

Original Article

Risk of Allergic Reactions to Recurrent Intravenous Penicillin Administration in Penicillin Skin Test Negative Patients

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What is already known about this topic? Patients with histories of penicillin allergy but with negative skin test results may be at increased risk for penicillin resensitization following intravenous penicillins.

What does this article add to our knowledge? The risk of having an immediate reaction to intravenous penicillin appears very low in penicillin skin test negative patients who have received repeated courses of intravenous penicillin therapy.

How does this study impact current management guidelines? Repeat penicillin skin testing after a well-tolerated course of intravenous penicillin therapy appears unnecessary.

BACKGROUND: Patients with a history of penicillin allergy who are found to be skin test negative to penicillin are able to tolerate repeated oral doses of penicillin with low rates of resensitization. However, the resensitization rate after repeated doses of intravenous penicillin is less clear.

OBJECTIVE: We sought to evaluate the risk of allergic reactions to repeated doses of intravenous penicillin in patients who previously reported penicillin allergy and were found to be penicillin skin test and oral challenge negative.

METHODS: A retrospective review was conducted between 2010 and 2016 of adult patients who were treated at our academically affiliated hospitals. Patients included in the review had negative penicillin allergy testing and were treated with 2 or more courses of intravenous penicillins. Charts were evaluated to identify any adverse drug reactions.

RESULTS: Thirty-two patients met our inclusion criteria. The index penicillin-associated reactions ranged from rash to hypotension and were, for the most part, remote as 75% had reported reactions more than 10 years previously. More than 50% of patients received 3 or more courses of intravenous penicillins. The most frequently repeated intravenous penicillin overall was piperacillin/tazobactam. Thirty-two patients received a total of

111 courses of intravenous penicillins and none developed an immediate hypersensitivity reaction.

CONCLUSIONS: In patients who report penicillin allergy and have negative penicillin allergy testing, repeated administration of intravenous penicillin antibiotics appears to be safe. Larger prospective studies should be performed to confirm these observations. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: Penicillin; Allergy; Resensitization; Intravenous; Drug allergy

Clinicians commonly encounter patients with a history of allergy to antibiotics and among these, penicillin allergy is the most often reported.¹ Approximately 10% of hospitalized patients in the United States report a history of penicillin allergy.^{1,2} Recent US studies indicate that approximately 98% of patients reporting penicillin allergy are not truly allergic and could safely receive penicillin.^{3,4} In addition, penicillin allergy wanes with time, with approximately 50% of allergic cases at 5 years and roughly 80% at 10 years showing tolerance.^{5,6} Despite these trends, penicillin antibiotics continue to be a major cause of anaphylaxis. A recent US study on fatal anaphylaxis found antibiotics to be the most common identifiable cause, with penicillins being the most common culprit antibiotic.⁷ Administration of intravenous penicillin (compared with other methods of administration) is considered to have the highest risk of provoking anaphylaxis in individuals sensitized to penicillin.⁸

Current evaluation for patients reporting penicillin skin testing includes a history and penicillin skin testing, and when negative, a confirmatory oral challenge, often with amoxicillin, is typically performed.³ Previous studies have shown that patients who have been evaluated and have negative penicillin skin test results are able to tolerate repeat oral doses of penicillin with low rates of resensitization (ie, redevelopment of a penicillin allergy).⁹⁻¹¹ What has not been conclusively evaluated is the risk of resensitization after repeated doses of intravenous penicillin.

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Abbreviations used
EMR- electronic medical record

Few studies have been performed to determine the risk of re-sensitization after parenteral courses of penicillin with mixed results. Parker et al¹² described 18 adults who reported penicillin allergy and had negative penicillin skin test results, followed by administration of intravenous penicillins or cephalosporins.¹² Of the 18 total subjects treated, 3 patients (16%) developed evidence of re-sensitization based on development of a positive penicillin skin test result. Lopez-Serrano et al¹³ evaluated 207 patients with penicillin allergy who had initially negative skin test results and negative challenges with both oral amoxicillin and intramuscular benzylpenicillin.¹³ Ten to 30 days after their initial evaluation, they performed repeat penicillin skin tests and challenges (if negative). Eleven patients (5%) had either converted to a positive penicillin skin test ($n = 6$) or reacted to challenge ($n = 5$) with benzylpenicillin or amoxicillin. Bittner and Greenberger¹⁴ described 30 subjects who reported penicillin allergy and had negative penicillin skin testing who received at least 1 course of a parenteral cephalosporin or β -lactam antibiotic. None of the identified patients had evidence of an IgE-mediated reaction with readministration of antibiotics. Based on this information, the Drug Allergy Practice Parameters states that “re-sensitization after high-dose parenteral treatment with penicillin appears to be more likely; therefore, repeat penicillin skin testing in this situation may be warranted.”¹⁵

In light of this conflicting data, we sought to evaluate the risk of allergic reactions after repeated courses of intravenous penicillins in subjects who report a history of penicillin allergy and have subsequent negative skin testing and challenge to a penicillin.

