APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Skin testing with β-lactam antibiotics for diagnosis of β-lactam hypersensitivity in children

Wiparat Manuyakorn,[1] Prapasiri Singvijarn,[1] Suwat Benjaponpitak,[1] Wasu Kamchaisatian,[1] Ticha Rerkpattanapipat,[2] Cherapat Sasisakulporn[1], Wanlapa Jotikasthira[1]

Abstract

Objective: Skin testing with penicilloyl-polylysine (PPL) and a minor determinant mixture (MDM) were previously recommended for evaluating β-lactam hypersensitivity. However, PPL and MDM have not been commercially available. This study was to determine the negative predictive value (NPV) of skin testing with β-lactam antibiotics for the diagnosis of β-lactam hypersensitivity.

Method: Patients age 1-18 years old with a history of β-lactam hypersensitivity were evaluated by skin tests (a skin prick test, an intradermal test) with penicillin G, ampicillin, amoxicillin-clavulanic acid, and the suspect β-lactam. The patients who had a negative skin test were performed with a drug provocation test (DPT) in a 3-dose-graded challenge. The hypersensitivity reactions were classified into immediate and non-immediate reactions.

Results: A total of 126 patients were evaluated for β-lactam hypersensitivity. Twenty two patients (17.4%) were confirmed with a β-lactam hypersensitivity. 12 (54.54 %) of them were confirmed by a skin test. There was no systemic reaction occurring after the skin tests. Ten patients (9.6%) from 104 patients with a negative skin test showed reactions after a DPT providing the NPV of the skin test with a 91.2% value.

Conclusions: Among those children with a history of β-lactam hypersensitivity, skin testing with penicillin G, ampicillin, amoxicillin-clavulanic acid, and the suspect β-lactam was safe and provided a good NPV when PPL and MDM were unavailable. However, a skin test with β-lactam antibiotics alone did not provide a high sensitivity, thus a DPT procedure was necessary in order to confirm the diagnosis of β-lactam hypersensitivity.

Keywords: β-lactam antibiotics, children, drug provocation test, minor determinant mixture, penicilloyl-polylysine, skin test

From:
[1] Division of Pediatrics Allergy and Immunology, Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[2] Division of Allergy, Immunology and Rheumatology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Corresponding author:
Wiparat Manuyakorn
Division of Pediatrics Allergy and Immunology
Faculty of Medicine, Ramathibodi Hospital, Mahidol University,
Bangkok, Thailand 10400
Email: mwiparat@hotmail.com

Introduction

β-Lactam antibiotics including penicillin and cephalosporin are common causes of drug hypersensitivity reactions. The prevalence of penicillin hypersensitivity is 5% to 10% in adults and children.[1] Drug hypersensitivity reactions are classified as "immediate" or "non-immediate" based upon the time interval between the last drug intake and the onset of the hypersensitivity symptoms. Immediate reactions occur within 1 hour (most often within 30 minutes) of a drug's administration. The non-immediate reactions occur more than 1 hour of the administration of the antibiotic.[2] The importance of evaluating patients with a history of a β-lactam allergy is increasingly recognized since those patients with a history of β-lactam hypersensitivity need to avoid β-lactam antibiotics. This leads to the use of alternative broader-spectrum antibiotics such as fluoroquinolones and vancomycin. The use of broader-spectrum antibiotics has been associated with additional costs and significantly increasing drug resistance and complications.[3,4]

