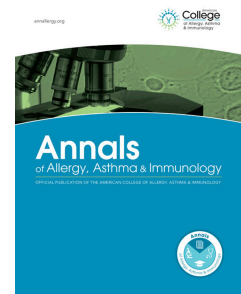


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Background: Extending the drug provocation test(DPT) period is recommended for patients with suspected nonimmediate beta-lactam antibiotic(BLA) allergy and negative DPT. There is no consensus regarding the duration of prolonged provocation. Objective: We aimed to determine the negative predictive value (NPV) of the 5-day extended DPT. Methods: Parents of patients with suspected non-immediate mild cutaneous reactions with BLAs who had been subjected to 5 day DPT with culprit drugs were questioned by telephone interview about re-exposure to the tested drug. Patients with reported reaction during reexposure were re-evaluated. Skin tests and serum-specific IgE analysis were not performed before first DPT. Results: A total of 355 patients had negative results in 5-day DPT. The median age at DPT was 4.2 years and 52.9% were male. The families of 255 patients(72%) could be contacted. Of these 255 patients, 179(70%) had used same drug and reactions were reported for 6(3.4%) of those patients, who were subsequently re-evaluated. Five of the 6 patients had DPT with amoxicillin-clavulanate and one with cefixime. When detailed history was taken, it was found that 2 of the 5 patients with amoxicillin-clavulanate reaction had used the drug unintentionally after their reaction to re-exposure and did not have any symptoms. One of the patients underwent allergy workup and tested negative, while the other two refused the test. The patient with reported cefixime reaction underwent repeated allergy workup and tested negative. Therefore, the NPV of 5-day prolonged DPT was 98.9%. Conclusion: The 5-day prolonged DPT has high NPV and seems appropriate in duration for children with suspected nonimmediate-BLA allergy.

Introduction

Beta-lactam antibiotics (BLAs) are the drug classes most suspected of causing drug-related hypersensitivity reactions in children¹. Hypersensitivity reactions to BLAs are classified as immediate or nonimmediate based on the history of the suspected reaction. Immediate reactions occur within the first hour of drug administration and are mediated by the production of specific IgE targeting penicillin and cephalosporin epitopes². Immediate reactions typically involve urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), anaphylaxis and anaphylactic shock. Nonimmediate reactions are often T cell-mediated and occur more than one hour after drug administration³.

Nonimmediate reactions to BLAs, are usually self-limited and involve mild skin reactions³. Maculopapular rashes are relatively common in the pediatric population⁴. In children, maculopapular eruptions due to various causes, especially infectious etiologies (bacterial or viral), may be misdiagnosed as beta-lactam allergy^{3,4}. Therefore, these conditions should be assessed in order to identify real hypersensitivity reactions.

The drug provocation test (DPT) is still the gold standard for the diagnosis of suspected immediate reactions. However, the DPT protocol for nonimmediate reactions is not well defined and or validated⁵. There are wide variations between centers in terms of dose steps, time intervals between doses, and the length of prolonged DPT⁶⁻¹³.

The duration of prolonged DPT varies from 1-10 days in previous studies^{12, 14-16}. Some authors have suggested that provocation should be extended to the same duration reported between beta-lactam initiation and symptom onset in the index reaction^{7,17}. The Standards of Care Committee of the British Society for Allergy and Clinical Immunology (BSACI) recommends that children with mild to moderate nonimmediate reactions to beta-lactams should take the therapeutic dose for 5 days at home after the initial oral challenge⁸.

In the present study, we evaluated patients with history of negative 5-day DPT for subsequent drug reactions after re-exposure to the suspected drug in order to determine the negative predictive value of the 5-day extended DPT.

Methods

Patients and Study Design:

The study included all patients who presented to our pediatric allergy clinic with history of nonimmediate mild cutaneous reactions attributed to BLAs between January 1, 2013 and December 31, 2017 and who had undergone 5-day DPT at least 6 months earlier.

As routine practice in our clinic, patients evaluated in our clinic for suspected nonimmediate beta-lactam allergy are given the first dose of the drug incrementally in our clinic and continue taking the drug at home for 5 days.