METHODS

Subjects

Records were reviewed retrospectively from adult patients treated at the University of Texas Southwestern Medical Center hospitals and clinics or the Parkland Health and Hospital System from September 1, 2010, to April 1, 2016. A list of subjects who underwent penicillin skin testing (either as an inpatient or as an outpatient) was obtained by way of electronic medical record (EMR) query of the University of Texas Southwestern Medical Center hospitals and clinics. At Parkland Hospital, a program of inpatient penicillin skin testing has been established since November 2014, and a list was obtained of patients who were identified as having been tested via this program.⁴ Patients were included in this retrospective study if they met the following criteria: (1) had evidence of a previous negative penicillin skin test and amoxicillin challenge and (2) after negative penicillin testing received at least 2 subsequent courses of a parenteral penicillin documented in the EMR.

Antibiotic courses and exposures

A “course” of intravenous penicillin could be as little as a single dose (such as perioperative dosing) or as long as needed to treat the underlying problem while hospitalized. A continuous antibiotic course was defined as intravenous penicillin administration with a break in dosing of no longer than 7 days. This definition allowed for subject differences with respect to dosing because dosing may differ among subjects with different comorbid conditions. It would

include breaks between hospitalizations and/or treatments for specific disease process (eg, a neutropenic patient finishing piperacillin/tazobactam for hospital-associated pneumonia and then, 4 days later, receiving piperacillin/tazobactam again for fever of unknown origin). Multiple penicillin types could be given during this time yet the period would still be defined as a continuous course. An “antibiotic exposure” was defined as having received a specific antibiotic. Patients may be exposed to more than 1 antibiotic during a single course (eg, to narrow treatment from piperacillin/tazobactam to ampicillin). After each course of penicillin, the EMR was reviewed for evidence of immediate allergic reactions as well as delayed adverse drug reactions.

Penicillin skin testing and amoxicillin challenge

A uniform testing protocol was used at both institutions. Penicillin skin testing was performed with PrePen (benzyl-penicilloyl-polylysine; AllerQuest LLC, ALK-Abello, Inc., Hørsholm, Denmark) and Penicillin G (potassium penicillin G; Sandoz, Inc, Princeton, NJ; diluted to 10,000 units/mL). If percutaneous test results are negative at 15 minutes, intradermal testing in duplicate is performed. A wheal of 3 mm or greater accompanied by flare on percutaneous testing is considered positive. A change in intradermal wheal (typically an initial wheal is 3-5 mm) of greater than 3 mm in any direction accompanied by a flare is considered positive. If skin testing is negative, an oral challenge with 500 mg of amoxicillin and 1-hour observation was performed. If patients were being evaluated in the hospitalized setting where intravenous penicillin is needed acutely, a dose of intravenous penicillin may be given in lieu of the amoxicillin challenge.

The study was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center (STU 122013-054).

RESULTS

Subjects

Thirty-two subjects met our inclusion criteria (Table 1). Of these, 4 underwent penicillin skin testing in an ambulatory setting and 28 were tested while hospitalized. Seventeen (53%) of the 32 subjects were women. The average age at penicillin skin testing was 46.9 years (range, 24-79 years). In regard to race, 13 were documented in the EMR to be black, 10 white, 3 Hispanic, and 6 unknown. Most subjects (75%) had remote (>10 years ago) historical reactions to penicillin; however, 16% had reported allergic reactions to penicillin within a year of penicillin testing. Historical reactions to penicillins varied, with the majority having cutaneous reactions. One subject reported symptoms and signs consistent with anaphylactic shock. Surprisingly, only 1 subject could not recall the type of reaction to penicillin.

Intravenous penicillin courses

The total number of parenteral courses of penicillin antibiotics observed was 111. The mean number of antibiotic courses per patient was 3.5 courses (range, 2-12 courses) (Figure 1). More than 50% of patients received 3 or more courses of intravenous penicillins. Patients were exposed to 5 different intravenous penicillins: ticarcillin, nafcillin, ampicillin, penicillin G, and piperacillin. Piperacillin was the most prolific, with 30 of the 32 subjects being exposed. Penicillin G was the least prolific, with 1 subject being exposed once.

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