A diagnostic evaluation of β-lactam hypersensitivity includes history taking and an *in vivo* allergic evaluation based upon clinical features and the type of reactions. Immediate reactions can be assessed by the immediate reading of a skin test and drug provocation tests. Non-immediate reactions can be evaluated by a delayed skin test reading and drug provocation tests. Those patients with history of β-lactam hypersensitivity are suggested to be skin tested with a panel of common reagents, including penicilloyl-polylysine (PPL), a minor determinant mixture (MDM), penicillin G, amoxicillin, and the suspect β-lactam.[2] However, PPL and MDM are not now commercially available in many countries including Thailand. Previous studies have estimated that skin testing without PPL may miss up to 75% of penicillin-allergic subjects.[5,6] Alternative approaches in the case of an absence of PPL and MDM have used a combination of penicillin G skin testing together with radioallergosorbent testing followed by 2 graded challenges.[5,7,8] A recent study have skin tested only with penicillin G and then underwent a one day 3-dose-graded challenge with the culprit penicillin if the skin test result was negative[9] – but there is still no consensus regarding the panel of penicillin skin test in the condition of unavailable of PPL and MDM. In addition, recent studies have proposed to perform a one week oral challenge with β-lactam in the diagnosis of β-lactam hypersensitivity.[10,11] The aim of this study was to determine the safety and the negative predictive value (NPV) of a skin test with penicillin G, ampicillin, amoxicilin-clavulanic acid, the suspect β-lactam, and a one week oral challenge test, in those children with a history of β-lactam hypersensitivity.

Methods

This study was performed in the Pediatric Allergy Unit of Ramathibodi Hospital, Mahidol University, Thailand, between June 2007 and May 2015. A total of 126 children aged 1-18 years with a history of β-lactam hypersensitivity were included. Those patients with a history of a severe cutaneous adverse drug eruption (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, a drug reaction with eosinophilia and systemic symptoms, and an acute generalized exanthematous pustulosis) or a serum sickness were excluded. This study was reviewed and approved by the human rights and ethics committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand. All of the participants were subject to an informed consent about the objective of the study.

Drug Hypersensitivity Test Procedure

A skin prick test (SPT) was performed with a penicillin panel including penicillin G (25,000 u/ml), ampicillin (25 mg/ml), amoxicillin-clavulanic acid (25 mg/ml of amoxicillin), plus the suspect β-lactam, as recommended from previous studies,[12,13] and were administered on the inner side of the children's forearms. The diameter of the wheal was measured after 15 minutes and the reaction was considered positive when the diameter was greater than 3 mm of the negative control. In the case of a negative skin prick test, an intradermal test was performed. Approximately 0.02 ml of a 1:10 dilution and undiluted drug was dispensed as the concentration that was used for an SPT and this was injected intradermally in the volar surface of their forearms. The diameter of the wheal was measured after 20 minutes and after 72 hours in order to determine the immediate and the non-immediate reactions, respectively. The results were defined as positive when the diameter was greater than 4 mm of the injected site wheal. A positive control for the skin prick test and the intradermal test were both tested with histamine (1 mg/ml). A normal saline solution was used as the negative control.

A Drug Provocation Test (DPT) was performed in those children with a negative skin test. The culprit drug was administered in a 3-dose-graded challenge. This was conducted initially with 1/100th of the therapeutic dose, 1/10th of the therapeutic dose, and a full therapeutic dose, every 20 minutes. The children who passed the drug evaluation test were administered the culprit drug in a therapeutic dose for 1 week. A reaction was considered to be an immediate reaction when the symptoms appeared within an hour of the drug intake; non-immediate reactions were those occurring more than one hour after the drug intake.

Statistical Analysis

The data analysis was performed by using the SPSS 17.0 software package. Descriptive statistics were used for the demographic data. A comparison between those cases with a true drug allergy and those cases with a non-allergic drug reaction was performed by using the Chi-Square Test or Fisher's Exact Test. A P-value of less than 0.05 was considered s tatistically significant.

Results

A total of 126 cases with a history of β-lactam hypersensitivity were evaluated in order to confirm true drug hypersensitivity. The median age was 8 years (1–18), 42 children (33.3%) were female, and 56 children (44.4%) had an atopic history. Forty children (31.74%) were reported with an immediate reaction to β-lactam. Amoxicillin and ampicillin (45.4%) were the main responsible drugs, followed by amoxicillin-clavulanic acid, cloxacillin and ceftriaxone. The most common clinical manifestation was urticaria (72.7%).

Characteristics of Patients with Positive Drug Evaluation Test Results

Twenty two children (17.4%) were confirmed to have true β-lactam hypersensitivity. Four (18.2%) of them were confirmed by a skin prick test, 8 (36.4%) cases were confirmed by an intradermal test, and 10 (45.4%) cases were confirmed by a drug provocation test (**Figure 1**). All of the children with a positive skin prick test to the β-lactam antibiotic had a history of an immediate reaction. Among 8 children with a positive intradermal skin test, 6 children were positive in 20 minutes and 2 children were positive after 4 hours.

