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# Validation of the cephalosporin intradermal skin test for predicting immediate hypersensitivity: a prospective study with drug challenge

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## Keywords

cephalosporin; drug hypersensitivity; intradermal test; skin test.

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## Abstract

**Background:** Cephalosporin is a major offending agent in terms of drug hypersensitivity along with penicillin. Cephalosporin intradermal skin tests (IDTs) have been widely used; however, their validity for predicting immediate hypersensitivity has not been studied. This study aimed to determine the predictive value of cephalosporin intradermal skin testing before administration of the drug.

**Methods:** We prospectively conducted IDTs with four cephalosporins, one each of selected first-, second-, third-, or fourth-generation cephalosporins: ceftazidime; cefotetan or cefamandole; ceftriaxone or cefotaxime; and flomoxef, respectively, as well as with penicillin G. After the skin test, whatever the result, one of the tested cephalosporins was administered intravenously and the patient was carefully observed.

**Results:** We recruited 1421 patients who required preoperative cephalosporins. Seventy-four patients (74/1421, 5.2%) were positive to at least one cephalosporin. However, none of responders had immediate hypersensitivity reactions after a challenge dose of the same or different cephalosporin, which were positive in the skin test. Four patients who suffered generalized urticaria and itching after challenge gave negative skin tests for the corresponding drug. The IDT for cephalosporin had a sensitivity of 0%, a specificity of 97.5%, a negative predictive value of 99.7%, and a positive predictive value (PPV) of 0%, when challenged with the same drugs that were positive in the skin test.

**Conclusion:** Routine skin testing with a cephalosporin before its administration is not useful for predicting immediate hypersensitivity because of the extremely low sensitivity and PPV of the skin test (CRIS registration no. KCT0000455).

Cephalosporins are currently one of the most widely prescribed antibiotics along with penicillins, because of their broad spectrum of activity on both gram-positive and gram-negative bacteria (1). The therapeutic use of cephalosporins has been increasing since the 1990s, and reports of hypersensitivity reactions to cephalosporins are also increasing. It has been reported that 15% of all severe drug allergies involved cephalosporins (2, 3). Immediate reactions occur in the first hour after administration and are manifested by urticaria, angioedema, anaphylactic shock, rhinitis, and bronchospasm (4). Urticaria is the most common of the cutaneous reactions

by cephalosporins (in 1–3% of cases), and there is a relatively low incidence of the other reactions, including anaphylactic shock (5).

Predicting hypersensitivity before administering a drug is the safest and most efficient way of preventing hypersensitivity reactions. Although the intradermal skin test (IDT) has been widely used for predicting immediate hypersensitivity reactions of cephalosporins, it has not been validated. In this study, we prospectively evaluated the sensitivity, specificity, and negative and positive predictive value (PPV) of the cephalosporin IDT for predicting immediate hypersensitivity.

## Methods

### Subjects

The subjects were recruited in the Department of Urology and Gynecology in the Asan Medical Center between November 2010 and September 2012. We enrolled subjects aged 14 years or older, because we sought to validate cephalosporin skin test in as diverse age range as possible. In fact, the recommended doses of cephalosporin and penicillin are the same for adults and adolescents. The patients with history of previous allergy to beta-lactam antibiotics, including penicillin and cephalosporin, were excluded from this study. And we also excluded any skin disease, pregnant women, current antihistamine users, and immunocompromised patients. Baseline clinical data including age, gender, history of allergic disease, allergic reaction to any drug, and exposure to cephalosporins were obtained.

All study participants were fully informed of the study protocol and provided written, signed statements of informed consent. The protocol was approved by the Institutional Review Board and Ethics Committee of Asan Medical Center (Approval number: 2010-0680).

### Skin test

Each subject underwent an IDT with four cephalosporins, one each of selected first-, second-, third-, or fourth-generation cephalosporins, as well as with penicillin G. Cephalosporins were as follows: ceftazidime (Shinpoong, Seoul, Korea) for first generation; cefotetan (Jeilpharm, Seoul, Korea) or cefamandole (Chunggei, Gyeonggi, Korea) for second generation; ceftriaxone (Shinpoong, Seoul, Korea) or cefotaxime (Handok, Seoul, Korea) for third generation; and flomoxef (Ildong, Seoul, Korea) for fourth generation. The concentrations used were 2 mg/ml in 0.9% NaCl. The concentration of penicillin G (Keunwha, Seoul, Korea) was 10 000 IU/ml. A positive control for the skin test was performed using histamine (1 mg/ml in 0.9% NaCl).