Patients who underwent DPT in our clinic and developed no reaction within 5 days were called by phone at least 6 months later. Those who could be contacted were asked whether they had used the same drug again since the DPT and if so, whether they had any reaction. Patients who reported having a reaction were invited to the clinic for re-evaluation. Based on the findings from this re-evaluation, the negative predictive value of the 5-day DPT was calculated.

The study was approved by the ethics committee of our hospital.

Diagnostic Protocol:

The initial drug allergy workup started with the standardized European Network of Drug Allergy (ENDA) questionnaire for drug allergy¹⁸. A detailed history included spectrum and

48 timing of symptoms, dose and route of administration, list of concomitant medication, history
49 and timing of previous hypersensitivity reactions, and physical examination findings. The
50 patients' symptoms were classified according to medical records or their guardians'
51 descriptions. If they were unable to describe the cutaneous reactions, typical pictures of
52 maculopapular and urticarial eruptions were shown and they were asked whether their
53 reaction resembled the lesions in the pictures. Reactions occurring more than one hour after
54 drug ingestion were labeled as 'nonimmediate reactions'. Patients with nonimmediate
55 reactions that manifested clinically as maculopapular eruptions and delayed-onset
56 urticarial/angioedema were included in the study. Patients who had immediate reactions and
57 patients who had a history of severe life-threatening drug reactions (Steven-Johnson's
58 syndrome, toxic epidermal necrolysis, hypersensitivity syndrome or drug reaction with
59 eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, nephritis,
60 pneumonitis, hepatitis, and vasculitis) were not included in the study.

61 Skin tests and serum-specific IgE analysis were not performed and patients were instead
62 subjected to DPT with the culprit drug. Drug provocation tests were done at least one month
63 after the initial reaction. Antihistaminics and all drugs that could affect DPT results were
64 stopped one week before the test. Written informed consent was taken from the patients' legal
65 guardians.

66 *Drug Provocation Test:*

67 In the first day of the provocation, an incremental drug provocation test (DPT) protocol was
68 administered in our clinic. The therapeutic daily dose of the drug was calculated according to
69 age and weight of the patient. The ENDA guidelines for DPTs were followed carefully¹⁹. The
70 DPT involved administering the suspected drug in divided doses every 30 min until reaching
71 a cumulative dose approximately the age/weight-adjusted daily dose of the drug. The

provocation was given maximally in 5 doses in order to prevent the possibility of patient desensitization^{19,20}. The test was discontinued in the event of any reaction. Administration was open and performed by a physician with full resuscitation backup. The DPT was considered positive if any objective symptoms or signs (e.g., urticaria, angioedema, circulatory depression, wheezing, or rhonchi) were documented. After the last dose had been administered without a reaction, the patient was kept under surveillance for at least 2 hours and told to continue to use the drug in two divided doses for 5 days at home to identify patients with delayed reactions. The doses (mg/kg) used in DPT are shown on Table 1. The extended 5-day DPT was considered negative if no reaction occurred by the end of this period.

Re-evaluation of Patients with Reported Reactions upon Re-exposure

Patients with reported reactions following repeated exposure after a negative DPT were invited to our clinic for re-evaluation. Prick and intradermal skin testing including the penicillin test kit [benzylpenicilloylpoly-L-lysine (PPL), minor determinant mixture (MDM)], penicillin G (10,000 IU/mL), amoxicillin-clavulanate (20 mg/mL), and the suspected drug were performed. We used Diater DAP kit (DAP kit; Madrid, Spain) as penicillin test kit. All of the drugs were initially tested on the volar forearm skin by using the prick method and reactions were considered positive when a wheal diameter equal or higher than 3 mm of the negative control with surrounding erythema was present 20 minutes later. When prick tests yielded negative results, 0.02 mL of the relevant agent was injected intradermally on volar forearm skin. Readings were made at 20 minutes, 48 hours and 72 hours after injections. Results were considered positive when an increase of 3 mm in the wheal diameter accompanied by erythema was present. Positive controls for prick tests were carried out with histamine at 10 mg/mL. A negative control sample, of 0.9% NaCl, for prick and intradermal tests was used. Drug provocation test with penicillin-V followed by the

suspected beta-lactam were performed for patients with negative skin tests. The extended 5-day DPT for suspected drug was considered negative if no reaction occurred

Statistical Analyses:

Statistical analyses were performed using the SPSS v.22 statistical software package (IBM, Chicago, IL, USA) for Windows. Numbers and percentages were reported for discrete variables; continuous variables were expressed as mean and standard deviation for data with normal distribution and as median and interquartile range (IQR) for data not normally distributed. The chi-square (χ^2) test was used to compare nonparametric data; the Mann-Whitney U test was used in comparisons of nonnormally distributed continuous data and independent samples t test for normally distributed continuous data. P value < 0.05 was considered statistically significant.