All the patients with a negative skin test result were submitted to a drug provocation test with reference to the culprit drug. Ten (8.78%) of 114 patients were reported to have positive drug provocation test. In 2 of the 10 cases, they had a reaction at a 1/10th value of the therapeutic dose and 8 cases had a reaction after the full therapeutic dose. The reactions were in common with skin manifestation (urticaria

Table 1. Characteristics of children with positive drug evaluation test results

Age at time of evaluation, Y	Sex	Time to evaluation, y	Initial reaction	Time to onset, h	Culprit drug	Dose at positive test	Challenge reaction
12	F	4	Urticaria	1	Amoxicillin	DPT: Full dose	Urticaria at 30 minutes
17	F	1	Urticaria/ angioedema	1	Amoxicillin	DPT: 1/10 of full dose	Anaphylaxis at 15 minutes
16	M	0.08	Urticaria	1	Ceftriaxone	DPT: 1/10 of full dose	Urticaria at 20 minutes
12	M	1	Urticaria	1	Cloxacillin	DPT: Full dose	Urticaria at 30 minutes
17	M	0.16	Urticaria	1	Piperacillin/ Tazobactam	DPT: Full dose	Urticaria at 60 minutes
8	M	0.25	Anaphylaxis	0.5	Cloxacillin	DPT: Full dose	Anaphylaxis at 30 minutes
4	F	0.25	Urticaria	120	Amoxicillin	DPT: Full dose	Maculopapular rash at 8 hours
3	M	1	Maculopapular rash	72	Amoxicillin	DPT: Full dose	Maculopapular rash at 2nd day
11	M	1	Maculopapular rash	24	Amoxicillin	DPT: Full dose	Maculopapular rash at 3rd day
9	M	0.5	Maculopapular rash	168	Amoxicillin/ Clavulanic acid	DPT: Full dose	Urticaria at 6 hours
9	M	0.08	Urticaria	1	Amoxicillin	SPT Ampicillin (25 mg/ml)	Positive SPT at 15 minutes
8	F	3	Urticaria/ angioedema	0.5	Amoxicillin	SPT Ampicillin (25 mg/ml)	Positive SPT at 15 minutes
11	M	0.08	Urticaria	1	Amoxicillin	SPT Ampicillin (25 mg/ml)	Positive SPT at 15 minutes
2	F	0.08	Urticaria	1	Cloxacillin	SPT Cloxacillin (25 mg/ml)	Positive SPT at 15 minutes
10	M	1	Urticaria	0.5	Amoxicillin	IDT Ampicillin (25 mg/ml)	Positive IDT at 20 mintues
11	M	4	Urticaria	1	Amoxicillin	IDT Ampicillin (25 mg/ml)	Positive IDT at 20 mintues
8	M	0.41	Urticaria	0.5	Amoxicillin	IDT Ampicillin (25 mg/ml)	Positive IDT at 20 mintues
13	M	1	Urticaria	1	Amoxicillin	IDT Ampicillin (25 mg/ml)	Positive IDT at 20 mintues
14	F	1	Anaphylaxis	0.1	Amoxicillin	IDT Ampicillin (25 mg/ml)	Positive IDT at 20 mintues
6	F	0.91	Urticaria	24	Amoxicillin	IDT Ampicillin (25 mg/ml)	Positive IDT at 20 mintues
3	M	1	Urticaria	168	Amoxicillin/ Clavulanic acid	IDT Augmentin (25 mg/ml)	Positive IDT at 4 hours
12	M	0.08	Fix drug	3	Amoxicillin/ Clavulanic acid	IDT Augmentin (25 mg/ml)	Positive IDT at 4 hours with fix drug eruption

and a maculopapular rash).A systemic reaction occurred in 2 of the cases and we can report that they responded well to treatments that included intramuscular epinephrine and antihistamines. Four cases had a delayed reaction with a time interval after the first dose of between 6 and 72 hours. Their condition was resolved spontaneously or with an oral antihistamine treatment (**Table 1**).