All the reagents were injected intradermally (0.02 ml) on the volar forearm skin. An increase in wheal size of more than 3 mm from the initial area 20 min after testing was considered a positive result (4, 6).

### Cephalosporin challenge

After the skin test, the respective cephalosporin was administered intravenously regardless of the result of the skin test to ascertain prospectively whether there was any immediate hypersensitivity reaction. We performed drug challenges with full therapeutic dose of each cephalosporin without graded challenges: 1 g for ceftazidime, cefotetan, cefamandole, and flomoxef; 2 g for ceftriaxone and cefotaxime.

Even if the skin test was positive, we challenged the patient to the same cephalosporin, which was skin test positive, if it was available. Each patient was carefully monitored during the challenge, and cardiopulmonary resuscitation equipment was available for immediate use if necessary.

**Table 1** Baseline characteristics according to the results of intradermal skin tests to cephalosporins and penicillin G

|                                   | Negative<br>( <i>n</i> = 1324) | Positive<br>( <i>n</i> = 97) | <i>P</i> -value |
|-----------------------------------|--------------------------------|------------------------------|-----------------|
| Gender: male (%)                  | 627 (47.4%)                    | 48 (49.5%)                   | 0.75            |
| Age                               | 54.5 ± 14.4                    | 54.2 ± 13.5                  | 0.8             |
| Previous cephalosporin exposure   | 186 (14.0%)                    | 8 (8.2%)                     | 0.27            |
| Previous allergic disease history |                                |                              |                 |
| Asthma (%)                        | 10 (0.8%)                      | 2 (2.1%)                     | 0.19            |
| Allergic rhinitis                 | 125 (9.4%)                     | 15 (15.5%)                   | 0.15            |
| Atopic dermatitis                 | 8 (0.6%)                       | 0                            |                 |
| Food allergy                      | 23 (1.7%)                      | 3 (3.1%)                     | 0.41            |

### Statistical analysis

Statistical analyses were performed using the SPSS 18 software package (SPSS, Chicago, IL, USA). Pearson's chi-square test was carried out for paired data. Differences between means were analyzed by Student's *t*-test. A value of *P* < 0.05 was considered significant.

### Results

A total of 1421 subjects ranging in age from 14 to 86 years were eligible for this study. Of these, 194 (13.6%) patients had previously been exposed to cephalosporin and 130 (9.1%) patients had not. The remaining 1097 (77.3%) patients did not know whether they had been exposed to cephalosporin or not.

Intradermal skin tests were performed on all participants. Ninety-seven (6.8%) of the 1421 patients had a positive response to at least one drug, and the remaining 1324 (93.2%) patients had negative responses. Among these 97 patients, 23 cases reacted only to penicillin, and 74 patients (74/1421, 5.2%) were positive to at least one cephalosporin. There were no significant differences between responders and nonresponders in baseline characteristics such as age, gender, previous exposure to cephalosporins, and previous allergic disease history (Table 1).

Penicillin was the most common skin test reagent used among the responders (40/97 cases, 41.2%). Cefotetan (25/97 cases, 25.8%) and ceftriaxone (22/97 cases, 22.7%) were the most frequently used types of cephalosporin (Table 2).

Of the 97 subjects who had positive skin tests, 73 (75%) were positive for a single drug and 24 were positive for two drugs. None gave a positive response to three or more drugs. Of the 24 patients who had positive responses to two drugs, 17 (70.8%) were positive to penicillin and one or more of the cephalosporins; five patients were positive to ceftriaxone, four patients were positive to cefotetan, and four patients were positive to ceftazidime. Two were positive to cefotaxime, and one was positive to cefamandole and another to flomoxef. The other seven patients reacted to two different cephalosporins, of which cefotetan and ceftriaxone were most frequent combination (in three patients) (Table 3).

