

Immediate hypersensitivity to cephalosporins

Like penicillins, cephalosporins may provoke allergic reactions, especially IgE-mediated ones, such as urticaria and anaphylactic shock. They may occur because of sensitization to determinants shared with penicillins or to unique cephalosporin haptens. Skin tests are sensitive in diagnosing immediate hypersensitivity to cephalosporins, but their sensitivity appears to decrease with time. For evaluating immediate reactions to cephalosporins, it is crucial to test the suspect drug in addition to penicillin determinants. In fact, allergic reactions to cephalosporins, especially second- and third-generation ones, may not be detected by tests performed only with penicillin determinants, particularly in cases where side chains are important in sensitization. As far as *in vitro* tests are concerned, IgE assays for cephalosporins are a potentially useful tool in evaluating immediate reactions. Even though they appear to be less sensitive than skin tests, IgE assays could be used as complementary tests, as has been observed in penicillin-allergic subjects. In assessing the selectivity of the response, negative results in skin testing with cephalosporins other than the culprit one appear to be a reliable indicator of tolerability.

**A. Romano^{1,2}, M. J. Torres³,
F. Namour⁴, C. Mayorga³,
M. C. Artesani¹, A. Venuti¹,
J.-L. Guéant⁴, M. Blanca³**

¹Department of Internal Medicine and Geriatrics, UCSC – Allergy Unit, Cl Columbus, Rome, Italy; ²IRCCS Oasi Maria SS, Troina, Italy; ³Research Unit for Allergic Diseases, Carlos Haya Hospital, Malaga, Spain; ⁴Laboratory of Cellular and Molecular Pathology in Nutrition, University of Nancy, Nancy, France

Antonino Romano
Unità di Allergologia
Complesso Integrato Columbus
Via G. Moscati, 31
I-00168 Rome
Italy

Introduction

Cephalosporins are the second most important β -lactams after penicillins for treating infectious diseases. Like the latter, they may cause allergic reactions, especially IgE-mediated ones (1). Many of these manifestations, such as urticaria and exanthema, are cutaneous, but anaphylactic reactions have also been reported. In a study of fatal anaphylaxis in the UK between 1992 and 1997, six of the 12, fatal reactions attributed to antibiotics followed the first dose of a course of cephalosporin (2). The frequency of skin reactions in patients treated with cephalosporins ranges from 1 (cefuroxime) to 3% (ceftriaxone) (3). The incidence of the reactions to cephalosporins does not seem to be less than that to penicillins, but immediate allergic reactions to cephalosporins and the nature of their allergenic determinants have been far less studied.

There are few useful data regarding several fundamental and applied aspects of cephalosporin immunochemistry, such as the characterization of their allergenic determinants, the role of side-chain structures in allergenicity, and allergenic cross-reactivity with other β -lactams.

However, we know that cephalosporins share the four-membered β -lactam ring with penicillins, but differ from the latter in that the five-membered thiazolidine ring of penicillin is replaced by a six-membered dihydrothiazine one. Other differences between the two regard their side-chain structures and the chemistry of their

degradation and transformation. Under physiological conditions, the cephalosporin β -lactam ring opens and with its carbonyl moiety binds a protein, forming the cephalosporoyl determinant (4), which tends to fragment extensively (5). Side-chain structures usually survive such fragmentation and may be responsible for cross-reactivity among β -lactams, including other cephalosporins, or selective sensitization (6).

In vitro studies have demonstrated IgE antibody reactivity with both ends of the cephalosporin molecule, i.e. the side-chain group (R_1 substituent) and the ring structures with the attached R_2 group (7).

The production of hybridomae has shown that, in addition to common determinants, cephalosporins can generate unique structures capable of inducing a specific immunologic response not cross-reacting with classic structures (8). Thus, allergic reactions to cephalosporins may occur because of sensitization to determinants shared with penicillins or to unique cephalosporin haptens (6, 7, 9).

It already seems clear that, as with penicillins, cephalosporins as allergens cannot simply be considered as a group of compounds with a common allergenic determinant structure.

Cross-reactivity studies

Studies on the cephalosporins as allergens are not nearly as numerous and thorough as those on

penicillins, and very few have been dedicated to the determinants responsible for allergic reactions. Consequently, the frequent questions on allergenic cross-reactivities among cephalosporins, and between cephalosporins and penicillins cannot currently be answered with confidence and this causes difficulties in the selection of antibiotics for some penicillin- and/or cephalosporin-allergic subjects (9). It has been demonstrated that antibodies to side-chain structures on cephalosporins are immunologically important and there appears to be less cross-reactivity among cephalosporins than among penicillins and even less cross-reactivity between cephalosporins and penicillins (9, 10).