The types of drug reactions during the drug hypersensitivity test were consistent with the type of those initially reported drug reactions. All of the true drug hypersensitivity children

Figure 1. Flow chart of β-lactam hypersensitivity evaluation

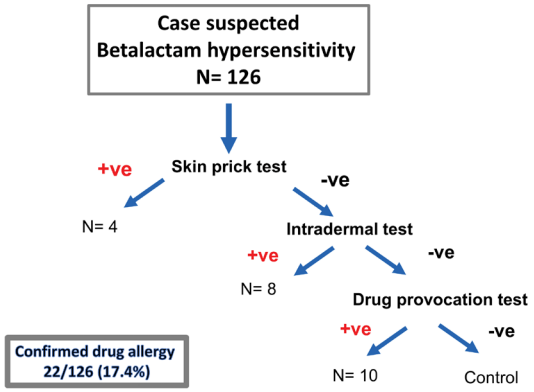

Table 2. Comparison of children with history of initial allergic reactions (immediate and nonimmediate reactions) to β-lactam antibiotics

Characteristic	Immediate reaction N=40	Non immediate reaction N=86	P value
Median of age, yr (min-max)	8.5 (1-18)	7.5 (1-18)	0.12
Female sex (%)	13 (32.5)	29 (33.7)	0.53
Atopy (%)	21 (52.5)	35 (40.7)	0.15
Culprit drug (%)			
Amoxicillin/ampicillin	21 (52.5)	42 (48.8)	
Amoxicillin-clavulanic acid	3 (7.5)	22 (25.6)	
Cloxacillin	3 (22.5)	5 (5.8)	
Ceftriaxone	9 (7.5)	5 (5.8)	
Other β-lactam	4 (10.0)	12 (13.9)	
Time to onset of reaction median(min-max) hr	1.0 (0.1-1.0)	24 (2-192)	<0.001
Time elapsed between allergic reaction and evaluation, median (min-max) yr	1.7 (0.08-12)	2.3 (0.08-12)	0.29
Drug evaluation test positive	15 (37.5)	7 (8.1)	<0.001
Skin test positive	9 (22.5)	3 (3.5)	
Graded challenge test positive	6 (15.0)	4 (4.6)	

with a history of an initial immediate drug reaction showed a positive result of an immediate reaction within one hour. However, 1 in 8 true drug hypersensitivity children with a history of an initial non-immediate drug reaction had a positive immediate reaction to the intradermal test.

Comparison of Patients with a History of Initial Allergic Reactions (immediate and non-immediate reactions) to β-Lactam Antibiotics

There were no differences in age, gender, history of atopy, clinical manifestations, and the time that elapsed between the allergic reaction and the evaluation for those children with a history of immediate and non-immediate reactions. However,

Table 3. Comparison of children with history of initial allergic reactions (anaphylactic and non-anaphylactic reactions) to β-lactam antibiotics

Characteristic	Anaphylactic N=6	Non anaphylactic N=120	P value
Age, median (min-max), yr	11 (3-17)	8 (1-18)	0.168
Female sex (%)	2 (33.3)	40 (33.3)	0.67
Atopy (%)	3 (50.0)	53 (44.2)	0.49
Culprit drug (%)			
Amoxicillin/ampicillin	1 (16.6)	62 (51.6)	
Amoxicillin-clavulanic acid	1 (16.6)	23 (19.2)	
Cloxacillin	1 (16.6)	7 (5.8)	
Ceftriaxone	3 (50.0)	11 (9.2)	
Other β-lactam	0 (0.0)	17 (14.2)	
Time to onset of reaction median(min-max) hr	0.3 (0.1-6)	6.0 (0.30-192)	0.03
Time elapsed between allergic reaction and evaluation, median (min-max) yr	1 (0.25-2)	1.0 (0.08-12)	0.07
Drug provocative test positive	2 (33.3)	20 (16.7)	0.28
Skin test positive	1 (16.7)	11 (9.2)	
Graded challenge test positive	1 (16.7)	9 (7.5)	

a significant association between the histories of the initial allergic reactions and the result of the β-lactam hypersensitivity test was observed (p<0.001). Thirty seven percent of the children with a history of an immediate reaction had a positive test result, while only 8.1% of the children with a history of a non-immediate reaction had a positive β-lactam test (**Table 2**).