**Table 2** Numbers of positive intradermal skin tests to the various drugs

| Drug         | Number of cases (%) |
|--------------|---------------------|
| Total        | 97                  |
| Penicillin G | 40 (43.2%)          |
| Cefotetan    | 25 (26.8%)          |
| Ceftriaxone  | 22 (23.7%)          |
| Ceftezol     | 19 (19.5%)          |
| Cefamandole  | 6 (6.1%)            |
| Flomoxef     | 5 (5.2%)            |
| Cefotaxime   | 4 (3.1%)            |

**Table 3** Drugs responsible for positive intradermal skin tests, by the number and combination of drugs used

| Single drug ( <i>n</i> = 73) |            | Two drugs ( <i>n</i> = 24) |           |
|------------------------------|------------|----------------------------|-----------|
| Penicillin G                 | 23 (30.5%) | Cefotetan + Ceftriaxone    | 3 (12.5%) |
| Cefotetan                    | 15 (20.8%) | Cefotetan + Ceftezol       | 2 (8.3%)  |
| Ceftriaxone                  | 14 (19.4%) | Ceftezol + Flomoxef        | 1 (4.2%)  |
| Ceftezol                     | 12 (16.7%) | Cefotetan + Flomoxef       | 1 (4.2%)  |
| Cefamandole                  | 5 (6.9%)   | Ceftriaxone + Penicillin G | 5 (20.8%) |
| Cefotaxime                   | 2 (2.7%)   | Cefotetan + Penicillin G   | 4 (16.7%) |
| Flomoxef                     | 2 (2.7%)   | Ceftezol + Penicillin G    | 4 (16.7%) |
|                              |            | Cefotaxime + Penicillin G  | 2 (8.3%)  |
|                              |            | Cefamandole + Penicillin G | 1 (4.2%)  |
|                              |            | Flomoxef + Penicillin G    | 1 (4.2%)  |

After the skin test, the scheduled cephalosporin was administered intravenously, whatever the results of the skin test. All 1421 patients agreed to this. After the cephalosporin was administered, only four patients had immediate hypersensitivity reactions, even though all four had given a negative response in both the cephalosporin and penicillin skin test. Ceftriaxone was the culprit drug in three cases (3/713, 0.4%) and cefamandole in one (1/62, 1.6%). All four patients experienced urticaria within 1 h after administration, and there were no severe reactions such as anaphylactic shock (Table 4).

When we analyzed the results from all 74 cases including a challenge with cephalosporins either the same with or different from the ones that were positive on skin testing, the cephalosporin IDT had a sensitivity of 0%, a specificity of 94.7%, a negative predictive value (NPV) of 99.7%, and a PPV of 0% (Table 5A).

The challenge test with the same cephalosporins that were positive in skin tests was carried out in 34 of 74 patients (45.9%) with positive skin test results. When we analyzed these 34 cases, the specificity increased to 97.5%, but other indicators including sensitivity, NPV, and PPV were similar to the results of all 74 patients who were challenged to either the same or different cephalosporins from those for which skin tests were positive (Table 5B). The drugs tested and challenged in these 34 cases are shown in Table 6.

## Discussion

None of the patients who were positive on the cephalosporin IDT displayed immediate hypersensitivity after a challenge dose of the same or different cephalosporin. However, 0.28% of the subjects who had negative skin tests developed an immediate hypersensitivity reaction.

The most effective way to manage drug hypersensitivity reactions is to detect those people who are hypersensitive to a drug before administering it. If the patient had previous history of drug hypersensitivity, drug provocation testing could be a good way to predict future reactions, because the long-term NPV of negative drug provocation tests under hospital surveillance in beta-lactam antibiotics was almost 100% (7). However, in most situations where there is information on the history of exposure to the drug, it may be necessary to perform skin test with the drug. If a skin test with cephalosporins could accurately predict immediate hypersensitivity, it would undoubtedly be the best way to prevent hypersensitivity reactions. A recent study involving 12 secondary or tertiary hospitals in Korea showed that 11 of the 12 hospitals (91.6%) routinely performed IDTs with cephalosporins for screening (8). However, there have been no studies assessing the validity of the skin test for cephalosporins for predicting hypersensitivity.