Results

During the study period, 365 patients underwent DPT in our clinic for suspected nonimmediate beta-lactam BLA allergy and the results were negative in 355 (97.2%) of those patients.

Drug provocation tests' results were positive in 10 of the 365 patients. All of patients with positive DPT developed mild cutaneous signs. Three Four patients developed a reaction after the first dose, 4 patients on day 2, and 2 patients on day 4 of provocation. Drug provocation tests' results from 135 children included between January 2014 and January 2015 have been previously published¹⁵.

All 355 pediatric patients whose initial DPT was negative and who continued to use the suspicious drug at home for 5 days were included in the study.

Of these patients, 255 (72%) were reached by phone (Figure 1). There was no statistically significant difference between the patients who were and were not reachable by phone in terms of their characteristics (Table 2).

The most common complaint of the 255 patients who were reachable by phone was maculopapular rash (66.2%), and other complaints at time of admission are shown in Table 2. The suspected drug was a penicillin in 210 (82.4%) of the cases and a cephalosporin in the remaining 45 patients. The most commonly suspected drug from the penicillin group was amoxicillin-clavulanate (76.4%). Suspected drugs reported by the patients are given in Table 2.

After conducting the phone interviews, it was determined that 179 (70%) of the 255 patients had used the same drug again since the test, 6 (3.4%) of whom had developed a reaction.

These 6 patients were invited for re-evaluation. Characteristics of the patients re-evaluated are given in Table 3.

Characteristics of the Re-evaluated Patients:

Six patients reported reaction during re-exposure. Five of these patients had had DPT with amoxicillin-clavulanate and 1 patient with cefixime.

Upon investigation of prescription data for 2 of the 5 patients with reported reaction to amoxicillin-clavulanate, it was found that they had later used the same drug again without realizing and did not develop any reaction. These two patients were considered reaction negative and no diagnostic tests were performed. Thus 4 of the 6 patients were re-evaluated. One of the other 3 patients reported urticaria 4 hours after dose 4 on day 2 of subsequent use. This patient underwent classic penicillin test and amoxicillin-clavulanate prick and intradermal skin test with early and delayed reading. Results of the skin tests were negative.

Drug provocation test was then performed with penicillin-V and amoxicillin-clavulanate, and the results were negative. One of the other 2 patients reported maculopapular rash 4 hours after dose 6 on day 3 of repeated use, and was also subjected to standard penicillin test and amoxicillin-clavulanate prick and intradermal skin test with early and delayed reading. The skin tests were negative. Drug provocation test with penicillin-V was also negative. Drug provocation test with amoxicillin-clavulanate was ordered but could not be performed because the family did not consent to the procedure. The last patient did not undergo any diagnostic tests because consent could not be obtained.

The patient who reported reaction with cefixime, reported urticaria 6 hours after dose 5 on day 5 of repeated use, so standard penicillin test with skin prick and intradermal early and delayed reading was performed. The skin tests were negative, after which DPT was done first with penicillin-V and then with cefixime, both of which were negative.

As one of our patients did not consent for re-evaluation and one other could not be fully re-evaluated (DPT with penicillin V negative but did not consent for amoxicillin), these 2 of 355 patients were considered reaction positive, resulting in a negative predictive value of 98.8% with 5-day extended DPT for nonimmediate mild cutaneous reactions associated with beta-lactam antibiotics.