Comparison between Patients with a History of Initial Allergic Reactions of Anaphylaxis with patients with Non-Anaphylactic Reactions

Six children (4.7%) had histories of anaphylactic reactions. One child with a history of an anaphylactic reaction from β-lactam developed the symptoms 6 hours after the drug exposure, but the result of his drug hypersensitivity evaluation study was negative. Among the 6 children with history of anaphylaxis to β-lactam antibiotic, only two (33.3%) were confirmed to have true drug allergy : one case by positive skin test and another case by drug provocation test. There was no significant difference in age, gender, history of atopy, and the result of a positive drug hypersensitivity evaluation test between these children with a history of anaphylaxis and non-anaphylaxis reactions (**Table 3**)

Comparison of Patients with a Positive and a Negative Drug Evaluation Test

When comparing between those children with a positive β-lactam hypersensitivity test and those who had a negative test, no significant differences in age, gender, allergic history, the time to the onset of a reaction, and the time that elapsed between the allergic reaction and the evaluation, were observed.

Table 4. Comparison of children with positive and negative drug evaluation test results

Characteristic	Positive test results N=22	Negative test results N=104	P value
Age, median (min-max), yr	9.81 (2-17)	7.65 (1-18)	0.65
Female sex (%)	7 (31.8)	35 (33.6)	0.86
Atopy (%)	10 (45.0)	46 (44.2)	0.91
Culprit drug (%)			
Amoxicillin/ampicillin	14 (63.6)	49 (47.1)	
Amoxicillin-clavulanic acid	3 (13.6)	21 (20.2)	
Cloxacillin	3 (13.6)	5 (48.0)	
Ceftriaxone	1 (4.5)	13 (12.5)	
Other β-lactam	1 (4.5)	16 (15.4)	
Type of reaction (%)			
Anaphylaxis	2 (9.1)	4 (3.8)	
Urticaria	16 (72.7)	52 (50.0)	
Maculopapular rash	3 (13.6)	47 (45.2)	
Other	1 (4.5)	1 (1.9)	
Allergic reaction			<0.001
Onset < 1 hr (%)	15 (68.0)	25 (24.0)	
Onset > 1 hr (%)	7 (32.0)	79 (76.0)	

There was a significant association of the type of allergic reaction [immediate (<1hr) vs non-immediate (>1hr) reaction] with the result of the drug hypersensitivity test (p<0.001). Sixty-eight percent of the children with true drug hypersensitivity had a history of an immediate reaction to the β-lactam antibiotic, while 76% of the children with a negative drug hypersensitivity test had a history for a non-immediate drug reaction (**Table 4**).

Comparison of the Negative Predictive Value of a β-Lactam Skin Test between Types of Reactions

Only one child from 5 children with a history of an anaphylaxis reaction and a negative skin test was confirmed to have true drug hypersensitivity, translating into an NPV of 80% of the skin test for predicting anaphylaxis from the β-lactam antibiotic. Among the children with a history of an immediate but non-anaphylaxis reaction and a negative skin test, 5 children from the 25 children with a history of a β-lactam induced urticaria had true drug hypersensitivity. However, none of the children with a history of drug induced MP rashes had true drug hypersensitivity, translating into an NPV of 81.5% of the skin test for predicting immediate non-anaphylactic reactions from the β-lactam antibiotic. Among the children with non-immediate non-anaphylactic reactions and a negative skin test, only one child from the 33 children that reported urticaria with or without angioedema had true drug hypersensitivity; 3 children from the 49 children with a history of MP rashes from β-lactam had true drug hypersensitivity, translating into an NPV of 95.1% of the skin test for predicting non-immediate non-anaphylactic reactions from the β-lactam antibiotic.