Our study included patients who did not know whether they were hypersensitive to cephalosporins, unlike most previous studies that targeted only patients with a known hypersensitivity response to cephalosporins. Furthermore, we administered a full therapeutic dose of cephalosporin to all the patients, regardless of the skin test results, to ascertain the relation between the results and the outcome of the intravenous challenge, whereas previous studies administered intravenous cephalosporins only to patients who gave negative skin test results (4, 6, 9, 10). To our knowledge, ours is the first prospective study to assess the validity of the skin test for cephalosporins before administration even when the skin test was positive.

Interestingly, the current study demonstrated a sensitivity of 0% for predicting the immediate hypersensitivity of cephalosporins. It is difficult to compare our results with those of other studies because they were not designed in a similar way. In the previous studies, the skin tests were performed on patients who had immediate reactions to cephalosporins, and they obtained sensitivities ranging from 1.2% (4/325 subjects) (11) to 72.1% (31/43 subjects) (10) in children and from 76.4% (39/51 subjects) (6) to 78.9% (60/76 subjects) (4) in adults. However, the skin test in these previous studies was not aimed at predicting immediate hypersensitivity before administering cephalosporins, but rather at confirming the culprit drug in patients who were hypersensitive to cephalosporins. The results of our study should be quite reliable, because the study was conducted prospectively on a large number of randomly selected subjects.

We presented both the results of the 34 patients who were challenged with the same drugs that were positive in the skin test and of all the 74 cases challenged with cephalosporins either the same or different from the ones positive on skin

**Table 4** Data for the four patients who had immediate hypersensitivity reactions after a challenge dose of cephalosporin

|   | Gender | Age (years) | Drug involved | Previous exposure to cephalosporins | Interval between IDT* and allergic reaction | Type of reaction | Skin test result |
|---|--------|-------------|---------------|-------------------------------------|---------------------------------------------|------------------|------------------|
| 1 | Female | 40          | Ceftriaxone   | Present                             | 15 min                                      | Urticaria        | Negative         |
| 2 | Male   | 43          | Ceftriaxone   | Unconfirmed                         | 1 h                                         | Urticaria        | Negative         |
| 3 | Female | 43          | Cefamandole   | Unconfirmed                         | 1 h                                         | Urticaria        | Negative         |
| 4 | Female | 58          | Ceftriaxone   | Unconfirmed                         | 6 h                                         | Urticaria        | Negative         |

\*IDT: the time when intradermal skin test was completed.

**Table 5** Outcome of drug challenge according to the skin test results. (A) Outcome of all 74 cases including a challenge with cephalosporins either the same or different from ones positive in the skin test. (B) Outcome of 34 patients who were challenged with the same drugs that were positive in the skin test

|                    | Allergic reaction positive | Allergic reaction negative | Total |
|--------------------|----------------------------|----------------------------|-------|
| A.                 |                            |                            |       |
| Skin test positive | 0                          | 74                         | 74    |
| Skin test negative | 4                          | 1343                       | 1347  |
| Total              | 4                          | 1417                       | 1421  |
| B.                 |                            |                            |       |
| Skin test positive | 0                          | 34                         | 34    |
| Skin test negative | 4                          | 1343                       | 1347  |
| Total              | 4                          | 1377                       | 1381  |

A. Sensitivity: 0%, specificity: 94.7%, positive predictive value: 0%, negative predictive value: 99.7%.

B. Sensitivity: 0%, specificity: 97.5%, positive predictive value: 0%, negative predictive value: 99.7%.

test. Because there is such a diversity in the types of cephalosporins now being used in the clinical practice, in particular with different side chains, it is not practical or possible to skin test to all available cephalosporins. With regard to this, we used the most commonly used cephalosporin from each generation to reflect as much of the diversity of side chains as possible. We think that the results in only those 34 patients may be more logical, in regard to the role of the side chain to antigenic recognition in cephalosporin allergy; however, it might also be meaningful to demonstrate the results of a challenge test with different cephalosporin regardless of the similarity in side chains. The reason is that common nuclear beta-lactam structure might play a role in the pathomechanism of cephalosporin allergy, considering that the cross-reactivity between drugs that did not share the same side chain was observed in our skin tests.