There are many studies on cross-reactivity between penicillins and cephalosporins (11–15). Most of them were carried out before 1980, using first-generation cephalosporins such as cephalothin and cephaloridine (11–14). These studies showed a frequency of cross-reactivity ranging from 16.6% to 66.6%. We must consider, however, that cephalothin and cephaloridine side chains are very similar to that of benzylpenicillin. Moreover, some early first-generation cephalosporins were contaminated with trace amounts of the latter (12).

In a study by Audicana et al. (15), there was less cross-reactivity (14.7%) with cephalexin than with any other first-generation cephalosporin in the previous studies, and none at all with the more recent ceftazidime.

Other authors administered cephalosporins to patients with histories of penicillin allergy to assess cross-reactivity between penicillins and cephalosporins (16–19). It is surprising that in some studies the percentage of positive challenges was higher among patients with histories of penicillin allergy and negative allergologic tests than in patients with both positive histories and positive allergologic tests (16, 19).

In addition to the β -lactam ring, sometimes the side-chain groups present structural features common to penicillins and cephalosporins (for example, ampicillin and cefaclor). Thus, theoretically, at least allergenic cross-reactions between some penicillins and cephalosporins seem likely. However, there are too few studies with reliable and detailed data on this question.

Two Spanish studies assessed cross-reactivity between amoxicillin and cefadroxil in patients with immediate hypersensitivity to amoxicillin (20, 21). These two β -lactams share the same side chain containing an aminogroup. The percentage displayed in the Miranda study (38%) was higher than that in the Sastre one (12.5%). In the former study, RAST inhibition indicated that the side chain contributed significantly to inhibition.

The importance of side-chain determinants has been demonstrated indirectly in the recent study by Novalbos et al. (22), which showed a lack of allergenic

cross-reactivity to cephalosporins among patients allergic to penicillins: 41 such subjects, diagnosed by positive skin tests and/or provocation tests, were challenged without any reaction with 3 cephalosporins (cefazolin, cefuroxime, and ceftriaxone) that do not share the same side chain with the culprit penicillin.

Few studies have been carried out to evaluate cross-reactivity between cephalosporins and penicillins or among cephalosporins in samples of at least 10 subjects with primary hypersensitivity to the latter (23, 24). The principles of allergenic cross-reactions among cephalosporins are similar to those among penicillins, i.e. recognition of the core ring structures may result in cross-reactivity with all cephalosporins, regardless of side-chain structure. However, because the R_2 as well as the R_1 side-chain group may differ between different cephalosporins, the situation is more complicated. Cross-reactivity may occur via R_1 recognition where side-chain groups are the same (for example, cefaclor and cephalexin, cefotaxime and ceftriaxone) or similar (cefaclor and cefadroxil), or it may be affected by R_2 recognition (cephalexin and cephradine, cephalothin and cefotaxime) (9).

In a previous study by our group – which evaluated 12 patients with immediate allergic reactions to different cephalosporins by performing skin tests and IgE assays with the culprit drugs and also by assessing the response to classic penicillin determinants – 50% of the cases presented positive responses only to cephalosporins, while in the others positivity to one or more penicillin determinants also appeared (23).

More recently, 30 patients with immediate allergic reactions to injectable cephalosporins (cefuroxime, ceftazidime, ceftriaxone and cefotaxime) were examined by carrying out skin tests and IgE assays with the responsible drugs and also assessing their responses to other cephalosporins as well as to classic penicillin determinants. Four subjects (group B, 13.3%) were positive to penicillin determinants. Twenty-six reacted only to cephalosporins (group A, 86.7%), displaying two patterns of skin-test reactivity: one characterized by selective responses to the culprit cephalosporins ($n = 15$, 57.7%) and the other by positive responses to different cephalosporins ($n = 11$, 42.3%). In the latter subjects, cross-reactivity might be explained by the fact that some drugs, such as ceftriaxone and cefotaxime, have the same side-chain structure and others, like ceftriaxone and cefuroxime, have a very similar one. Moreover, although the ceftazidime side-chain structure is slightly different from the others, a certain cross-reactivity also occurs between this cephalosporin and cefuroxime, cefotaxime and ceftriaxone (24). In this study, the percentage of subjects who displayed skin-test and/or RAST positivity to penicillin determinants (Group B) is much lower than that (50%) found in a previous study (23). This could be due to the fact that most of the former subjects had experienced adverse reactions to third-generation cephalosporins and

none to first-generation ones, while some patients in the previous study had reacted also to first-generation ones, whose structural features are more similar to those of penicillin (25).