Discussion

In our study evaluating pediatric patients presenting to our hospital with suspected nonimmediate beta-lactam allergy, we determined that 365 patients underwent DPT and the result was negative in 355 (97.2%). Of the 255 of these patients who could be reached by phone, 179 (70%) used the same drug again after the test, and 4 developed reaction upon re-exposure. Of the 4 patients who were re-evaluated, 2 patients underwent allergy workup and tested negative, while the other two refused the test. We determined that extended DPT with

5-day provocation had a high (98.8%) negative predictive index in patients with mild cutaneous reactions due to suspected nonimmediate beta-lactam allergy.

Nonimmediate mild cutaneous reactions are the most frequent drug hypersensitivity reactions to beta-lactam antibiotics³. Suspected nonimmediate reactions have lower confirmation ratio with allergy workup. In a prospective study including 1026 children with a mean age of 7.7 years, results of complete allergy workup confirmed nonimmediate hypersensitivity reactions to beta-lactam antibiotics in only 7.4% of the children²¹. Mill et al. evaluated 818 pediatric patients (median age: 1.7 years) with a history of amoxicillin hypersensitivity and reported that the majority of the children showed nonimmediate benign reactions to amoxicillin and only 48 (5.8%) had a positive DPT²². In our study the confirmation rate after allergy workup was 2.8% in our patients, whose median age was 4.4 years. The lower confirmation rate in our study may be due to our young patient group, because most skin eruptions during beta-lactam treatment in children are likely due to viral infections, but can mimic allergic reaction²³.

Although DPT is the gold standard when investigating pediatric hypersensitivity reactions to beta-lactams in children, there is no consensus on the optimal length of the DPT protocol to investigate nonimmediate reactions to beta-lactam antibiotics. The duration of prolonged DPT varies from 1-10 days in previous studies. While shorter protocols are more efficient and have fewer side effects, longer protocols may increase the sensitivity of DPT³. Although no studies have compared short and long protocols, it was reported that 7-day amoxicillin treatment has a significantly impact on the gut microbiota²⁴. On the other hand, the occurrence of a hapten protein or hapten peptide specific immune response needs time to form the hapten protein complex, process the hapten protein, present the hapten peptides on HLA molecules and expand drug-specific T and B cells. This time is approximately 7-12 days for amoxicillin²⁵.

DPT protocols of different lengths have been used and their negative predictive values determined in various studies. Mill et al. reported a negative predictive value of 89.1% in 1-day DPT for suspected amoxicillin allergy²². Tonsonla Tour et al. reported a negative predictive value of 96.7% in patients who underwent 3-day DPT for suspected penicillin allergy²⁶. Labrosse et al. reported this value to be 97.6% in their study evaluating the negative predictive value of 5-day DPT for suspected amoxicillin allergy¹⁴. In the present study, we determined a negative predictive value of 98.8% for 5-day DPT in patients presenting with a history of nonimmediate beta-lactam allergy.

The negative predictive value of 5-day provocation for extended DPT was high in our study. However, because none of our patients underwent DPT for other lengths of time, we could not compare negative predictive value between different provocation durations.

Although recent studies have shown that the negative predictive value of 1-day DPT is comparable to that of longer DPTs, there are also studies indicating that extended DPTs are better in terms of future patient and physician drug compliance²³. Ratzon et al. compared 26 patients who underwent 7-day DPT and 23 patients who underwent 1-day DPT for diagnosis of beta-lactam antibiotic allergy and found that the frequency of using the same drug again was higher in patients who underwent 7-day DPT²⁷. Moreover, in the study by Labrosse et al. comparing pediatric patients with a history of amoxicillin allergy who underwent 5-day DPT versus single-dose DPT, 25% of the families or physicians of patients who underwent single-dose DPT were hesitant to use the same drug again, while this rate was only 1.3% for patients who underwent 5-day DPT¹⁴. As mentioned earlier, we could not make such comparisons in the present study because all of our patients underwent 5-day DPT.

In conclusion the 5-day prolonged drug provocation test had high negative predictive value in our study. Therefore, we believe that 5 days is an effective duration for extended DPT in the

214 diagnosis of nonimmediate beta-lactam allergy. Further studies including different time period
215 are needed to better define the optimal length of DPT for nonimmediate reactions to BL
216 antibiotics.

