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Safety of direct oral provocation testing using the Amoxicillin-2-step-challenge in children with history of non-immediate reactions to amoxicillin

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ABSTRACT

Background: Previous studies have shown that direct oral provocation tests, without prior skin testing, in children having delayed onset, benign rashes to beta-lactam antibiotic is safe and effective. Although, this test is useful in confirming drug hypersensitivity reactions, there is no standard protocol recommendation of drug provocation tests. This study aimed to evaluate the safety of the direct oral provocation test, using the Amoxicillin-2-step-challenge without prior skin testing, in children with history of non-immediate reactions to amoxicillin.

Methods: The Amoxicillin-2-step-challenge protocol was performed in children with history of non-immediate reactions to amoxicillin. This protocol is composed of 2 doses of amoxicillin, with a 30-min interval; continued for a total of 5 days. All of the patients had not undergone skin testing before the oral provocation test.

Results: This study included 54 children, having a median age of 6.6 years, with 70.4% being male. Amoxicillin and amoxicillin-clavulanic acid were reported as the culprit drug in 75.9% and 24.1%, respectively. The index reactions were maculopapular (MP) rash in 79.6% and delayed urticarial rash/angioedema in 20.4%. Five patients (9.3%) had a reaction during the provocation test, all of these patients had delayed urticaria and were treated with oral antihistamine. However, 1 patient developed a fever alongside an MP rash. Laboratory investigation for this patient showed increased atypical lymphocytes and liver enzymes elevation.

Conclusions: Direct oral provocation tests, using the Amoxicillin-2-step-challenge, without prior skin testing, revealed good, immediate safety for the diagnosis of amoxicillin hypersensitivity in children with history of non-immediate reactions to amoxicillin.

Keywords: Amoxicillin hypersensitivity, Non-immediate reactions, Drug provocation test

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INTRODUCTION

Amoxicillin is one of the most commonly prescribed drugs for community acquired bacterial infections.[1] Five to 10 percent of children reported maculopapular (MP) or urticarial rashes on aminopenicillins; including amoxicillin.[2] However, there are many potential causes of pediatric rashes. These include, children with an intercurrent illness being treated with antibiotics and viral infections, which is a common cause of rashes, independent of medication.[3] In clinical practice, these children are frequently catalogued as being allergic to amoxicillin without further investigation, which leads to frequent over-diagnosis of drug allergies.[1] The consequence of an unproven amoxicillin allergy is an avoidance of all beta-lactam antibiotics.[4] Moreover, it is associated with a greater number of prescriptions of alternative antibiotics, with higher costs and an emergence of multidrug resistant pathogens.[5] The true incidence of amoxicillin allergies is only 1–10% of patients. Therefore, allergy diagnostic testing should be performed to establish a correct diagnosis.[6–8]

Amoxicillin hypersensitivity is classified as: an immediate or a non-immediate reaction. Immediate reactions occur within 1 h after drug administration that are characterized by urticaria and/or angioedema, bronchospasm, and anaphylaxis. Non-immediate reactions occur beyond 1 h of the last drug administration, which are mostly seen as maculopapular exanthemas or delayed urticaria-angioedema.[2,9–11]

For non-immediate reactions, a drug provocation test (DPT) is the gold standard for the diagnosis of a drug allergy. Although patch testing, delayed reading intradermal testing (IDT), and lymphocyte transformation tests can be useful in children with non-immediate reactions, none have been standardized. In addition to this, their positive predictive value, sensitivity and specificity are low.[12,13] Furthermore, a skin test causes pain, making it difficult to implement in children; it is also time-consuming.[14] There have been previous studies showing that the direct oral provocation test, without prior skin testing in children with delayed onset benign rashes to beta-lactam antibiotics, is safe and effective in confirming drug hypersensitivity reactions.[15,16] Moreover, recent studies suggest that a direct penicillin or amoxicillin challenge without skin testing is probably appropriate for children with history of benign rashes, which are excluded from anaphylaxis and severe cutaneous adverse drug reactions (SCARs).[17,18]

However, there is no standard protocol recommendation for the drug provocation test. Hence, the aim of this study was to evaluate the safety of direct oral provocation tests, using the Amoxicillin-2-step-challenge without prior skin testing, in children with history of non-immediate reactions to amoxicillin.

