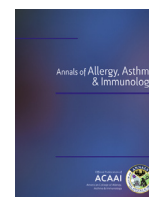




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## Letter

## Additional provocation testing in patients with negative provocation test results with $\beta$ -lactam antibiotics

Positive reactions after a prior negative drug provocation test (DPT) result with  $\beta$ -lactam antibiotics have been reported. In previous studies, the frequency of these reactions was reported in a wide range as 0% to 27.9%.<sup>1–6</sup> The frequency in children was reported as 0.9% to 10.5%, but data are limited.<sup>2,3,7,8</sup> Reevaluating patients with negative DPT results has been suggested to confirm or rule out allergy to  $\beta$ -lactam antibiotics, especially for patients admitted with a history of an anaphylactic reaction.<sup>2</sup> We performed a second DPT in children who had a previous negative DPT result with  $\beta$ -lactam antibiotics 4 weeks after the first evaluation and wanted to share our results.

All patients who were referred to our pediatric allergy department because of a suspicion of  $\beta$ -lactam allergy and who had experienced no reaction during DPT between June 2014 and December 2014 were included in our study. A DPT (but not the preceding skin testing) was performed again 4 weeks after the initial evaluation. Local ethics committee approved the study design and protocols.

The initial drug allergy workup was started with the standardized European Network Drug Allergy (ENDA) questionnaire on drug allergy.<sup>9</sup> If the suspected reaction was compatible with drug hypersensitivity, skin tests (prick and intradermal) and an oral provocation test with the suspected drug were proposed according to guidelines.<sup>10</sup> Skin testing was not performed in patients with mild nonimmediate skin symptoms.

The ENDA guidelines for drug provocation tests were followed carefully.<sup>9,10</sup> Additional provocation testing involved administering the suspected drug at divided 3 doses every 30 minutes, until a cumulative dose close to the age- and weight-adjusted daily dose of the drug was achieved, and skin testing was not repeated. A DPT was performed by a physician with full resuscitation back-up. The test was discontinued in the event of any adverse drug reaction. After the last dose, the patient was kept under surveillance for at least 2 hours. Patients continued to take the drug for 5 days at home. All patients were contacted after the 5-day antibiotic course, and any reaction was recorded. If a patient had a reaction during the second DPT, a third evaluation was performed with skin tests and a DPT.

Seventy-one patients who had negative initial DPT results underwent additional DPTs 4 weeks after the first evaluation. Characteristics of all patients are listed in Table 1. Six patients (8.5%) reported anaphylactic reactions, 31 patients (38%) reported urticaria-angioedema, and 38 patients (53.5%) reported maculopapular rash.

Suspected drugs (71 cases) were as follows: 62 penicillin (57 amoxicillin-clavulanate, 1 penicillin, 2 amoxicillin, 2 ampicillin-

sulbactam) and 9 cephalosporin (4 cefixime, 1 cefdinir, 1 cefprozil, 2 cefuroxime, 1 cefpodoxime).

Only 2 patients (2.8%) had reactions during the second DPT. The first patient had a history of urticaria with amoxicillin-clavulanate 2.5 hours after the eighth drug dose when she was 13 months of age. She was evaluated 3 months after the initial reaction, and skin testing and DPT results were negative. On the second day of additional provocation, she experienced maculopapular rash 5 hours after the first dose of the drug. Her parents did not give consent for a third evaluation.

The second patient had a history of maculopapular rash with amoxicillin-clavulanate 3 hours after taking the fifth dose when she was 5 years 8 months old. Six months later she was evaluated and had negative skin test and DPT results. During additional provocation, she experienced urticaria 4 hours after the daily dose of the drug on the fourth day. Skin tests and a third DPT were performed 6 weeks later, and all results were negative.