Table 5. Type of initial reaction and the NPV of β-lactam skin test

Type of reaction	Anaphylaxis N=5	Non anaphylaxis N=109	
		Immediate N=27	Non immediate N=82
Urticaria/angioedema	N/A	20/25(80.0)	32/33(96.9)
MP	N/A	2/2(100.0)	46/49(93.9)
Total	4/5 (80.0)	22/27(81.5)	78/82(95.1)

Discussion

PPL and MDM are not commonly available. The present study has demonstrated that a skin test with a penicillin panel including penicillin G, ampicillin, amoxicillin-clavulanic acid, plus the culprit drug, is a good alternative skin test panel for testing patients with β-lactam hypersensitivity. There was no systemic reaction developed after the skin test. The skin test was positive in 10.5% of the children with a history of β-lactam hypersensitivity. Among the 22 children with a confirmed β-lactam hypersensitivity, 12 children (54.54%) were confirmed by a skin test. Our skin test yielded an NPV of 91.2% which was comparable to the NPV of 92% from a previous study that included PPL, MDM, penicillin G, amoxicillin, ampicillin, and the suspect β-lactam, in the skin test panel.[13] A recent study has done skin testing with penicillin G in children with a history of a penicillin allergy and reported an NPV of 95.2% based on the challenge outcome of a one day graded challenge test.[9] However, in addition to the 3-dose-graded challenge, we also performed a one week oral challenge test to confirm the true drug tolerance. Previous study have shown that 20% of the patients with a positive penicillin challenge were detected by an additional one week oral challenge.[14] As a result, using a one day graded challenge in those children with a negative skin testing with penicillin G[9] some children with true penicillin hypersensitivity may be missed , and thus, resulting in a higher NPV when compared to the present study. The types of hypersensitivity reactions from β-lactam have also had an impact on the NPV of the test. A study of patients with histories of immediate reactions from β-lactam has reported an NPV of 87.5% among the patients who tested negative to PPL and MDM plus β-lactam.[15] In the present study, an NPV of 80% - 81.5% was observed in the children with a history of an immediate reaction and that showed a negative skin test result. At the same time, an NPV of 95.1% was observed in those children with a history of a non-immediate reaction and that showed a negative skin test result.

A diagnostic evaluation including a skin test and a drug provocation test in children with a history of β-lactam hypersensitivity is important. We have shown that only 17.4% of the children had true drug hypersensitivity. A history of the type of drug reaction cannot be used in predicting true drug hypersensitivity, even in those children with a history of drug induced anaphylaxis. In the present study, only 33.3% of the children with a history of anaphylaxis were confirmed to have

true drug hypersensitivity. Similar to a previous study, only 40% of the children with a history of anaphylaxis from penicillin had true penicillin hypersensitivity, as evaluated by the skin test and the drug provocation test.[9] However, we have shown that children with history of an immediate reaction revealed a higher percentage of true drug allergy. Thirty seven percent of the children with a history of an immediate reaction were confirmed with true drug hypersensitivity: 22.5% by the skin test and 15% by the DPT procedure. In contrast, only 8% of the children with a history of a non-immediate reaction were confirmed with true drug hypersensitivity: 3.5% by the skin test and 4.6% by the DPT procedure. Among the children with a positive drug evaluation test, almost all with a non-immediate reaction showed a non-immediate reaction during the skin test and the DPT procedure. Among those children with a history of non-immediate reactions who performed DPT, all of their positive symptoms were mild and self-limited. Vezir et al have previously reported the safety of oral provocation tests in children with non-immediate mild cutaneous reaction from β-lactam.[16] A DPT in children with a history of non-immediate mild reactions without a prior skin test may be an alternative management tool when a skin test with β-lactams is not available. This will decrease the unnecessary drug avoidance.

However, a skin test alone is not a good diagnostic evaluation for those children displaying a suspect β-lactam allergy. Bousquet et al have demonstrated that 17.4% of patients with a negative skin test to PPL, MDM, penicillin G, amoxicillin, ampicillin, and the suspect β-lactam, were positive to β-lactam during the DPT procedure.[13] In the present study, it was found that the NPV of the β-lactam skin tests in children with history of an immediate reaction from β-lactam was 80%. Among the 31 children with a history of an immediate reaction and a negative skin test, 6 (19.35%) children had a positive DPT and two developed clinical mild anaphylaxis, but they responded well to treatment. In contrast, the NPV of the β-lactam skin test in the children with a history of a non-immediate reaction from β-lactam was 95.1%. Among the 83 children with a history of a non-immediate reaction and a negative skin test, only 4 (4.82%) children had a positive DPT and all of the symptoms were mild and self-limited. Consequently, a drug provocation test is necessary when confirming true drug hypersensitivity after a negative skin test, especially those with a history of an immediate reaction.

