Original Article

Oral Challenge without Skin Testing Safely Excludes Clinically Significant Delayed-Onset Penicillin Hypersensitivity

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What is already known about this topic? Penicillins are the drug family most commonly associated with hypersensitivity reactions. Current guidelines recommend negative skin tests before re-administering penicillins to patients with previous nonimmediate reactions.

What does this article add to our knowledge? In patients with a history of nonimmediate reactions to penicillin, we found no relationship between the appearances of late reactions to penicillin challenge and skin test results.

How does this study impact current management guidelines? A 5-day oral challenge without a preceding skin test is safe and sufficient to exclude penicillin allergy after nonimmediate reactions developing during penicillin treatment.

BACKGROUND: Penicillins are the drug family most commonly associated with hypersensitivity reactions. Current guidelines recommend negative skin tests (ST) before re-administering penicillins to patients with previous nonimmediate reactions (NIR).

OBJECTIVE: The objective of this study was to examine whether ST are necessary before re-administering penicillin to patients with NIR.

METHODS: Patients with NIR to penicillins starting longer than 1 hour after last dose administration or starting any time after the first treatment day or patients with vague recollection of their reaction underwent penicillin ST. Disregarding ST results, patients were challenged with the relevant penicillins. One-tenth of the therapeutic dose followed by the full dose was administered at 1-hour interval and patients continued taking the full dose for 5 days.

RESULTS: A total of 710 patients with alleged BL allergy were evaluated. Patients with a history of immediate reaction (52, 7.3%) or cephalosporin allergy (16, 2.2%) were excluded. Of the remaining 642 patients, 62.3% had negative ST, 5.3% positive ST, and 32.4% equivocal ST. A total of 617 (96.1%) patients were challenged. Immediate reaction was observed in 9 patients (1.5%): 1—positive ST, 7—negative ST, and 1—equivocal ST ($P = .7$). Late reaction to the first-day challenge occurred in 24 patients (4%). An at-home challenge was continued by 491 patients. Complete 5-day and partial challenges were well tolerated by 417 (85%) and 44 patients (8.9%), respectively, disregarding ST results. Thirty patients (6.1%) developed mild reactions to the home challenge regardless of their ST results.

CONCLUSION: A 5-day oral challenge without preceding ST is safe and sufficient to exclude penicillin allergy after NIR developing during penicillin treatment. **(J Allergy Clin Immunol Pract 2017;5:669-75)**

Key words: *Beta-lactams; Nonimmediate penicillin allergy; Drug hypersensitivity; Oral challenge*

The dilemma faced by any physician dealing with suspected drug reaction is whether the culprit drug can be re-administered safely. Guidelines for the evaluation of beta-lactam (BL) hypersensitivity reactions have been made by the European Network for Drug Allergy (ENDA).[1] However, these guidelines require 1 or 2 separate sessions of skin tests (ST) in the evaluation of immediate hypersensitivity reactions occurring within 1 hour after the last drug administration. In nonimmediate hypersensitivity reactions, occurring later than 1 hour after the last drug administration, the guidelines require 3 sessions, on separate days, each including ST, late reading of intradermal (ID) tests, and patch testing.[1,2] In both immediate and nonimmediate reactions, the gold standard procedure to determine acute BL tolerance is an oral challenge with a therapeutic BL dose and at least 1 hour of observation to rule out a clinically significant immediate reaction. Obviously, following these guidelines is costly and time consuming. A different approach was presented in a recent study by Mill et al[3] where a direct challenge without prior ST was performed on a large group of children with alleged

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Abbreviations used
BL- Beta-lactams
ENDA- European Network for Drug Allergy
ID- Intradermal
PPL- Penicilloyl-polylysine
ST- Skin tests

amoxicillin allergy. However, a substantial number of the children with a history of immediate reaction reacted to the challenge. The study did not include adults and is also subjected to the limitations of a retrospective work. The commercial penicillin skin-test reagent, penicilloyl-polylysine (PPL), was unavailable in the United States between 2004 and 2010. Consequently, an approach of using partial testing and if negative a divided dose challenge was suggested by different authors.[4] However, a direct challenge disregarding ST results is not a widely accepted practice. Practically, anaphylactic reaction is the major hazard in re-administering BL to a patient with suspected previous hypersensitivity reaction. On excluding rare rashes with potential life-threatening reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug-related eosinophilia with systemic symptoms, or acute generalized eczematous pustulosis, all other nonimmediate reactions, although inconvenient, represent no real risk to the patient. Therefore, the ENDA guidelines that at the present time are one of the approaches for diagnosis and the European gold standard for diagnostic evaluation of BL nonimmediate hypersensitivity reactions might not be necessary in everyday life.