Selective responses

Some patients display positive skin tests only to the implicated cephalosporins, which may be explained by reactivity with the entire molecule, as demonstrated with cefaclor (7). These patients are not usually challenged with β -lactams found to be negative in the allergologic work-up other than the culprit cephalosporin. However, there are also cases of selective immediate hypersensitivity to cephalosporins such as cefazolin, cefuroxime, cefixime, ceftriaxone, and ceftazidime, in which selective responses are confirmed by skin-test, RAST and negative challenges with other β -lactams (including first-, second-, and third-generation cephalosporins) (26–33). Such studies indicate that negative results in skin testing with β -lactams other than the responsible cephalosporin seem to be a reliable indicator of tolerability. Studies on larger samples are required, however, to allow the routine prescription, for patients allergic to cephalosporins, of alternative cephalosporins and/or penicillins selected on the basis of skin-test and RAST negativity.

Diagnostic approach

Both *in vivo* (skin tests) and *in vitro* (immunoassays) tests may be performed along with accurate histories to help in the diagnosis of suspected immediate hypersensitivity reactions to cephalosporins. There is no general and widespread agreement yet on the selection of reagents to employ. Penicilloylpolylysine (PPL) (Allergopharma Merck, Reinbeck, Germany) and minor determinant mixture (MDM) (Allergopharma) may be used, but such a selection frequently takes no account of reactions specifically due to the side-chain determinants on individual cephalosporins. Since the exact haptenic determinants of cephalosporins produced by their degradation are largely unknown, the free individual drugs are employed mainly as skin test agents to detect IgE antibodies reactive to these antibiotics (1, 9).

Another major problem for the allergologic evaluation of adverse reactions to cephalosporins is that many of the latter are not available in aqueous solution for therapeutic use and therefore require manipulation for both *in vivo* and *in vitro* testing.

Skin tests

In most studies, free individual cephalosporins diluted in normal saline are employed as skin test agents. Recently, we proved that a concentration of 2 mg/ml in

normal saline of several injectable cephalosporins (cephalothin, cefamandole, cefuroxime, ceftazidime, ceftriaxone, and cefotaxime) was nonirritant in a control group of 30 subjects (24). In our opinion, skin testing at such concentration is a very sensitive tool for evaluating subjects with immediate reactions to cephalosporins. In fact, all 30 subjects except one with immediate hypersensitivity to cephalosporins in whom we recently performed cross-reactivity studies were diagnosed on the basis of skin-test responses to the culprit drugs; one subject displayed skin-test and RAST positivity to PPL. These 30 subjects represented more than the 80% of all those evaluated from January 1995 to June 1998 because of immediate reactions to the aforementioned cephalosporins.

In other studies, different concentrations of drugs – ranging from 0.5 to 250 mg/ml in normal saline – have been used to diagnose immediate hypersensitivity to injectable cephalosporins such as cefazolin, cefuroxime, and ceftriaxone by intradermal testing (26–29, 34, 35). Some authors diagnosed cases of IgE-mediated hypersensitivity to noninjectable cephalosporins such as cefapirin and cefixime by prick testing with the pure drug in powder (36) or at 200 mg/ml in normal saline (31). Therefore, standardization of skin tests requires further studies.

In assessing patients with immediate reactions to cephalosporins, negative skin-test results should be interpreted in light of the time elapsed since their last exposure to the drug. In fact, there are indications that in cases of IgE-mediated allergy, skin tests are more likely to be positive the less time has elapsed since the clinical reaction. In cases of immediate reactions to penicillins, the frequency of positive skin-test results could decline as the interval between drug exposure and testing increases, as demonstrated in patients allergic to penicillins (37–41). In a follow-up study of 42 children with documented IgE-mediated hypersensitivity to penicillins, Chandra et al. (39) observed the negativization of skin tests in one-third of those who had had positive responses one year earlier. Moreover, a recent study on subjects allergic to penicillins shows that negativization of skin tests can be observed as early as one year after performance of the first allergologic evaluation (42). Similar studies in subjects with immediate hypersensitivity to cephalosporins are lacking. However, the importance of the time interval between the most recent reaction to a cephalosporin and allergologic evaluation is supported by the fact that in a recent study describing 30 subjects with immediate hypersensitivity to cephalosporins (24), the mean of such time interval (12.36 ± 13.4 months) was shorter than that observed in 40 subjects with IgE-mediated responses to aminopenicillins (24 ± 39.01 months) (43). Therefore, among subjects with immediate reactions to cephalosporins who present negative skin tests more than one year after their immediate reactions, skin-test