Patients who had a negative DPT result with a  $\beta$ -lactam antibiotic may sometimes have a reaction after subsequent exposure to the culprit drug.<sup>8</sup> In some studies that followed up patients with negative DPT results, the frequency of reactions with additional exposure in daily life was reported as 1.7% to 17.2%.<sup>1,2,4,8</sup> However, these reactions might be caused by other triggers (presence of infection or taking another drug). To overcome these complicating situations, in some previous studies, skin testing and/or DPTs were performed on patients with a negative first evaluation result. The frequency of positive allergic test result was reported in a wide range of 3.3% to 27.9% for adults.<sup>1,4,5</sup> For children, the frequency of reactions during reevaluation was reported as 0.9% to 10.5%.<sup>2,3,7</sup> Hershkovich et al<sup>7</sup> reported that penicillin skin tests were performed 1 to 5 months after the first DPT in 98 of 166 children who had negative first evaluation results; 2 patients had positive intradermal test results with penicillin, and 1 patient experienced maculopapular rash by DPT. Mendelson et al<sup>3</sup> reevaluated 219 children with prior negative workup results 4 weeks later, and the frequency of positive skin test results was 0.9%.<sup>3</sup> The frequency of allergic reaction by reevaluation in our study was low (2.8%), which is consistent with most of the studies among children. Another study<sup>2</sup> among children reported a high frequency. One hundred eighty-nine children were reevaluated with penicillin skin tests 4 weeks after the first test, and the frequency of sensitization was reported as 10.5% (26 patients).

A positive reaction after a negative DPT result may be caused by the presence of cofactors, resensitization, or false-negative test results.<sup>4,8,10</sup> Too short or too long an interval from reaction may be one of the causes. The interval from reaction was likely not too short or long for any of our patients. It is argued that too short an exposure or observation time can also lead to false-negative results.

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**Table 1**  
Characteristics of the study group

| Characteristic                                                    | Finding (N = 71)                     |
|-------------------------------------------------------------------|--------------------------------------|
| Male sex, No. (%)                                                 | 37 (52.1)                            |
| Age at reaction time, mean (SD) [range], y                        | 4.88 (3.76) [3 months to 17.5 years] |
| Age at first evaluation, mean (SD) [range], y                     | 6.52 (4.19) [1.2–18]                 |
| Time between reaction time and first evaluation, median (IQR), mo | 7.2 (3.2–20.4)                       |
| Immediate reaction, No. (%)                                       | 20 (28.2)                            |
| Nonimmediate reaction, No. (%)                                    | 51 (71.8)                            |

Abbreviation: IQR, interquartile range.

The exposure and observation time for the DPT is not well agreed on. It is suggested that the drug should be given for 2 to 10 more days at home after the DPT. In our study, patients continued to take the drug at home for 5 days after the DPT. Two of our patients had a reaction during the second DPT, on the second day and the other on the fourth day of reevaluation. For evaluating resensitization, one of these patients was tested with skin testing and DPT, and the result were negative. The other patient could not be evaluated.

In conclusion, a reaction during reevaluation of patients with previously negative DPT results with  $\beta$ -lactam antibiotic is low. Our results suggest that performing additional DPTs after a prior negative evaluation is not necessary in most pediatric patients. Reprovocation tests may be considered in selected groups as recommended by ENDA.

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## References

- [1] Macy E, Mangat R, Burchette RJ. Penicillin skin testing in advance of need: multiyear follow-up in 568 test result-negative subjects exposed to oral penicillins. *J Allergy Clin Immunol*. 2003;111:1111–1115.
- [2] Pichichero ME, Pichichero DM. Diagnosis of penicillin, amoxicillin, and cephalosporin allergy: reliability of examination assessed by skin testing and oral challenge. *J Pediatr*. 1998;132:137–143.
- [3] Mendelson LM, Ressler C, Rosen JP, Selcow JE. Routine elective penicillin allergy skin testing in children and adolescents: study of sensitization. *J Allergy Clin Immunol*. 1984;73:76–81.
- [4] Bittner A, Greenberger PA. Incidence of resensitization after tolerating penicillin treatment in penicillin-allergic patients. *Allergy Asthma Proc*. 2004;25:161–164.
- [5] Goldberg A, Confino-Cohen R. Skin testing and oral penicillin challenge in patients with a history of remote penicillin allergy. *Ann Allergy Asthma Immunol*. 2008;100:37–43.
- [6] Solensky R, Earl HS, Gruchalla RS. Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. *Arch Intern Med*. 2002;162:822–826.
- [7] Hershkovich J, Broides A, Kirjner L, Smith H, Gorodischer R.  $\beta$ -lactam allergy and resensitization in children with suspected beta lactam allergy. *Clin Exp Allergy*. 2009;39:726–730.
- [8] Misirlioglu ED, Toyran M, Capanoglu M, Kaya A, Civelek E, Kocabas CN. Negative predictive value of drug provocation tests in children. *Pediatr Allergy Immunol*. 2014;25:685–690.
- [9] Johansson SG, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy: an EAACI position statement from the EAACI nomenclature task force. *Allergy*. 2001;56:813–824.
- [10] Blanca M, Romano A, Torres MJ, et al. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy*. 2009;64:183–193.