Provocation Tests in Nonimmediate Hypersensitivity Reactions to β-Lactam Antibiotics in Children: Are Extended Challenges Needed?

García Rodríguez R, Moreno Lozano L, Extremera Ortega A, Borja Segade J, Galindo Bonilla P, Gómez Torrijos E. *J Allergy Clin Immunol Pract*. 2019;7(1):265–269

PURPOSE OF THE STUDY: To determine if repeated doses of a β-lactam antibiotic are required to reproduce a nonimmediate hypersensitivity reaction in children.

STUDY POPULATION: This retrospective observational study included 97 patients younger than 14 years of age with history of at least 1 reaction to a β-lactam antibiotic and with symptoms that began at least 6 hours after the first dose of the implicated medication.

METHODS: All patients underwent a 1-day in-hospital graded provocation test, with a cumulative dose of 65% of the daily dose of the β-lactam antibiotic under study, followed by hospital observation for 2 hours. If no reaction appeared over the same amount of time between dosing and symptoms during the index reaction, the patient was instructed to continue 2 daily antibiotic doses at home over the same number of days it took for the index reaction to appear. The total duration of study was variable for each patient.

RESULTS: A positive reaction was recorded in 14 patients (14.4%). The hospital provocation triggered 3 immediate reactions and 8 delayed reactions. The home provocation triggered 1 immediate reaction and 2 delayed reactions. The most frequent manifestation of an adverse reaction was a maculopapular exanthem. Previous symptoms, implicated medication, and demographic characteristics of patients (with exception of sex) were not predictors for the appearance of delayed reactions. Male sex and a history of more than 1 previous reaction with any β-lactam antibiotic were associated with immediate or late reactions during hospital provocation.

CONCLUSIONS: Nonimmediate reactions to β-lactam antibiotics in children may be triggered with a 1-day provocation test. The authors suggest a 1-day provocation test followed by an observational period of at least the time interval observed in the index reaction. If this provocation is negative, an extended home provocation could be pursued.

REVIEWER COMMENTS: The results of the current study are encouraging, with the minority of studied patients exhibiting adverse symptoms, most of which were triggered during the hospital rather than the home provocation. Data from the current study do not exclude the possibility that reactions may occur hours to days after a single-day provocation attempt. The authors pose the question of whether all patients who will react are able to be provoked with a single-day attempt with prolonged subsequent observation. Additional study is needed to assess larger numbers of children with nonimmediate adverse reactions to β-lactam antibiotics. Additional data on risk assessment and pretest predictive measures will lead to benefits both for individual patients and community antibiotic stewardship.

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Efficacy and Safety of 5-Day Challenge for the Evaluation of Nonsevere Amoxicillin Allergy in Children

Labrosse R, Paradis L, Lacombe-Barrios J, et al. *J Allergy Clin Immunol Pract*. 2018;6(5):1673–1680

PURPOSE OF THE STUDY: To determine if the use of a 5-day challenge with amoxicillin would not only be safe but also lead to an increase in future amoxicillin use in nonallergic patients compared with a single-dose graded drug provocation.

STUDY POPULATION: The population included 130 consecutive children <18 years of age referred to the allergy unit with a history of amoxicillin or amoxicillin and clavulanate. Children with life-threatening reactions or severe non–immunoglobulin E–mediated reactions were excluded. A total of 57.7% presented with a maculopapular rash, 35.4% presented with hives.

METHODS: Initial evaluation included skin testing done in a blinded fashion and a graded drug provocation test (DPT) with 45 mg/kg amoxicillin in 3 steps (1/100, 1/10, and full dose) at 30-minute intervals, independent of skin test results. Patients with negative single-dose DPT results were sent home with a 4-day course of amoxicillin. Phone follow-up was done 2 years later.

RESULTS: A total of 2.3% had an immediate reaction during the single-dose DPT, and all were mild. Three of the remaining 127 patients had a confirmed nonimmediate reaction during the 4-day challenge (1 on the second day, 1 on the third day, and 1 3 days after completion). All 3 reactions were a mild, isolated maculopapular rash. Three patients had equivocal reactions that were determined to be negative with reassessment. At 2 years, 65.8% had used antibiotics again, and 89.3% had used amoxicillin. Three patients (4.5%) had a mild delayed cutaneous reaction with later use of amoxicillin. In a previous study using a single-dose provocation, 18.3% of patients had refusal to use amoxicillin again compared with 1.3% of the current study.

CONCLUSIONS: Five-day oral challenge with amoxicillin is safe and effective and greatly increases the compliance with future use of penicillin antibiotics.

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