METHODS

Participants and study procedure

The inclusion criteria were all patients less than 15 years of age, who had history of maculopapular rashes for more than 1 h, or urticarial rash/angioedema for more than 6 h after their last dose of ingested amoxicillin or amoxicillin-clavulanic acid, at tertiary care hospital; from January 2012 and April 2017. Exclusion criteria were patients diagnosed as severe life-threatening drug reactions; consisting of: Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), exfoliative dermatitis, vasculitis, or history of previous anaphylaxis. In addition, patients who had a high risk of severe anaphylaxis, due to taking beta blockers or angiotensin-converting enzyme inhibitors, or having systemic mastocytosis, hereditary angioedema, uncontrolled asthma, chronic diseases (eg, cardiovascular disease, kidney disease, liver disease, and immunodeficiency disease), or were taking immunosuppressive drugs and were pregnant were also excluded from the study. This study was approved by the Institutional Ethics Committee. All parents were asked to sign written informed consent before their children were tested.

Drug provocation test

All patients were interviewed by a physician and followed the standardized European Network on Drug Allergy (ENDA) questionnaire for drug allergy before beginning the challenge. Demographic parameters, clinical presentation, chronology of the reaction, clinical allergy history, and duration from initial reaction to the drug test were recorded.

The DPT was performed at least 3 months after the index reaction. Antihistamines as well as all drugs that could affect the results of the provocation test were discontinued at least 1 week before the test. The DPT was performed according to the ENDA guidelines, without any other prior evaluation. The challenge was performed in the clinic, which was equipped with full resuscitation backup, using an open challenge protocol. Amoxicillin was given in 2 divided doses until the daily recommended dose was reached, based on the patient's weight, every 30 min according to the Amoxicillin-2-step-challenge protocol (Table 1). Patients were monitored for acute reactions for 2 h from the last dose given in the clinic. If the first day of the challenge test was negative, a daily therapeutic dose (30–50 mg/kg/day) of amoxicillin was prescribed for home use for 4 days. Parents were advised to call and come to the hospital whenever their child had any suspicious reactions, or come back for follow-up and conclude the DPT results at the clinic 7 days later.

The challenge test was considered negative if there were no objective symptoms, or signs of reaction occurring during the challenge, or within 48 h after the end of their amoxicillin intake.

In children with history of non-immediate reactions to amoxicillin-clavulanic acid, who had a negative DPT result to amoxicillin, DPT with amoxicillin-clavulanic acid was subsequently performed.

Statistical analysis

Quantitative variables were expressed as mean and standard deviation. A P value less than 0.05 was regarded as significant. The data were recorded using Epidata and analyzed using R statistical software.

RESULTS

One hundred and five patients were suspected as having non-immediate cutaneous reactions related to amoxicillin, or amoxicillin-clavulanic acid administration. Twenty-four guardians of participates patients did not give consent for the study, and 27 could not be contacted. The DPTs using the Amoxicillin-2-step-challenge protocol were performed in the remaining 54 patients. The median age of the patients was 6.6 years, and 70.4% were male (Table 2). Twenty children (37%) had personal history of atopy; with allergic rhinitis being the most common comorbidity. Adverse reactions to amoxicillin and amoxicillin-clavulanic acid were reported in 41 subjects (75.9%) and 13 subjects (24.1%), respectively. The index reactions were maculopapular rash in 43 (79.6%) children and delayed urticarial rash/angioedema in 11 (20.4%).

Five patients (9.3%) had a reaction during the amoxicillin provocation test; whereas, 49 (90.7%) tolerated the culprit drug. The amoxicillin-clavulanic acid was well tolerated by all 49 children who previously had a negative result of direct amoxicillin challenge.

The characteristics of the patients with positive oral provocation tests are given in Table 3. Just over half of these patients had an index reaction against amoxicillin-clavulanic acid. After DPT, almost all of these patients developed delayed urticaria only, and received treatment with oral antihistamine drugs. None of the patients had immediate reactions or

Body weight (kg)	Dose of amoxicillin 250 mg/5 mL (mL)	
	1st dose (10%)	2nd dose (90%)
5–10	0.5	5.5
11–20	1	10
21–30	1.5	15
31–40	2.5	20
41–50	3	25
>50	3.5	30

Table 1. The Amoxicillin-2-step-challenge protocol[a]. *a. Orally administered 2 doses of amoxicillin suspension, 250 mg/5 mL, with a 30-min interval*