results might not be very reliable, and it is thus possible that the reactions experienced by some of these patients are actually manifestations of IgE-mediated hypersensitivity to the drug. In these cases, considering the risk of triggering another reaction and the fact that patient resistance to these procedures is normally high, we generally defer challenges. In selected cases in which there is a greater-than-normal likelihood that cephalosporin therapy will be necessary, challenge confirmation of skin-test negativity may be more appropriate. If necessary, residual doubt can be eliminated with retesting. In any case, it is advisable to retest such patients after four weeks or more, as some authors have done, to exclude a possible resensitization after loss of sensitivity (34, 44). In fact, in such studies skin-test positivity has been observed in 2 out of 216 (0.9%) (44) and in 26 out of 247 (10.7%) (34) patients retested more than three weeks after negative challenges. In particular, in the latter study one patient suspected of cefuroxime allergy, who was skin-test negative initially, was skin-test positive to cefuroxime on retesting after a negative cefuroxime axetil oral challenge.

In vitro tests

Even though some researchers have performed assays of serum-specific IgE for cephalosporins (7, 23–26), they have proven to be more difficult than those for penicillins, and for this reason are not routinely used.

Baldo et al. developed a drug-solid phase radio-immunoassay (RIA) for the detection and identification of specificities of IgE antibodies to cephalothin. They also studied the molecular basis of recognition of different cephalosporins by IgE antibodies of subjects allergic to cefaclor (7, 25).

In the previously cited study assessing 12 subjects with immediate reactions to cephalosporins, we used a drug-solid phase RIA. Such assay proved to be useful in demonstrating immediate hypersensitivity to these drugs: it confirmed skin-test positivity in 5 patients, was positive in two skin-test negative subjects, and was negative in five skin-test positive ones (23).

We also performed IgE assays in 30 subjects with immediate hypersensitivity – diagnosed on the basis of histories and skin-test positive responses – to one or more of the following cephalosporins: cefuroxime, ceftazidime, cefotaxime, and ceftriaxone (24). The culprit drugs were conjugated to polylysine, and assays were made as previously described with penicillins (45); only nine subjects were positive to the implicated cephalosporins (4 to cefuroxime, 4 to ceftriaxone and 1 to cefotaxime) (24). No conclusions can be drawn with regard to the sensitivity of the

methods used because we performed IgE cephalosporin assays only in subjects who presented positive skin-test results.

We have also reported single cases of immediate allergic reactions to individual cephalosporins like cefuroxime, ceftriaxone and ceftazidime (30, 32, 33, 46). In such studies, specific IgE antibodies for cephalosporins were determined in serum by experimental prototypes of CAP System RAST FEIA (Pharmacia, Uppsala, Sweden). The substances were conjugated to a macromolecule and covalently coupled to the solid phase by methods analogous to those used for the penicilloyl derivatives. However, IgE assays did not always confirm skin-test positivity (32, 33). It should be considered that we used experimental prototypes and that cephalosporin allergenic determinants have not been fully identified (9). Furthermore, in some cases the assays were performed more than one year after the reactions and it is possible that meanwhile the IgE titre had fallen below the cut-off value, as observed with penicilloyl IgE antibodies (47). Specific IgE assays have not, in general, proven more reliable, less expensive, or less time-consuming than skin tests, and are less sensitive than the latter (48). Moreover, RAST sensitivity decreases more rapidly than that of skin tests (49).

Concluding remarks

Skin testing is sensitive in diagnosing immediate hypersensitivity to cephalosporins, but its sensitivity appears to decrease with time.

For evaluating immediate reactions to cephalosporins, it is crucial to test the responsible drug in addition to penicillin determinants. In fact, allergic reactions to cephalosporins, especially recent ones, may not be detected by tests performed only with penicillin determinants, particularly in cases where side chains are important in sensitization.

With regard to *in vitro* tests, the IgE assay for cephalosporins is a potentially useful tool in assessing immediate reactions to these antibiotics. Even though it appears to be less sensitive than skin tests, the IgE assay could be used as a complementary test, as has been observed in penicillin-allergic subjects. In fact, there may be rare skin-test negative, RAST positive cases (23).

In assessing the selectivity of the response, negative results in skin testing with cephalosporins other than the culprit one appear to be a reliable indicator of tolerability. However, the routine prescription of alternative cephalosporins on the basis of skin-test negativity would require further studies. Meanwhile, such prescription should only be given in selected cases after a careful allergologic examination including specific IgE assay and, particularly, the relevant challenge.

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