Clinical Outcome in the Use of Cephalosporins in Pediatric Patients with a History of Penicillin Allergy

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Abstract

\textbf{Background:} The risk of cephalosporin administration in patients with a history of penicillin allergy is unclear. Few studies have looked at the risk of cephalosporin administration in children following penicillin skin testing for suspected penicillin allergy. The goal of this study was to determine whether children with penicillin allergy were at increased risk for adverse drug reactions when administered a cephalosporin. \textbf{Methods:} A retrospective chart review was conducted in pediatric patients (\(\leq 18\) years) with a history of penicillin allergy and a positive or negative penicillin skin test who were administered a cephalosporin after testing. Charts were reviewed for adverse drug reactions to the cephalosporin. \textbf{Results:} A total of 173 patients (91 males) were included in this study. The mean age of the patients was 4.1 ± 3.1 years. Twenty-one patients (12\%) tested positive in a penicillin skin test and 152 patients (88\%) tested negative. One patient with a negative penicillin skin test (0.7\%) had an adverse drug reaction (eye swelling) to cephalexin. None of the patients with a positive penicillin skin test who received a course of cephalosporin had an adverse drug reaction. \textbf{Conclusion:} Among all patients with a history of penicillin allergy (penicillin skin test positive and negative), only 1 person had an adverse drug reaction. Further large prospective studies examining the safety of administering cephalosporins in pediatric patients with confirmed penicillin allergy are needed.

K.A.A. and M.A.P. contributed equally to this paper.

Key Words

Adverse drug reaction \cdot Cephalosporin allergy \cdot Penicillin allergy \cdot Skin testing \cdot Penicillin
or third-generation cephalosporins in patients with a history of penicillin allergy who did not experience urticaria or anaphylaxis to penicillin [14]. Most of the data studying the clinical cross-reactivity between penicillins and cephalosporins have included an adult population, and the studies lacked control groups [4, 6, 10–13]. Hence, we conducted a study to determine whether patients with a history of penicillin allergy and a positive penicillin skin test had a higher rate of adverse drug reactions to cephalosporins compared to those with a negative penicillin skin test.

Methods

Study Patients
Consecutive pediatric patients (0–18 years of age) with a history of penicillin allergy who underwent penicillin skin testing from July 1993 to May 2010 and who met the inclusion/exclusion criteria participated in the study. The patient was defined as having a history of penicillin allergy if he/she had a self-reported history of penicillin allergy, physician diagnosis and/or was documented in the medication allergy module in our electronic medical record. The Mayo Clinic Institutional Review Board approved the study.

Inclusion criteria were: (1) patients with a history of penicillin allergy; (2) positive or negative penicillin skin test, and (3) subsequent course of a cephalosporin after penicillin skin test. Exclusion criteria were: (1) patients with a sole history of cephalosporin allergy without a history of penicillin allergy; (2) subjects who did not undergo a cephalosporin challenge or received a course of cephalosporin after penicillin skin testing, and (3) age >18 years.

Study Design
We conducted a retrospective chart review in which the medical records were reviewed for basic demographics (age and sex), penicillin skin test result, type of cephalosporin given, and whether the patient had an adverse drug reaction to the cephalosporin. Two reviewers were employed to review the patient charts. If any questions arose during the review process, the reviewers discussed the question to establish consistency in data collection. If more than one penicillin skin test was done, we chose the most recent test. Adverse drug reaction (according to the World Health Organization definition) was defined as any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy [15]. We modified the definition by excluding any known common side effects of the medication or non-immunologically mediated adverse drug reaction such as headaches, fatigue, and others. IgE-mediated adverse drug reaction was defined as urticaria, angioedema, shortness of breath, wheezing, rash with pruritus, anaphylaxis and/or hypotension. All data were put into a spreadsheet program (Microsoft Excel; Microsoft Corp., Redmond, Wash., USA) and converted into a JMP file (see Statistical Analysis) for statistical analysis.

Penicillin Allergy Testing
Penicillin allergy testing was conducted by using benzylpenicilloyl polylysine, penicillin G potassium (Pfizerpen®; Pfizer, New York, N.Y., USA) and penicilloate, as previously reported [9]. The penicilloate was produced by reacting penicillin G with 1 N NaOH at a pH of 11 for 60 min, after which the pH was adjusted to 7.0 by addition of 1 N HCl. The penicilloate was diluted with phosphate-buffered saline to 0.01 M and filtered through a 0.22-μm membrane for sterility. The benzylpenicilloyl polylysine (Pre-Pen®) was used according to the manufacturer’s instructions, and the penicillin G potassium was used in a concentration of 6,000 U/ml in phosphate-buffered saline. To prepare an amoxicillin solution of 0.01 M for testing, we dissolved 36.5 mg amoxicillin (Sigma Chemical Co.) in 10 ml warm (37°C) sterile saline and sterilized it by membrane filtration through a 0.22-micron filter. It was used undiluted for intradermal testing, stored at 4°C and replaced at weekly or biweekly intervals. Histamine at 0.05 mg/ml was used as the positive control, and the negative control was phosphate-buffered saline.