Diagnostic skin testing with cephalosporins is currently considered a useful tool for detecting patients with immediate allergic responses (9, 12, 13). However, there is still much controversy about the validity of these tests because the antigenic determinants of the immunologic responses to cephalosporin are not known (5, 14). Furthermore, different diagnostic protocols for skin tests in different countries and different hospitals make it difficult to interpret results (13).

One study revealed that different hospitals in Korea injected different volumes of drugs (0.1–10 ml) and the drug concentrations also differed (0.1–5 mg/ml) (8). Several *in vivo* studies including measuring the degree of basophil activation to specific allergens (15, 16) and identifying specific IgE (17, 18) have been proposed as complements to the skin test. Unfortunately, these have been unsuccessful and are not commercially available, because of lack of information about the antigenic determinants of cephalosporins (5, 19). As the skin test for cephalosporins has now been shown to lack validity, there is no alternative practical diagnostic tool for predicting immediate hypersensitivity to cephalosporins and it is therefore important to investigate past adverse drug reactions (ADRs). In fact, in a previous study taking advantage of an ADR surveillance system involving mandatory reporting of previous ADRs, we demonstrated a significant reduction in the rate of ADRs (20).

In the current study, we performed drug challenges with full dose of each cephalosporin without graded challenges, because graded challenges are for patients with a history of penicillin or cephalosporin allergy, not for those who are positive only in skin tests without any allergic history. We excluded patients with such a history; therefore, we have determined that graded challenge of cephalosporin is not necessary, even though the skin test was positive.

In this study, 17 of 40 patients (42.5%) with a positive response to penicillin G in a skin test showed cross-reactivities to cephalosporins; however, there was no structural similarity in side chains between the penicillin and those cephalosporins. Moreover, the percentage (7/74, 9.4%) of patients who showed cross-reactivities to different cephalosporins among those who were positive only to cephalosporins in the skin test was relatively higher than that in previous studies (3.8–5.2%) (6). However, we could not compare the incidence of cross-reactivity between cephalosporins that shared similar side chains, because we performed skin test with one cephalosporin from each generation. In those seven cases with positive response to two or more different cephalosporins, involved cephalosporins did not share similar side chains with each other. Therefore, our results suggest that cross-reactivity between beta-lactam antibiotics in the skin test may be related to the similarity of the common nuclear determinant (21, 22) or unique haptens (17, 23) of the drugs, although it is currently known that the R1 side chain may contribute to allergic responses to cephalosporin rather than beta-lactam ring (18, 24). One possibility that

**Table 6** The drugs used in 34 patients who were challenged with the same drugs that were positive in the skin test

| Patient no. | Drugs positive to skin test |             | Administered cephalosporin | Drug challenge test results |
|-------------|-----------------------------|-------------|----------------------------|-----------------------------|
| 17          | Cefotaxime                  |             | Cefotaxime                 | —                           |
| 33          | Cefotaxime                  | Penicillin  | Cefotaxime                 | —                           |
| 83          | Ceftriaxone                 |             | Ceftriaxone                | —                           |
| 94          | Ceftriaxone                 |             | Ceftriaxone                | —                           |
| 100         | Ceftriaxone                 |             | Ceftriaxone                | —                           |
| 112         | Cefotetan                   |             | Cefotetan                  | —                           |
| 114         | Cefotetan                   |             | Cefotetan                  | —                           |
| 181         | Ceftriaxone                 |             | Ceftriaxone                | —                           |
| 316         | Ceftriaxone                 |             | Ceftriaxone                | —                           |
| 342         | Cefotetan                   |             | Cefotetan                  | —                           |
| 357         | Ceftriaxone                 |             | Ceftriaxone                | —                           |
| 367         | Ceftriaxone                 |             | Ceftriaxone                | —                           |
| 381         | Ceftazidime                 | Flomoxef    | Flomoxef                   | —                           |
| 455         | Ceftazidime                 | Cefotetan   | Cefotetan                  | —                           |
| 543         | Cefamandole                 |             | Cefamandole                | —                           |
| 546         | Ceftriaxone                 |             | Ceftriaxone                | —                           |
| 587         | Flomoxef                    |             | Flomoxef                   | —                           |
| 632         | Cefamandole                 |             | Cefamandole                | —                           |
| 633         | Cefamandole                 |             | Cefamandole                | —                           |
| 644         | Cefotetan                   |             | Cefotetan                  | —                           |
| 673         | Cefamandole                 |             | Cefamandole                | —                           |
| 713         | Cefamandole                 |             | Cefamandole                | —                           |
| 730         | Cefamandole                 | Penicillin  | Cefamandole                | —                           |
| 738         | Ceftriaxone                 |             | Ceftriaxone                | —                           |
| 903         | Cefotetan                   |             | Cefotetan                  | —                           |
| 995         | Cefotetan                   |             | Cefotetan                  | —                           |
| 1073        | Cefotetan                   |             | Cefotetan                  | —                           |
| 1086        | Cefotetan                   | Flomoxef    | Flomoxef                   | —                           |
| 1103        | Cefotetan                   | Ceftriaxone | Cefotetan                  | —                           |
| 1154        | Cefotetan                   | Ceftriaxone | Ceftriaxone                | —                           |
| 1170        | Cefotetan                   | Ceftriaxone | Cefotetan                  | —                           |
| 1233        | Ceftriaxone                 | Penicillin  | Ceftriaxone                | —                           |
| 1234        | Ceftriaxone                 | Penicillin  | Ceftriaxone                | —                           |
| 1243        | Flomoxef                    | Penicillin  | Flomoxef                   | —                           |

