Original Article

Frequency and Risk Factors of Penicillin and Amoxicillin Allergy in Suspected Patients with Drug Allergy

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Abstract

Background: Unconfirmed beta-lactam allergy is a significant public health problem because of the limitations it imposes in drug selection. In this study, we aimed to evaluate patients referred for beta-lactam allergy to determine the frequency of confirmed beta-lactam allergy and identify some risk factors.

Methods: In a prospective cohort study, all referred patients to Immunology, Asthma and Allergy Research Institute in Tehran University of Medical Sciences (between 2007 – 2009) who suspected to have beta-lactam allergy were entered into this study based on having the inclusion criteria. Follow-up was performed 6 – 8 years after the final diagnosis. Diagnosis of beta-lactam allergy relies on thorough history and specific IgE measurements (ImmunoCAP), skin prick testing (SPT), intradermal testing (IDT), patch testing, and oral drug challenge test.

Results: Fifty-one patients with mean age of 24.5 (±18.5) years were enrolled in this study. Based on workups, beta-lactam allergy was confirmed in 16 (31.4%) patients, suspicious in 22 (43.1%) patients and ruled out in 13 (25.5%) patients. During the follow-up, 3 patients with suspicious drug allergy consumed the culprit drug with no reaction so allergy was finally ruled out in 16 (31.4%) patients. Age, sex, atopy and family history of drug allergies were not significantly different between the patients with confirmed or ruled-out diagnosis of penicillin and amoxicillin allergy.

Conclusion: At least up to one-third of patients with a history of beta-lactam allergy are proven to be safe using the drug. Also, a clear protocol consists of serum sIgE assay and SPT can be helpful to the physicians in the health care system.

Keywords: Amoxicillin, drug allergy, hypersensitivity, penicillin

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Introduction

Adverse drug reactions (ADR) affect 10% – 20% of hospitalized patients and more than 7% of the general population.[1] It is estimated that immunologic drug reaction (i.e. drug allergy or hypersensitivity) occurs in about one third of all adverse drug reactions, however in most of the cases, allergic reactions are not confirmed or overvalued.[2] The most common cause of drug hypersensitivity is an allergy to beta-lactam antibiotics.[1,3]

Ten percent of patients report a history of penicillin allergy; however, most is proved otherwise.[4] Beta-lactam allergy represents as a public health problem if not verified due to its limitations in drug selection. Over-diagnosis is common and avoidance is a universally accepted strategy.[5] It seems that the label of "beta-lactam allergy" needs to be applied with caution after the occurrence of an ADR. Mislabeling of penicillin allergy increases the risk of frequent hospitalization, antibiotic-resistant infections and medical costs.[6] These findings highlight the significance of a confirmed diagnosis of beta-lactam antibiotic allergy.

Diagnosis of beta-lactam allergy relies on a thorough history and skin prick testing (SPT), intradermal testing (IDT), patch testing, in vitro specific IgE measurement and oral drug challenge. As reported by Salkind, et al. SPT with major and minor determinants of penicillin (penicilloyl-poly-lysine [ppl] and penicillin G, respectively) has a sensitivity and specificity of 95% and 98%, respectively.[7]

There are few reports regarding ADR or drug allergy in Iran,[8–10] but this is the first prospective study conducted with standard protocols about beta-lactam allergy.

The goal of this study was to evaluate patients with suspected beta-lactam allergy. Therefore, we aimed to determine the frequency of beta-lactam allergy, identify some risk factors and assess the occurrence of any reactions in these patients prospectively.

Methods

This study was a prospective cohort study started in 2007 and continued to 2015. All referred patients suspected to have beta-lactam allergy were evaluated in Immunology, Asthma and Allergy Research Institute in Tehran University of Medical Sciences. In the first two years of study, referred patients were

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entered based on having the inclusion criteria (symptoms of immunologic drug reactions of type 1 and 4 according to Gel and Coombs classification including urticarial, angioedema, anaphylaxis and maculopapular or mobilliform rashes) and lack of exclusion criteria (non-immunologic drug reactions, type 2 or 3 of Gel and Coombs hypersensitivity reactions, or syndromic allergic disorders such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), fixed drug eruption, as well as drug rash with eosinophilia and systemic symptoms (DRESS).

A standard questionnaire based on the European Network for Drug Allergy (ENDA) guidelines,[11–14] including demographic information, clinical symptoms and risk factors, such as age, sex, family history of drug allergy and atopic state was filled for all participants.[11] Participants, who reported several reactions, were classified based on their most recent reactions. Patients were then followed up for 6 – 8 years by regular visit (at least every year) or they were questioned over telephone to investigate whether they had used the culprit drugs and if they had experienced any immediate or delayed reactions.

