

Skin tests in the diagnosis of betalactam allergy

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Summary

The sensitivity of prick and intradermal tests in the diagnosis of immediate reaction to betalactams mainly depends on the drug that elicited the reaction and the time elapsed from the clinical reaction. For penicillins the use of the major determinant (BPO-polylysine), a mixture of minor determinants (MDM), benzylpenicillin and aminopenicillins have a sensitivity of 60–90%. Taking into consideration that 10% of cases of penicillin allergy were made during rechallenge study, it supports the need to include this procedure in the study of penicillin allergy. This is particularly important in patients with immediate reactions sensitised only to aminopenicillin with good tolerance to penicillin and if the time elapsed from last reaction is more than 6 months. For immediate reactions to cephalosporins the sensitivity of the skin test is less than for penicillins, approximately 50%. For other betalactams the experience is limited and no conclusion can be drawn. The value of late reading of intradermal tests and the patch test in late reactions to betalactams is also limited but can be useful in approximately 40–80% of cases. © 2002 Éditions scientifiques et médicales Elsevier SAS

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Betalactam antibiotics share in common the betalactam ring. Other ring are attached to it, thiazolidine in the case of penicillins, dihydrotiazine for cephalosporins, five radicals for carbapenems, and without a ring in the case of monobactams. On the other side of the ring a side chain confers different microbiological and pharmacokinetic properties. Some cephalosporins also share a side chain with penicillins. For example, the amoxicillin side chain is the same as that of cephadroxil, and ampicillin has the same side chain as cephalixin.

The pattern of allergic reaction to β -lactams is changing, as is also the consumption of different penicillins. In Spain, for example, during 1994, the consumption of PG was 1,311,300 units, while that of semi-synthetic penicillins was 268,551,000 units, amoxicillin comprising 95% of those. This fact is

responsible for different pattern of sensitization to penicillins. In 1988, Blanca et al. [1] first described patients allergic to amoxicillin, but with good tolerance to penicillin G. Years later, the same group [2] reported that 54 of 177 (30.5%) patients allergic to betalactams were allergic to amoxicillin, but with good tolerance to penicillin G. In our study [3], this percentage was slightly lower (21%) but this difference is not statistically significant.

Hypersensitivity reactions to cephalosporin are less common than with penicillins, and anaphylactic reactions are rare. Probably, this is in part due to the wider consumption of penicillins, which are the most commonly prescribed antibiotics in the world. There are some contradicting data about a true allergic cross-reactivity to cephalosporins in patients who have had a previous allergic reaction to penicillins [3-8]. Clinical cross-reactivity in allergic reactions between penicillin and cephalosporin with the same side chain observed by different authors is between 12% and

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38% [3, 6, 7]. However, the cross reactivity with cephalosporins with different side chain seems to be less [4, 5]. In a recent study published by our group [9], 41 patients allergic to penicillin G or amoxicillin tolerated cephalazolin, cefuroxime and ceftriaxone, all cephalosporins with a different side chain to that of the penicillin which caused the reaction.

According to the time interval between drug administration and the onset of symptoms, reactions to betalactams have generally been classified as immediate and non-immediate or late reactions. Immediate reactions occur within the first hour and include entities such as anaphylaxis and urticaria. They are known to be IgE-mediated although they needed the collaboration of activated T-cells. In the case of late or non-immediate reactions there is also evidence of T-cell involvement in their pathogenesis [10]. The clinical spectrum includes maculopapular rash, exanthems, desquamative exanthems, urticaria/angioedema, interstitial nephritis, serum sickness-like syndrome, bullous reactions and fixed drug eruption.

ANTIGENIC DETERMINANTS OF BETALACTAMS

Betalactams are reactive structures with the capacity to induce an immune response. Apart from the unmodified penicillin molecule, and in addition to penicilloyl or the so-called major determinant of penicillin, other minor determinants seem clinically important, e.g., penicilloic acid, penicillenate, penicillanyl, penamaldate, penaldate, d-penicillamide and penicoyl. Penicillin antigens can be formed by linkage of the drug to carrier protein via different functional groups of the molecule, for example, opening of the betalactam ring (peniciloyl determinant), through the C-3 carboxyl (penicillanyl determinant) and attachment to the ring S (penicillenate determinant). During the last years, it has been reported that the side chain seems to play a role as antigenic determinant in some allergic reactions to betalactams [2, 3].

Experimental studies on identification of cephalosporin epitopes, confirmed by clinical studies, indicate that there are antibodies that recognize structures unique to cephalosporins, with little or no recognition of penicillins. But few allergenic determinants of cephalosporins have been identified so far.

REAGENTS FOR DIAGNOSIS OF IMMEDIATE REACTIONS TO BETALACTAMS

Penicillins

The major determinant, BPO-polylysine conjugate, a mixture of minor determinants (benzyl-penicillin and benzylpenicilloate) and aminopenicillins have been used as reagents for skin tests for diagnosis of immediate or IgE-mediated reactions to penicillins. Several studies have shown that all of these reagents must be used to increase the sensitivity of the diagnosis. The following reagents are used for the skin tests in our clinic [3, 9]: penicilloyl-polylysine (PPL) 5×10^{-5} M and a minor determinant mixture with benzylpenicillin and benzylpenicilloate (MDM) 1×10^{-2} M from Allergopharma JGKG (Hamburg, Germany), benzylpenicillin (penicillin G) sodium salt diluted in saline solution until reaching a concentration of 10,000 IU/mL; sodium amoxicillin or other aminopenicillin was applied in a concentration of 25 mg/mL in saline.

