Perno P, Lisi P. I test cutanei nella diagnostica delle reazioni cutaneo-mucose da farmaci. *Ann Ital Dermatol Clin Sper* 1992; 46: 33–36.
4. Kraft D, Berglund A, Rumpold H, Roth A, Ebner H. Radioallergosorbent test with conjugates specific for minor

- haptenic determinants in the diagnosis of IgE-mediated penicillin allergy in man. *Clin Allergy* 1981; 11: 579-587.
5. Weiss M E, Adkinson N F. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy* 1988; 18: 515-540.
 6. Società Italiana di Allergologia e Immunologia Clinica. Diagnostica di allergia a farmaci. *Folia Allergol Immunol Clin* 1989; 36: 437-465.
 7. Jarisch R, Roth A, Boltz A, Sandor I. Diagnosis of penicillin allergy by means of Phadebas® RAST penicilloyl G and V and skin tests. *Clin Allergy* 1981; 11: 155-160.
 8. Terrados S, Blanca M, Garcia J, Vega J, Torres M J, Carmona M J, Miranda A, Moya M, Juarez C, Fernandez J. Nonimmediate reactions to betalactams: prevalence and role of the different penicillins. *Allergy* 1995; 50: 563-567.
 9. Sertoli A, Gola M, Farli M, Lombardi P. Test cutanei e test dose nelle reazioni indesiderate da farmaci. *Folia Allergol Immunol Clin* 1989; 36: 423-430.
 10. Patterson R. Diagnosis and treatment of drug allergy. *J Allergy Clin Immunol* 1988; 81: 380-384.
 11. Kraft D, Wide L. Clinical patterns and results of radioallergosorbent test (RAST) and skin tests in penicillin allergy. *Br J Dermatol* 1976; 94: 593-601.
 12. Blanca M, Vega J M, Garcia J, Miranda A, Carmona M J, Suarez C, Terrados S, Fernandez J. New aspects of allergic reactions to betalactams: crossreactions and unique specificities. *Clin Exp Allergy* 1994; 24: 407-415.
 13. Soley G O, Gleich G J, Van Dellen R G. Penicillin allergy: clinical experience with a battery of skin test reagents. *J Allergy Clin Immunol* 1982; 69: 238-244.
 14. Saxon A, Swabb E A, Adkinson N F Jr. Investigation into the immunologic cross-reactivity of aztreonam with other betalactam antibiotics. *Am J Med* 1985; 78: 19-26.
 15. Martin J A, Igea J M, Fraj J, Lezaun A A, Parra F, Losada E. Allergy to amoxycillin in patients who tolerated benzyl penicillin, aztreonam and ceftazidime. *Clin Infect Dis* 1992; 14: 592-593.

Address:

Paolo Lisi
Dermatologia allergologica e ambientale
Dipartimento di Specialità medico-chirurgiche
Policlinico Monteluce
I 06100 Perugia
Italy

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.