To address this question, we prospectively challenged patients with previous nonimmediate reaction to penicillin with the culprit drug followed by a 5-day full therapeutic course, disregarding the precise nature of the initial reaction or the ST results performed before the initiation of the challenge. We similarly evaluated patients with vague or completely no recollection of the hypersensitivity reaction.

METHODS

Patients and skin tests

From June 2011 to April 2015 all subjects referred for allergic evaluation of BL hypersensitivity underwent ID ST with PPL (0.04 mg/mL, 1:10 and 1:1), minor determinants mixture (0.5 mg/mL, 1:10 and 1:1) and amoxicillin (20 mg/mL, 1:10 and 1:1) (all produced by Diater, Madrid, Spain), and penicillin G 10,000 U/mL (Teva, Petach-Tikva, Israel). If the culprit BL was different, patients were also tested ID with the relevant drug: amoxicillin-clavulanic acid 20 mg/mL (Augmentin by GSK, Brentford, UK), cefuroxime 2 mg/mL (Zinnat by GSK), ceftriaxone 2.8 mg/mL (Rocephin by Hoffman-La Roche, Basel, Switzerland), and cefazolin 1 mg/mL (Kefazin by Vitamed, Binyamina, Israel). Histamine phosphate (Histatrol 2.75 mg/mL for ID ST and 0.275 mg/mL for prick ST, by ALK, Washington, NY) and phenol saline (ALK) served as positive and negative control, respectively.

Patients with a history of an immediate reaction starting within 1 hour after the last drug administration were first tested with prick ST. If negative, ID ST were performed, first with the lower concentrations and if negative, higher concentrations were performed. Prick ST was considered positive when the wheal largest diameter was $\geq$3mm of the negative control in the presence of flare. Intradermal ST was considered positive when the wheal largest diameter was $\geq$5 mm of the negative control in the presence of positive flare. Intradermal ST was considered equivocal when the wheal largest diameter was 3 to 4 mm greater than the negative control in the presence of flare.

All other patients—(1) patients with nonimmediate reaction starting longer than 1 hour after the last drug administration; (2) patients with a reaction starting any time after the first treatment day; and (3) patients with no recollection of the hypersensitivity reaction who, for the unknown reason, were "tagged" as penicillin allergic—underwent ID ST with all concentrations simultaneously, without preceding prick ST. In patients who had Stevens-Johnson syndrome, toxic epidermal necrolysis, drug-related eosinophilia with systemic symptoms, or acute generalized eczematous pustulosis, ST were not performed and the patients were excluded from the study and advised to avoid BL.

Oral challenges

Patients who did not have an initial immediate hypersensitivity reaction were invited to participate in the study, regardless of the results of their ST. A challenge was performed with the culprit penicillin. In cases of no recollection of the initial adverse reaction to penicillin, the challenge was performed with amoxicillin. Challenges and ST were performed in the Allergy Unit where trained personnel as well as medications and equipment to treat anaphylactic reactions were present at all times.

According to their weight, patients were given one-tenth of their daily therapeutic dose divided by 2 or 3, according to the number of the daily doses usually administered for the challenged drug. For example, a child weighing 20 kg whose full daily dose of amoxicillin would have been 50 mg/kg $\times$ 20 kg = 1000 mg received 1/10 $\times$ 1000 mg/2 = 50 mg. One hour later, the patients were administered the full daily therapeutic dose divided by 2 or 3 (500 mg for that child) and were observed for 2 hours. Patients were then discharged and instructed to take on that night another full daily therapeutic dose divided by 2 or 3 and to continue taking the same dose, 2 or 3 times a day, for the next 4 days (ie, 500 mg of amoxicillin twice a day). Patients were instructed to stop taking the BL and call the allergy clinic should any adverse reaction develop. Five to seven days after their visit to the allergy clinic, patients were contacted by phone and interviewed about their reactions since the initial visit.

The study was approved by the ethics committee and registered in the National Institutes of Health clinical studies website (No. NCT01520181).

Statistical analysis

Results are expressed as frequencies and percentage, mean, and standard deviation, as appropriate. Differences between groups were analyzed by a χ^2 test for categorical data, a *t*-test for continuous normally distributed variables, and Mann-Whitney for nonnormally continuous parameters (for comparison between 2 groups). Differences among 3 groups were analyzed with the Kruskal-Wallis nonparametric test. P values $<.05$ were considered statistically significant.

Data were analyzed using SPSS-23 software (IBM, NY).

RESULTS

Patients

Seven hundred and ten patients with alleged beta-lactam hypersensitivity were screened (Figure 1). Fifty-two patients (7.3%) had histories of an immediate reaction to BL. Therefore, they were excluded from the oral challenge portion of the study.