Based on their clinical history, reactions were categorized as immediate if they occurred in the first hour after drug exposure and as late (delayed) if they occurred several hours or days after exposure. Specific IgE to penicillin and amoxicillin (ImmunoCAP, Phadia Diagnostics, Uppsala, Sweden) was measured in patients with immediate symptoms. Diagnosis of type one beta-lactam allergy was confirmed in patients with positive sIgE > 0.35 kU/l for beta-lactams and patients with negative results underwent SPT with soluble form of minor and major determinants of Penicillin (Diater Laboratories, Madrid, Spain) and Amoxicillin (GSK, London, UK). Serial dilution was performed with sterile normal saline and concentrations of 0.035 mg/mL for PPL, 0.11 – 1.1 mg/mL for penicillin minor determinants and 2.5 – 25 mg/mL for amoxicillin that were used for SPT and IDT. Skin prick testing was read in two immediate (15 minutes) and delayed (48 – 72 hours) time points. Wheals of 3 mm larger than the negative control were considered positive in SPT if response to histamine was positive.

Deferred readouts of IDT and Patch tests were used for diagnosis of patients with delayed-type allergy. Patch testing was carried out in petrolatum-based media in concentrations of 5% – 20%, which were applied on the back and reported as positive when erythema, wheals, vesicles and/or bullae were present after 48 – 72 hours.[15]

Oral challenge tests were performed in cases with negative sIgE or negative SPT and IDT who consented for further tests for a final diagnosis. Oral challenge tests were performed in hospital and in the presence of emergency equipment. Challenge tests were performed by ingesting increasing doses of the culprit drug every 30 minutes, until the appropriate dose was reached.[13,16] Any objective allergic adverse reaction during the challenge or within 24 – 72 h after the treatment was considered as positive.

Diagnosis was confirmed when sIgE, SPT, IDT or challenge tests were positive and ruled out when challenge test was negative. The diagnosis was suspicious when history was compatible, but tests were not conclusive and the challenge was not performed to exclude this diagnosis.

The study was approved by the ethics committee of the Immunology, Asthma and Allergy Research Institute and written informed consent was obtained from the participants or parents before inclusion into the study. Statistical analysis was performed by Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA, version 16) and *P*-values less than 0.05 were considered significant. *T*-tests and Chi-square tests were used for analysis.

Results

During the first two years of study, 51 patients were enrolled. Mean age of patients was 24.5 (±18.5) years (range: 1 – 65 years) and male to female ratio was 22:29. Demographic features of patients in each group are summarized in Table 1.

Thirty-six patients had immediate reactions. Among these

Table 1. Demographic features of patients

Variable	All patients referred with drug allergy complaint (n = 51)	Confirmed Allergic patients (n = 16)	Suspicious patients for drug allergy (n = 19)	Ruled out patients for drug allergy (n = 16)
Female/male ratio	29/22	10/6	12/7	7/9
Age, mean ± SD, years	24.5 ± 18.5	26.6 ±19.2	28.8 ± 17.2	17.4 ± 18.3
History of atopy, n (%)	35 (68.6)	12 (75)	13 (68.4)	10 (62.5)
Family history of drug allergy, n (%)	8 (15.7)	2 (12.5)	4 (21.1)	2 (12.5)
Type of reactions, n (%)				
Immediate	36 (70.6)	13	14	9
Delayed	15 (29.4)	3	5	7
Presenting symptoms, n (%)				
Anaphylaxis	17 (32.4)	7 (43.8)	7 (36.8)	3 (18.8)
Urticaria	20 (39.2)	6 (37.5)	8 (42.1)	6 (37.5)
Angioedema	9 (17.6)	2 (12.5)	4 (21.1)	3 (18.8)
Maculopapular rash	5 (9.8)	1 (6.3)	0	4 (25)
Culprit Drug, n (%)				
Penicillin	15 (29.4)	7 (43.8)	4 (21.1)	4 (25)
Amoxicillin	23 (45.1)	5 (31.3)	10 (52.6)	8 (50)
Cefixime	8 (15.7)	1 (6.3)	4 (21.1)	3 (18.7)
Amoxicillin+Penicillin	5 (9.8)	3 (18.8)	1 (5.3)	1 (6.3)

patients, 7 had positive sIgE results (4 to penicillin and 3 to penicillin and amoxicillin) and 5 patients had positive IDT to beta-lactam (3 immediate reactions to penicillin, 2 immediate reactions to amoxicillin). In the group with delayed reactions (15 patients), there were also 3 patients with delayed type reactions in IDT, who were classified as a confirmed drug allergic group. The result of patch tests was negative in all patients with delayed reactions. The oral challenge test was done in 14 patients and definite diagnosis was confirmed in one patient. Based on initial workups, beta-lactam allergy was confirmed in 16 (31.4%) patients, suspicious in 22 (43.1%) patients, and 13 (25.5%) patients were confirmed to have no beta-lactam allergy. During the follow-up, 3 patients with suspicious drug allergy consumed the culprit drug with no reaction so allergy was finally ruled out in 16 (31.4%) patients.