Prick skin tests were performed on the volar surface of the forearm with each penicillin and control reagent. The skin test sites were examined after 15 min. A positive test result was defined as a wheal of 3 × 3 mm or greater with a surrounding zone of erythema [16]. Patients with negative prick test results to penicillin underwent intradermal testing.

Intradermal skin tests were performed on the volar surface of the forearm. The test reagents were injected intradermally to produce an initial wheal of 2 × 2 mm. The skin test sites were examined after 15 min. A positive intradermal test was defined as a wheal of 3 × 3 mm or greater with a surrounding zone of erythema.

Patients with a wheal but without a flare on the penicillin skin test (skin prick and intradermal) were considered to be equivocal. Allergy skin testing was performed where resuscitation equipment was available in case of anaphylaxis.

Statistical Analysis
Descriptive statistics were used to describe age and sex, the proportion of adverse drug reaction of patients with a history of penicillin allergy, and positive penicillin skin test given a course of cephalosporin. For these analyses, adverse drug reaction to cephalosporin was the dependent variable and patients with a history of penicillin allergy with a positive or negative penicillin skin test was the explanatory variable. A software program (JMP version 7.0; SAS Institute Inc., Cary, N.C., USA) was used to perform the statistical analyses. A p value ≤0.05 was considered statistically significant.

Results
Demographics
The mean age ± SD of patients in this study was 4.1 ± 3.1 years. Ninety-one patients were males (53%).

Clinical Characteristics of the Penicillin Allergy and Penicillin Skin Test Results
One hundred and seventy-three patients with a history of penicillin allergy received a cephalosporin after penicillin skin test; 21 (12%) of these patients had a posi-
tive penicillin skin test (table 1) and 152 (88%) a negative penicillin skin test. For patients with a negative test, 126 patients experienced a clinical reaction described in the medical record as a rash, 22 patients had an unknown reaction, and 1 patient each experienced a reaction characterized in the medical record as respiratory difficulty, erythema multiforme, facial swelling, and a non-IgE-mediated reaction.

**Cephalosporins Received**

The distribution of cephalosporins administered among patients with a negative or positive skin test is detailed in table 2. Among the penicillin skin test-positive patients, 1 patient received cefazolin, 10 cephalaxin, 1 cefadroxil, 1 cefuroxime, 4 cefprozil, 2 ceftriaxone, and 2 cefdinir. In the penicillin skin test-negative patients, 22 received cefazolin, 64 cephalaxin, 6 cefadroxil, 11 cefuroxime, 27 cefprozil, 4 ceftriaxone, 15 cefdinir, 4 cepodoxime, and 2 cefepime. Among the penicillin skin test-negative or -positive patients, the total number of cephalosporins given exceeds the number of patients, as some

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age years</th>
<th>Penicillin skin test result</th>
<th>Drug</th>
<th>Clinical reaction</th>
<th>Cephalosporin given</th>
<th>Months between cephalosporin administration and penicillin reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>PPL</td>
<td>amoxicillin</td>
<td>rash</td>
<td>cefadroxil</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>PPL, amoxicillin</td>
<td>penicillin</td>
<td>rash</td>
<td>cefazolin</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>PPL, penicillin G</td>
<td>amoxicillin</td>
<td>rash</td>
<td>cefdinir</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>penicilloate</td>
<td>amoxicillin</td>
<td>unknown</td>
<td>cefdinir</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>penicilloate</td>
<td>amoxicillin</td>
<td>rash</td>
<td>cefprozil</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
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<td>amoxicillin</td>
<td>unknown</td>
<td>cefuroxime</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
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<td>rash</td>
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<td>75</td>
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<tr>
<td>8</td>
<td>3</td>
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<td>amoxicillin</td>
<td>rash</td>
<td>ceftriaxone</td>
<td>11</td>
</tr>
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PPL = Benzylpenicilloyl polylysine.

<table>
<thead>
<tr>
<th>Table 2. Cephalosporins administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin skin test</td>
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<tr>
<td>----------------------</td>
</tr>
<tr>
<td>positive</td>
</tr>
<tr>
<td>negative</td>
</tr>
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</tbody>
</table>

1 The total number of cephalosporins given exceeds the number of patients because some patients received more than one cephalosporin.
patients received more than one cephalosporin. Cephalosporins were administered for a median of 14 months (range 1–160) following the reaction to penicillin.