some degraded products from beta-lactam ring might be involved in antigenic recognition should be considered.

An interesting finding is that 4 (0.28%) of the 1347 patients with negative skin test results were proved false negative thorough the drug challenge. The result suggests the possibility that the allergic reactions may be caused by degraded metabolites following drug metabolism rather than falsely negative skin tests to the parent drug per se. Therefore, the skin test with crude drugs may not be reflective of the outcome of a drug challenge. In a study by Sanches et al. (18), R1 side chain-containing amino acid residue formed after aminolysis of beta-lactam ring was supposed to be important to immunologic recognition. On the other hand, positive responses to the skin test were also demonstrated without any allergic reactions after drug challenge in this study, implying that certain components of the crude drug may cause positive skin responses, but are not sufficient to trigger clinical allergy. Taken together, we assumed that one or more degraded products might be involved in developing

cephalosporin hypersensitivity. Further studies are needed to elucidate the allergenic determinants of cephalosporin, which remain unknown.

There are some limitations to this study. We studied only those patients who needed prophylactic antibiotics before surgery, because we had to assess the results of a full dose of cephalosporin administered after the skin test. However, we could not include patients who needed antibiotic therapy to treat overt infection to avoid any possible confounding effects of comorbidity. For this reason, we could not examine all types of cephalosporin. As the side chains of cephalosporins are thought to be the leading cause of IgE-mediated hypersensitivity reactions (25), this may limit generalization about the hypersensitivity reactions of cephalosporins. Because it is impossible, in practice, to investigate all types of cephalosporin side chains, we selected the most widely used cephalosporins from each generation (26, 27). A further prospective study with cephalosporins with various side chain structures in a larger population is needed.

We also think that it would be better to use penicilloyl polylysine (PPL) and penicillin G together for skin testing. However, PPL is not available in Korea and we acknowledge this as a limitation to our results in clarifying the cross-reactivities between penicillin and cephalosporins. Severe reactions including anaphylaxis by penicillins are known to be associated with the minor determinant (28), penicillin G in this study. Therefore, we felt that penicillin G was sufficient to determine cross-reactivities even without PPL.

Although skin prick test would usually be used before proceeding to IDT in usual clinical practice, it was not performed in this case to determine the true sensitivity of the IDT, because those with positive skin prick test would still have undergone a drug provocation test anyway.

The incidence of immediate hypersensitivity reactions in this study is consistent with that reported from previous studies (5, 29) and is thought to be acceptable, particularly as all the reactions were urticaria. However, our findings may apply also to severe reactions, such as anaphylaxis, assuming that immediate hypersensitivity reactions are all based on similar immunologic mechanisms.

In summary, an IDT to predict immediate hypersensitivity reactions to cephalosporins before administration is not valid because it had zero PPV, suggesting that research is needed into alternatives to the skin test.

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## Conflict of interest

There are no potential conflict of interests related to this article or the research described.

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