217

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Table 1. Drug doses used in oral provocation test

Drug	Dose
Amoxicillin-clavulanic acid	40 mg/kg/day
Amoxicillin	40 mg/kg/day
Ampicillin-sulbactam	50 mg/kg/day
Penicillin V	25 mg/kg/day
Cefixime	8 mg/kg/day
Cefixime-clavulanic acid	8 mg/kg/day
Cefuroxime	20 mg/kg/day
Cefdinir	14 mg/kg/day
Cefprozil	15 mg/kg/day
Cefaclor	20 mg/kg/day
Cefpodoxime	10 mg/kg/day

Table 2. Comparison of the patients contacted and those who could not be contacted

	Patients contacted (n=255)	Patients who could not be contacted (n=100)	p
Gender n, %			
female	120 (47.1)	45 (45)	0.4
male	135 (52.9)	55 (55)	
Age at reaction (years)			
median (IQR)	3.0 (1.5-5.98)	3.0 (1.5-5.82)	0.83
Age at DPT (years)			
median (IQR)	4.2 (1.98-7.02)	4.17 (2.05-6.89)	0.85
Interval between DPT and reaction (months)			
median (IQR)	3.12 (2.04-7.74)	3.12 (2.04-8.84)	0.91
Duration of exposure at time of reaction (days)			
median (IQR)	2 (2-5)	2 (2-5)	0.6
Number of doses taken at time of reaction			
median (IQR)	4 (3-9)	4 (3-9.7)	0.62
Interval between last dose and reaction (hours)			
median (IQR)	8 (5-10)	8 (5-10)	0.63
Eosinophil count			
median (IQR)	1.9 (0.8-3)	1.5 (0.8-3.3)	0.41
IgE level			
median (IQR)	20 (12-85)	27 (14-83)	0.34
Presence of allergic disease, n (%)	36 (14.1)	11 (11)	0.47
Suspected drugs, n (%)			
Penicillin	210 (82.4)	86 (86)	0.76
<i>Amoxicillin-clavulanic acid</i>	195	78	
<i>Amoxicillin</i>	6	3	
<i>Penicillin V</i>	6	3	
<i>Ampicillin-sulbactam</i>	3	2	
Cephalosporin	45 (17.6)	14 (14)	0.85

<i>Cefixime</i>	15	5	
<i>Cefuroxime</i>	14	4	
<i>Cefdinir</i>	9	3	
<i>Cefprozil</i>	4	2	
<i>Cefpodoxime</i>	2	-	
<i>Cefixime + clavulanic acid</i>	1	-	
Presenting reaction, n (%)			
Maculopapular rash	170 (66.2)	70 (70)	
Urticaria	47 (18.0)	15 (15)	
Urticaria + Angioedema	14 (6.1)	7 (7)	
Hyperemia	14 (6.1)	7 (7)	
Angioedema	7 (1.9)	1 (1)	
Hyperemia + Angioedema	2 (0.6)	-	
Maculopapular rash + Angioedema	1 (0.3)	-	

Table 3. Result of re-evaluation

	Drug	Presenting reaction	First reaction time	Subsequent use reaction	Second reaction time	Result of re-evaluation
Patient 1	Amoxicillin-clavulanate	Urticaria + Angioedema	2nd day 10 h after last dose	Urticaria	2nd day 5 h after last dose	Used the drug unintentionally after their reaction to re-exposure and did not have any symptoms
Patient 2	Amoxicillin-clavulanate	Maculopapular rash	2nd day 22 h after last dose	Maculopapular rash	2nd day 3 h after last dose	Used the drug unintentionally after their reaction to re-exposure and did not have any symptoms
Patient 3	Amoxicillin-clavulanate	Maculopapular rash	2nd day 4 h after last dose	Urticaria	2nd day 4 h after last dose	Tests were negative.
Patient 4	Amoxicillin-clavulanate	Urticaria	1st day 2 hour after last dose	Maculopapular rash	3rd day 4 h after last dose	Refused re-evaluation
Patient 5	Amoxicillin-clavulanate	Urticaria + Angioedema	6th day 6 h after last dose	Urticaria	2nd day 4 h after last dose	Refused re-evaluation
Patient 6	Cefixime	Maculopapular rash	2nd day 10 h after last dose	Urticaria	5th day 6 h after last dose	Tests were negative

Figure1. Algorithm of the study

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