In confirmed drug allergic patients, 13 (81%) patients had immediate reactions with presenting symptoms of anaphylaxis, angioedema, and urticaria and 3 (19%) patients had delayed reactions with symptoms of maculopapular rash and urticaria

Age, sex, atopy and family history of drug allergies were not significantly different between the patients with confirmed or ruled-out diagnosis of penicillin and amoxicillin allergy.

During the follow-up period, we could contact 54.9% of participants. Of patients being followed up, 39.3% reported using the culprit drug and 60.7% did not report using the drug. Only one patient with confirmed drug allergy gave a history of consumption and reported adverse drug reactions upon ingestion. Eight patients out of 10 ruled-out patients, who were followed-up, reported drug consumption without any reactions.

Discussion

Due to a high rate of reported beta-lactam allergy, the need for appropriate diagnosis is relatively appreciable and requires a simple protocol, which is safe and cost-effective. Research is still needed to develop optimal protocols to diagnose true allergy and prevent unnecessary avoidance.[17] Foong, et al. in 2016 questioned clinicians in 16 countries and showed the lack of uniformity in diagnosis of beta-lactam allergy in children. Currently, the gold standard for testing is oral challenge tests and 94% of respondents to the study by Foong, et al. used it as a gold standard in the previous year of their practice.[18] However, SPT and IDT are more rapid and easier-to-perform methods that reduce the number of oral challenges needed to confirm the diagnosis.[17]

When patients with a history of penicillin allergy are evaluated, up to 90% are proven to tolerate penicillin.[5] Trubiano, et al. in 2016 demonstrated that around half of patients with antibiotic allergy labels were willing to be tested and 48% were proved to be at low risk for allergic reactions.[19] In this study, 31% of patients were confirmed to tolerate beta-lactams or were unlikely to react to this class and also 31% were likely to have beta-lactam allergy, which was higher than the reported rates in the previous publications. The reason could be the design of this study, which included referred cases of suspicious drug allergy with a robust history that were more probable to have drug allergy. However, even in these patients with positive history, one-third was proved not to have allergies. The proof of no allergy to beta-lactams is very important to reduce the use of broad-spectrum antibiotics with all their health implications and also reduce the economic costs imposed to the health system.[20–22]

Immediate reactions occur in a time period of one hour. In our patients, all immediate reactions happened within one hour of drug consumption with the exception of one patient with typical clinical immediate reaction who reported the reaction within two hours. Because of the probability of false interpretations, some authors recommend "up to several hours (eg ≤ 6hours)" as an arbitrary cutoff of immediate reactions.[23]

In this study diagnosis of drug allergy in most of the patients with maculopapular cutaneous eruptions were ruled out by oral challenge test. Many drugs can trigger these reactions but mostly related to viral as concomitant infections.[24] In our study, all patch tests were negative. This method is safer than IDT and can be done with any form of drugs; however, patch tests are less sensitive and are dependent on the vehicle used.[25]

Regarding risk factors, contrary to the study of Albin, et al.[5] we found no significant differences between males and females in allergy to beta-lactams. Albin, et al. have mentioned the possibility of reporting bias because of the retrospective nature of their study, which was not compatible with our study. However, similar to the above mentioned study, we could not find an association between beta-lactam allergy and age of the patients. Also Consistent with the study of Ponvert, et al. performed in children with beta-lactam allergy, atopy was not a risk factor for beta-lactam hypersensitivity.[26,27]

In this follow-up study, surprisingly we found 80% of patients for whom the diagnosis of beta-lactam allergy was ruled out, used antibiotic. This finding was in contrast to studies that report the fear of using the drug despite negative testing and lack of confidence in removing of penicillin allergy label[28] or incomplete documentation.[29]

This study had some limitations. The standard protocol including the challenge test could not be performed in all patients due to lack of consent. Also, the follow up was not completed for all included patients because of inaccessibility during the follow up period.

In conclusion, in a referral center, up to one-third of patients with a strong history of beta-lactam allergy are proven to be safe using the drug and a clear protocol especially consisting serum sIgE (ImmunoCAP) assay and SPT can be a great help to physicians in the health care system to confirm or rule out drug allergies.

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