Characteristic	Total (N = 54)
Age (years), mean (SD)	6.6 (4.3)
Sex, male, n (%)	38 (70.4)
Weight (kg), mean (SD)	26.7 (17.4)
Height (cm), mean (SD)	116.1 (29.1)
Personal history of atopy, n (%)	20 (37.0)
- Allergic rhinitis	14 (25.9)
- Asthma	8 (14.8)
- Atopic dermatitis	5 (9.3)
- Food allergy	7 (13.0)
Culprit drug	
- Amoxicillin	41 (75.9)
- Amoxicillin-clavulanic acid	13 (24.1)
Type of skin rash (index reaction)	
- MP rash	43 (79.6)
- Delay urticaria/angioedema	11 (20.4)
Time interval between the last dose and index reaction (hours), mean (SD)	8 (6.1)
Duration of index reaction (hours), mean (SD)	35.4 (23.9)

Table 2. Baseline characteristics. ***Abbreviation:*** *SD, Standard deviation*

anaphylaxis. However, one patient, a 13-year-old boy, developed a severe, non-immediate reaction during DPT. He had past history of angioedema at 12 h after he had taken amoxicillin-clavulanic acid, occurring 7 years ago. During this visit, he underwent DPT with the Amoxicillin-2-step-challenge protocol, and did not have an immediate reaction after the challenge. Therefore, he was prescribed amoxicillin to be taken at home over the next 4 days; however, on the third day of the amoxicillin challenge he had a fever. His mother then gave him antipyretic drugs, as acetaminophen combined with amoxicillin. On the fourth day of the challenge, he developed a MP rash and amoxicillin was discontinued. A day later, he still had a fever, and the MP rash had increased. His physical examination showed generalized MP rashes at trunk and all extremities, without lymphadenopathy, hepatosplenomegaly, or mucositis. Laboratory investigations illustrated an absolute eosinophil count (AEC) mean of 211 cell/mm3, increased atypical lymphocyte to 5%, and liver enzymes elevation (SGOT 101 U/L, SGPT 84 U/L); a skin biopsy was not conducted. This patient was treated with oral prednisolone, 1 mg/kg/day, for 2 weeks. After this, his clinical symptoms and laboratory investigations improved, and he was tapered off prednisolone within 1 month.

DISCUSSION

In our study, we performed direct amoxicillin provocation tests, without prior skin testing, in children with history of non-immediate and non-severe hypersensitivity reactions to amoxicillin or amoxicillin-clavulanic acid, using the Amoxicillin-2-step-challenge protocol. Our results found that 9.3% had reactions during the provocation test. Almost all of the patients, who had a positive oral provocation test, had delayed urticaria that required treatment with only oral antihistamine

Gender	Age (years)	Culprit drug	Time interval between the index reaction and DPT	History of index reaction	Oral provocation test result
Male	12	Amoxicillin-clavulanic acid	3 years	MP rash, 12 h after the last dose	1st day, 4 h after the last dose, urticaria
Male	8	Amoxicillin-clavulanic acid	4 months	MP rash, 12 h after the last dose	1st day, 7 h after the last dose, urticaria
Female	8	Amoxicillin	4 months	MP rash, 12 h after the last dose	1st day, 4 h after the last dose, urticaria
Male	13	Amoxicillin-clavulanic acid	7 years	Angioedema, 12 h after the last dose	4th day, 7 h after the last dose, MP rash and fever Investigation: AEC 221 cell/mm3, atypical lymphocyte 5%, SGOT 101 U/L, SGPT 84 U/L, BUN 7.3 mg%, Cr 0.54 mg%
Male	3	Amoxicillin	5 months	Angioedema, 7 h after the last dose	1st day, 14 h after the last dose, urticaria

Table 3. Characteristics of patients with positive provocation tests

drugs. However, there was 1 patient that developed a fever with a MP rash at day 4 of the drug provocation test, and his laboratory investigation showed increased atypical lymphocytes and liver enzymes elevation.

Infections in children can commonly cause MP or urticarial rashes. Simultaneously, these children usually receive beta-lactam antibiotic for treatment of these infections. Consequently, these children are frequently catalogued as being allergic to beta-lactam antibiotics, without further investigation, which leads to frequent over-diagnosis of drug allergies. Therefore, it is important to evaluate diagnosis, so as to discriminate between true drug allergies and rashes due to infection. Our study demonstrated the true incidence of amoxicillin allergies being confirmed by DPT as being less than 10%. This result was similar to the results found by Zambonino et al (7.3%),[14] Holm et al (2.4%),[19] and Mori et al (4%).[20] Although, lower than the results of Bousquet et al (21.1%);[21]; wherein these results confirm that a self-reported allergic history without a drug challenge test leads to over estimation of drug hypersensitivity.