**Cephalosporin Adverse Drug Reactions**

One (0.7%) of 152 patients from the penicillin skin test-negative population experienced an adverse drug reaction to the administered cephalosporin (table 3). A 4-year-old male was found to have a negative penicillin skin test. He had a history of a rash 8 days following the administration of amoxicillin. Approximately 6 years later, the patient experienced swelling of the eyes on the 5th day after the start of cephalexin. The patient did not experience any other signs of anaphylaxis and rash. The cephalexin was discontinued and the patient was given a course of oral diphenhydramine. No adverse drug reactions occurred among the positive penicillin skin test patients when given a cephalosporin.

**Discussion**

The clinical safety of administering a cephalosporin to patients with a history of penicillin allergy is still uncertain [16]. Most recent studies examining the clinical safety and in vitro cross-reactivity between penicillin and cephalosporins have been done in adults [4, 7, 10–13] and only few in the pediatric population. Our study examined the safety of cephalosporin use in pediatric patients with a history of penicillin allergy. In the current study, 0.7% (1 of 152 patients) had an adverse drug reaction to a cephalosporin in patients with a history of penicillin allergy and negative penicillin skin test compared to none in penicillin skin test-positive patients with a history of penicillin allergy. The low rate of adverse drug reaction to a cephalosporin in patients with a history of penicillin allergy and a negative penicillin skin test is consistent with our recent study in adults that showed an adverse drug reaction rate of 0.7% when challenged with a cephalosporin in patients with a history of penicillin allergy and a negative penicillin skin test [8]. Our study is also consistent with the literature review by Kelkar and Li [17] who found an adverse drug reaction of 0.6% in patients challenged with a cephalosporin with a history of penicillin allergy and a negative penicillin skin test.

The lack of any adverse drug reaction to a cephalosporin in patients with a history of penicillin allergy and a positive penicillin skin test contrasts with our recent study in adults that showed a 6% adverse drug reaction rate to cephalosporins in patients with a history of penicillin allergy and positive penicillin skin test [8]. Moreover, Atanaskovic-Markovic et al. [18], in a pediatric population, showed that patients with a history of penicillin allergy and a positive penicillin skin test were also more likely to be skin test positive to cephalexin (23.9%), cefaclor (23.8%), ceftriaxone (0.7%) and cefotaxime (0.3%). The small number of patients challenged with a cephalosporin in our positive penicillin skin test group may explain the discrepancy with other studies by Park et al. [8] and Atanaskovic-Markovic et al. [18]. In the study by Atanaskovic-Markovic et al. [18], the safety or cross-reactivity between penicillin and cephalosporin was confirmed by cephalosporin skin testing; however, the strength of our study involves the oral or intramuscular challenge with cephalosporin in patients with a history of penicillin allergy and positive penicillin skin test compared with a control group (negative penicillin skin test). Hence, it is possible that cephalosporin skin testing may

<table>
<thead>
<tr>
<th></th>
<th>Positive penicillin skin test (n = 21)</th>
<th>Negative penicillin skin test (n = 152)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no ADR to cephalosporin</td>
<td>ADR to cephalosporin</td>
</tr>
<tr>
<td>First-generation cephalosporin</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Second-generation cephalosporin</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Third-generation cephalosporin</td>
<td>4</td>
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</tr>
<tr>
<td>Fourth-generation cephalosporin</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>0</td>
</tr>
</tbody>
</table>

ADR = Adverse drug reaction.
overestimate the true cross-reactivity between penicillin and cephalosporins.

Studies that were conducted before 1980 showed 8.1–66.6% cross-reactivity between penicillin and cephalosporins [3, 7, 19, 20]. More recently, Kelkar and Li [17] summarized studies looking at adverse drug reaction to cephalosporins in patients with a history of penicillin allergy and a positive penicillin skin test versus those with a negative penicillin skin test from 1974 to 1994. Among patients with a history of penicillin allergy and a positive penicillin skin test, 4.4% had an adverse drug reaction to cephalosporin compared to 0.6% of those with a negative penicillin skin test. Park et al. [8], in a cohort of patients from the same institution, showed that 6% of patients with a history of penicillin allergy and a positive penicillin skin test had an adverse drug reaction to a cephalosporin (mostly cefazolin) compared to 0.7% (p = 0.0019) among patients with a negative penicillin skin test. The lower rates of adverse drug reaction to cephalosporins in penicillin-allergic patients in more recent studies compared to those before 1980 may be due to the administration of first-generation cephalosporins such ascephalothin and cephaloridine which have side chains very similar to benzylpenicillin. The similarity between side chains may increase the cross-reactivity between penicillin and cephalosporins [4, 10–12]. In addition, some of the earlier first-generation cephalosporins may have contained trace amounts of penicillin [20]. Hence, in general, there does seem to be a slight increased risk of an adverse drug reaction to cephalosporins in penicillin-allergic patients in adults.