In conclusion, skin testing with penicillin G, ampicillin, amoxicillin-clavulanic acid, and the suspect β-lactam, was safe and provided a good NPV when PPL and MDM were unavailable. However, a skin test with β-lactam antibiotics alone did not provide a enough high sensitivity, thus a DPT procedure is necessary in order to confirm the diagnosis of β-lactam hypersensitivity.

Acknowledgements

This study was financially supported by Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand and National Research Council of Thailand under the project entitled 'Pharmacogenomics studies of common adverse reactions in Thais (PGx-COMART).

References

1. Solensky R. Allergy to beta-lactam antibiotics. J Allergy Clin Immunol. 2012; 130: 1442-2 e5.
2. Romano A ,Caubet JC. Antibiotic allergies in children and adults: from clinical symptoms to skin testing diagnosis. J Allergy Clin Immunol Pract. 2014; 2: 3-12.
3. Lee CE, Zembower TR, Fotis MA, Postelnick MJ, Greenberger PA, Peterson LR, et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. Arch Intern Med. 2000; 160: 2819-22.
4. Sade K, Holtzer I, Levo Y,Kivity S. The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital. Clin Exp Allergy. 2003; 33: 501-6.
5. Macy E ,Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. J Allergy Clin Immunol Pract. 2013; 1: 258-63.
6. Gadde J, Spence M, Wheeler B,Adkinson NF, Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. JAMA. 1993; 270: 2456-63.
7. Wang HC ,Yousef E. Two-challenge approach to evaluation of penicillin allergy in the absence of skin testing reagents. Ann Allergy Asthma Immunol. 2006; 97: 713-5.
8. Solensky R. Evaluation of penicillin allergy without benzylpenicilloyl-polylysine. Ann Allergy Asthma Immunol. 2007; 98: 402-3; author reply 403-4.
9. Picard M, Paradis L, Begin P, Paradis J,Des Roches A. Skin testing only with penicillin G in children with a history of penicillin allergy. Ann Allergy Asthma Immunol. 2014; 113: 75-81.
10. Blanca M, Romano A, Torres MJ, Fernandez J, Mayorga C, Rodriguez J, et al. Update on the evaluation of hypersensitivity reactions to betalactams. Allergy. 2009; 64: 183-93.
11. Romano A, Gaeta F, Valluzzi RL, Caruso C, Alonzi C, Viola M, et al. Diagnosing nonimmediate reactions to cephalosporins. J Allergy Clin Immunol. 2012; 129: 1166-9.
12. Co Minh HB, Bousquet PJ, Fontaine C, Kvedariene V,Demoly P. Systemic reactions during skin tests with beta-lactams: a risk factor analysis. J Allergy Clin Immunol. 2006; 117: 466-8.
13. Bousquet PJ, Pipet A, Bousquet-Rouanet L,Demoly P. Oral challenges are needed in the diagnosis of beta-lactam hypersensitivity. Clin Exp Allergy. 2008; 38: 185-90.
14. Hjortlund J, Mortz CG, Skov PS, Eller E, Poulsen JM, Borch JE, et al. One-week oral challenge with penicillin in diagnosis of penicillin allergy. Acta Derm Venereol. 2012; 92: 307-12.
15. Celik GE, Aydin O, Dogu F, Cipe F, Boyvat A, Ikinciogullari A, et al. Diagnosis of immediate hypersensitivity to beta-lactam antibiotics can be made safely with current approaches. Int Arch Allergy Immunol. 2012; 157: 311-7.
16. Vezir E ME, Civelek E, Capanoglu M, Guvenir H, Ginis T, Toyran M, Kocabas CN. Direct oral provocation tests in non-immediate mild cutaneous reactions related to beta-lactam antibiotics. Pediatr Allergy Immunol. 2015; DOI:10.1111/pai.12493.