Skin tests are performed on the forearm by prick testing. A wheal 3 mm greater than glycerosaline with a surrounding area of erythema was considered positive. If the prick tests were negative a minimal amount (0.01–0.03 mL) of the testing material was injected intradermally. A wheal, 5 mm greater than the control, with a surrounding area of erythema was considered positive. Skin tests were evaluated at 20 minutes at 6, 24 and 48 hours. As controls, histamine HCL 10 or 1 mg/mL and glycerosaline or saline were used.

If the intradermal skin test with PPL, MDM and penicillin G was negative, penicillin G was administered intramuscularly, beginning with 1,000 IU and increasing progressively to as much as 1,200,000 IU. Oral aminopenicillins are administered in progressively increasing doses from 25 mg up to 500 mg (or adjusted by weight) every 45 minutes, unless a reaction occurred. After completing the dose of penicillin G or aminopenicillins, the patient was requested to return 20 days later to be skin-tested and challenged in a manner identical to the initial evaluation (rechallenge). During this period, the patients were carefully monitored for symptoms compatible with an allergic reaction. All challenge tests were carried

out in a single blind fashion. Complete equipment for cardiopulmonary resuscitation is always available in our clinic.

Cephalosporins and other betalactams

Cephalosporins and other betalactams are prepared in saline at 25 mg/mL and 250 mg/mL for prick test and 2.5 mg/mL and 25 mg/mL for intradermal tests. These concentrations had previously been shown to be non-irritating in subjects with no history of betalactam sensitivity, although in some cases doubtful reactions may be elicited. If skin tests were negative with cephalosporin reagents, oral/intramuscular doses were administered beginning with 25 mg and increasing progressively to as much as 500 mg (adjusted by age/weight) in 2 days. Oral cephalosporins are administered in progressively increasing doses from 25 mg up to 500 mg every 45 minutes, unless a reaction occurred.

SKIN TEST FOR DIAGNOSIS OF LATE REACTIONS TO BETALACTAMS

Intradermal tests reading at 6, 24 and at 48 hours. A wheal with induration 5 mm greater than the control was considered positive.

Patch tests reagents are prepared with penicillin G at 5,000 IU/g petroleum jelly, aminopenicillins and cephalosporins at 5% in petroleum jelly. Occlusion time is 48 hours. Readings are done 15 minutes after removal strip and 24 hours later. Readings are made as recommended by contact dermatitis groups.

SENSITIVITY AND SPECIFICITY OF SKIN TEST FOR DIAGNOSIS OF IMMEDIATE REACTIONS TO BETALACTAMS

The sensitivity of prick and intradermal tests in the diagnosis of immediate reaction to betalactams mainly depends on the drug studied and the time elapsed from the clinical reaction. In our experience, the sensitivity is very high when studying reactions to penicillin, independent of the time elapsed from last reaction. In nearly 1,000 cases studied in recent years in our clinic only two patient had negative skin tests but positive parenteral challenge test. Nevertheless, this is not the case for aminopenicillins because the predicted value depends on the time elapsed from

the last reaction in many cases. In the interval of 3 years many patients may have negative skin tests and positive challenge test [12]. This is particularly important in patients sensitised only to aminopenicillin with good tolerance to penicillin. In a large study in a sexually transmitted diseases clinic, using penicilloyl polylysine and benzylpenicillin as minor determinant reagent [13] the appearance of an IgE-mediated reaction in patients with negative skin tests was 2.6% and 5.4% for any immunologic reaction. Other studies [1-3, 8, 9, 14-16] confirm the high sensitivity of skin tests if all reagents are used.

An important issue to keep in mind is the possibility of resensitisation, albeit the very low rate – 2–3% [17]. In our study protocol we include retesting and rechallenge 2 weeks after the first study. In our experience [12, 13], and of others [11, 18], 10% of cases of penicillin allergy were made during rechallenge study. These findings support the need to include this procedure in the study of penicillin allergy. Probably, this procedure is detecting a booster effect on the immunologic memory more than detecting a new sensitisation.

For cephalosporins the sensitivity of the skin test is not very well established since fewer patients have reactions to these antibiotics and in most cases are descriptions of unique cases. However, a recent publication from Romano et al. [19] describes 30 patients allergic to cefotaxime, ceftriaxone, cefuroxime and ceftazidime; most of them (86%) had a positive skin test to the cephalosporin implied in the reaction. From other isolated reports of allergic reactions to cephalosporins [19-25] the sensitivity is variable, around 50%, as is the case of other betalactams (carbapenems and monobactams). Cefaclor is probably the most common cephalosporin used in infancy and childhood and therefore induces allergic reactions. In our experience and that of other Spanish groups the sensitivity of the skin test with cephaclor is very low (30%).

The specificity of the skin test for diagnosing betalactam allergy is assumed to be very high, nearly 100%, although for ethical reasons there are no studies to confirm this hypothesis. However, the presence of IgE antibodies to a particular betalactam does not mean that the subject will automatically experience an allergic reaction to the drug, as with allergies to aeroallergens or food.

SENSITIVITY AND SPECIFICITY OF SKIN TEST FOR DIAGNOSIS OF LATE REACTIONS TO BETALACTAMS

Delayed reactions to penicillins are also frequent and can account in some studies for 39% of immunological reactions [12], although in our experience this percentage is smaller.

Late reading of intradermal test and patch test with these antibiotics has been useful in the diagnosis of non-immediate reactions [26]. Terrados et al. [27] has shown that 65% of patients with non-immediate reactions had positive skin tests. In a recent study by the same group, Luque et al. [28], from 19 patients with late reactions to penicillins only seven (36%) had positive skin tests.

A positive patch test on the previous lesion has been described in cases of fixed drug eruption by aminopenicillins. In cases of localized pustulosis induced by betalactams [29, 30] intradermal and patch tests have been negative [30].

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