Several studies have demonstrated the higher propensity for cross-reactivity between penicillin and a cephalosporin with the same side chain [10, 11, 13]. Indirectly, Novalbos et al. [12] also demonstrated the importance of the side chain in the cross-reactivity between penicillin and cephalosporins. In the study by Novalbos et al. [12], 41 patients with a clear history of penicillin allergy confirmed by positive penicillin skin test or oral challenge with amoxicillin were administered cephalosporins (cephazoline, cefuroxime and ceftriaxone) with dissimilar side chain to amoxicillin without any adverse drug reaction. Interestingly, in our study, the one patient who had an adverse drug reaction to cephalaxin originally had an adverse drug reaction to amoxicillin. Amoxicillin has a similar side chain to cephalaxin. This patient had a negative penicillin skin test but there is some evidence that penicillin skin testing with benzylpenicilloyl polylysine, penicillin G and amoxicillin may not detect all patients with a history of amoxicillin allergy [21]. Hence, the one patient may have had a false-negative penicillin skin test.

There are several limitations to this study, including a possible selection bias. In the study, only patients with a history of penicillin allergy who underwent penicillin skin testing and challenge and/or were given a course of cephalosporin were included in the study. Few patients with a history of penicillin allergy confirmed by penicillin skin test were administered a cephalosporin. Children with a history of penicillin allergy confirmed by skin testing may not have been administered a cephalosporin due to physician and/or parent vigilance to avoid an adverse drug reaction because of the severity of the adverse reaction to the original penicillin. Thus, these results may underestimate the true risk of an adverse drug reaction in children following the administration of a cephalosporin with a history of penicillin allergy confirmed by skin testing. Many of the patients in the study listed had an allergic reaction to amoxicillin. Amoxicillin has been associated with the development of a maculopapular rash (non-IgE-mediated adverse reaction) in 5–10% of patients [22] in addition to the possibility of the original ‘rash’ being caused by the underlining infection. Hence, the population chosen may not accurately represent a group of penicillin-allergic patients who had an IgE-mediated adverse drug reaction to penicillin but may represent a group of patients with an amoxicillin allergy that is mediated by a non-IgE-mediated adverse drug reaction. Another limitation of the study is the selection of patients. Because the study is retrospective, we are dependent on the accuracy of the medical record and are not able to interview the patient in order to gather a population with a high likelihood of a penicillin allergy. The medical record did not allow us to distinguish between self-reported, physician-diagnosed or register-recorded penicillin allergy. However, many studies have demonstrated that clinical history and penicillin skin test results are rarely associated. In a retrospective study of 319 patients with a positive history of penicillin allergy, patients were divided into three groups based on penicillin allergy history: convincing (history consistent with an IgE-mediated reaction to penicillin), vague (plausible history of penicillin allergy) and unacceptable (either never been exposed to penicillin or an unbelievable history) [23]. Among the convincing group, 19 (14.1%) of 135 patients had a positive penicillin skin test, 10 (6.7%) of 150 had a positive penicillin skin test in the vague group, and 0 of 34 patients had a positive penicillin skin test in the unacceptable group. In a review of the literature, Solensky et al. [24] showed that 33% (347/1,063) of patients with a his-
tory of penicillin allergy and a positive penicillin skin test had a vague history of prior reaction to penicillin. A ‘vague’ history was defined as one unlikely to be IgE mediated (such as maculopapular rash, gastrointestinal symptoms, or an unknown reaction). The authors conclude that patients with a vague history should undergo penicillin skin testing because a large number of true penicillin allergies could be missed. Moreover, in a retrospective study of 91 patients evaluated for penicillin allergy, clinical history (type of reaction, time of reaction after penicillin ingestion, or time since the last reaction) was not associated with penicillin skin test positivity [25]. Hence, although the patient’s history is an important element in the evaluation of penicillin allergy, the clinical utility seems to be limited and penicillin skin testing can be useful for many patients with a history of penicillin allergy. Finally, the size of our cohort was small for the cases compared to similar studies conducted in adults [8]; hence, a type II error may have occurred. However, many of the other studies examining the cross-reactivity between penicillin and cephalosporins do not include a control group, in contrast to our study [4, 10–13, 18]. Moreover, our low rate of adverse drug reaction to cephalosporins is consistent with the incidence rate of cephalosporins reported in the literature (1–10%) [26].

In conclusion, among all patients with a history of penicillin allergy (penicillin skin test positive and negative), only 1 person had an adverse drug reaction. Further large prospective studies examining the safety of administering cephalosporins in pediatric patients with confirmed penicillin allergy are needed.

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