DPT is the gold standard for the diagnosis of non-immediate beta-lactam hypersensitivity, and previous studies have shown that direct oral provocation tests, without prior skin testing in children, with delayed onset benign rashes to beta-lactam antibiotic, are safe and effective. However, there are variations in the protocols of DPT. For example, a previous study by Vezir et al[15]

performed directed DPT without an antecedent skin test in non-immediate mild cutaneous reactions related to beta-lactam antibiotics. The protocol of this study was the culprit drug being given at divided doses every 30 min, for a total of 5 doses in the first day, and continuous taking of the full dose at home for 5 days. The results showed that a total of 4 patients (3.4%) had an urticarial rash after provocation tests; three patients developed reactions at the first DPT, and 1 patient developed a reaction on the fourth day of DPT. While a previous study by Mill et al[17] performed the amoxicillin challenge with a two-dose therapeutic dosage: 10% of the therapeutic dose, then 20 min later 90% of the therapeutic dose. The results of this study showed that this protocol also maintained safety; with 2.1% having mild, immediate reactions, and 3.8% having non-immediate, mild reactions. Because there is previous study demonstrating the safety of challenge with a two-dose protocol, and this challenge protocol has the advantage of being less expensive, less time-consuming, less invasive, and more applicable for children. So, in our study, we selected the step of challenge to 2 doses: 10% followed by 30 min of observation, then residual 90%, until the daily therapeutic dose was reached. In order for easy use in a clinical setting, we created a dosing chart of amoxicillin by range from the body weight of children. In our study, all participants had only mild cutaneous reactions that only required oral antihistamine for treatment, with the exception of 1 patient who developed fever and a MP rash at the fourth day of DPT. This patients' laboratory investigation could not rule out DRESS. Our protocol was similar with the protocol of Confino-Cohen et al;[16] wherein, this study performed the drug challenge with one-tenth of the therapeutic dose, followed by the full dose at a 1-h interval, and the continuation of at home prescription for 5 days. The results of this study showed 1.5% had mild immediate reactions, 4% developed late reactions in the first day, and 6% developed mild reactions during the at home challenge.

Our study represented the immediate safety of direct DPT, by challenge with 2 doses of the culprit drug administered in the first day, in children with history of non-immediate, non-severe rashes. Although, patients may not have any immediate reactions, the challenge test should be continued for 5 days, because some patients may incur reactions later at home. Moreover, even if the provocation tests were negative, the parent or guardian should be attentive to any reaction that may occur after the administration of beta-lactams, and only administer medications under medical supervision, so as to avoid false safety and abuse in their use.

The strengths of this study were that all of the patients completed the performed direct oral challenge, following the Amoxicillin-2-step-challenge protocol. Additionally, all of these patients conducted a follow up at our hospital, 1 week after DPT. Hence, we were able to confirm no loss of data in regards to adverse reactions. There were some limitations of this study; because some patients did not consent or could not be contacted, there was only a small sample size. Therefore, this may not be enough to evaluate the risk factors associated with true drug allergies.

In conclusion, our results showed that direct oral provocation tests, using the Amoxicillin-2-step-challenge without prior skin testing as an alternative protocol, has good immediate safety for the diagnosis of amoxicillin hypersensitivity in children with history of non-immediate reactions to amoxicillin.

Abbreviations

AEC, absolute eosinophil count; AGEP, acute generalized exanthematous pustulosis; DPT, drug provocation test; DRESS, drug reaction with eosinophilia and systemic symptoms; ENDA, European Network on Drug Allergy; IDT, intradermal testing; SCARs, severe cutaneous adverse drug reactions; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Availability of data and materials

The datasets generated during this current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee and Institutional Review Board of the Faculty of Medicine, Prince of Songkla University. IRB number is 59-186-01-1. Written informed consent was obtained from all individual participants included in this study.

Consent for publication
All authors agree to the publication of this work in World Allergy Organization Journal.

Authors' contributions
VK, AY designed the study, performed the analysis and manuscript preparation. PS designed the study and performed the analysis. DW, WJ, PJ designed the study and performed the data collection. All authors have read and approved the final manuscript.

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Declaration of competing interest
The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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