นิพนธ์ต้นฉบับ ▪ Original Article

ลักษณะทางคลินิก และผลลัพธ์ของผู้ป่วยเด็กที่ได้รับการทดสอบแพ้ยาในโรงพยาบาลรามาธิบดี

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Clinical Presentation and Outcomes of Pediatrics Patients Undergoing Evaluation for Drug Allergy in Ramathibodi Hospital

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Received: 24 February 2020

Accepted: 13 May 2020

หลักการและวัตถุประสงค์: การแพ้ยาเป็นปัญหาที่สำคัญ โดยผู้ป่วยจำนวนมากได้รับการวินิจฉัยว่าแพ้ยาโดยไม่ได้รับการทดสอบอย่างเหมาะสมว่าแพ้ยาจริงหรือไม่ การศึกษานี้มีวัตถุประสงค์เพื่อประเมินความชุก ลักษณะทางคลินิก และผลลัพธ์ของผู้ป่วยเด็กที่มีข้อสงสัยแพ้ยาจากประวัติและได้รับการทดสอบแพ้ยา

วิธีการศึกษา: ศึกษาโดยทบทวนเวชระเบียนของผู้ป่วยเด็กที่มีประวัติสงสัยแพ้ยา และมาทดสอบแพ้ยา ณ โรงพยาบาลรามาธิบดี ผู้ป่วยได้รับการยืนยันวินิจฉัยแพ้ยาโดยการทดสอบผิวหนัง และ/หรือทดลองให้ยาที่สงสัยว่าแพ้

ผลการศึกษา: ผู้ป่วยเด็ก 60 รายได้รับการทดสอบแพ้ยา ค่ามัธยฐานของระยะเวลาตั้งแต่ได้รับยาจนถึงมีอาการคือ 4.5 ชั่วโมง พบอาการทางผิวหนังและเยื่อบุได้บ่อยที่สุด (ร้อยละ 95) โดยเฉพาะการบวมใต้ชั้นผิวหนัง และผื่นลมพิษ (ร้อยละ 66.7) ยาที่สงสัยว่าทำให้เกิดอาการแพ้มากที่สุดคือยาต้านปฏิชีวนะ โดยเฉพาะกลุ่มเบต้า-แล็คแตม (ร้อยละ 71.7) ยาลดไข้/ต้านอักเสบ (ร้อยละ 11.7) และยาที่ใช้ในระบบหายใจ (ร้อยละ 6.7) มีผู้ป่วยเพียงร้อยละ 26.7 เท่านั้นที่แพ้ยาจริงหลังจากการทดสอบ ปฏิกิริยาต่อการทดลองให้ยาที่สงสัยว่าแพ้ไม่สัมพันธ์กับอาการนำของผู้ป่วย ผู้ป่วยที่แพ้ยาจริงมีลักษณะทางคลินิกต่าง ๆ ไม่แตกต่างกับผู้ป่วยที่ผลการทดสอบเป็นลบ

สรุป: ผู้ป่วยเป็นส่วนน้อยเท่านั้นที่มีภาวะแพ้ยาจริงหลังจากได้รับการทดสอบอย่างเหมาะสม การใช้ลักษณะทางคลินิกไม่สามารถวินิจฉัยแยกผู้ป่วยกลุ่มนี้ได้ ดังนั้นการศึกษานี้จึงช่วยสนับสนุนว่าการทดสอบแพ้ยายังคงเป็นมาตรฐานของการวินิจฉัย

Background and objectives: Drug allergy is a major problem frequently encountered. Patients are frequently over diagnosed as having drug allergy without proper confirmatory tests. The aims of this study were to assess prevalence, clinical presentation and outcomes among pediatric patients suspected of having a drug allergy form medical history, and undergoing drug allergy evaluation.

Methods: Medical records of pediatric patients who had undergone evaluation for drug allergy in Ramathibodi Hospital were reviewed. Patients were confirmed to have a true drug allergy by a positive skin test and/or drug provocation test.

Results: Sixty patients were evaluated for drug allergy. Onset of symptoms was highly variable (median 4.5 hours; min-max 0.08-168). Skin and mucocutaneous reactions were the most common presentations (95%) particularly angioedema and urticaria (66.7%). The most common suspected group of drugs was antibiotics (71.7%), followed anti-pyretic/anti-inflammatory (11.7%) and respiratory drugs (6.7%). Within the group of antibiotics, Beta-lactam antibiotic was the most common suspected drug causing allergy. Only sixteen out of sixty patients (26.7%) were confirmed to have a true drug allergy, 12 patients by skin

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คำสำคัญ: แพ้ยา, การทดสอบแพ้ยา, ลักษณะทางคลินิกของการแพ้ยา

test and 4 patients by drug provocation test. Drug provocation test reactions did not correlate with presenting symptoms of drug allergy. There were no significant differences in age, onset or primary symptoms of drug allergy between the confirmed true drug allergy and no drug allergy groups.

Conclusions: Drug allergy is frequently reported, but only a minority of patients have true drug allergy. There were no precise clinical predictors for drug allergy. Thus, drug provocation tests remain the gold standard for diagnosis.

Keyword: drug allergy, drug provocation test, clinical presentation of drug allergy

ศรีนครินทร์เวชสาร 2563; 35(4): 397-403. ● Srinagarind Med J 2020; 35(4): 397-403.

Introduction

Drug allergy is a major problem encountered among general practitioners and allergists[1, 2] However, only a few patients have a true drug allergy[3]. Rashes are major manifestations of drug allergy reactions[4, 5]. Children with viral exanthem usually receive medication especially antibiotics for their illness. As a result, when rashes develop, it can be difficult to distinguish rashes from viral exanthem and drug allergy. A number of children with viral exanthem were misdiagnosed with drug allergy in the absent of proper confirmatory testing. This can lead to lifelong avoidance of mislabeled drugs, unnecessary usage of more expensive or less effective second line drugs and increased prevalence of drug resistant bacteria[6,7]. Unfortunately, drug provocation tests used to confirm true drug allergy are insufficiently performed due to concerns about potential reactions especially in children[8].

This study aimed to assess drug allergy prevalence and clinical presentation of drug allergy among pediatric patients suspected of having a drug allergy medical history, and to determine the safety and outcomes of pediatric patients undergoing evaluation for drug allergy.

Methods

Patients

Medical records of children aged < 18 years whom were suspected of having a drug allergy and underwent evaluation during 2007 to 2013 at Ramathibodi Hospital, Mahidol University were reviewed.

The patients were consulted by pediatricians or other subspecialists, or visited pediatric allergy clinic due to suspected of having a drug allergy by parents. After thorough history-taking, including details related to onset and clinical manifestation of the suspected drug allergy, the patients underwent skin tests if the recommended concentrations were available[9]. If skin test results were negative, the patients underwent drug provocation tests. Patients were confirmed allergic to the suspected drugs (true drug allergy group) by a positive skin tests or drug provocation test (Figure 1).

Baseline characteristics were also collected including gender, age, allergic diseases and underlying illnesses such as autoimmune and malignancy. This study was reviewed and approved by the Research Ethics Committee of Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Skin tests

Skin tests were performed if non-irritating concentrations and intravenous forms of the drug were available[9]. Skin prick tests were performed initially and if the results were negative, then intradermal tests were done. Skin tests were read at 15 minutes for history of immediate reaction and at 72 hours for delayed reaction[9]. Skin tests were considered positive if they were greater than 3 mm in wheal diameter than the negative control.

Drug provocation tests

If skin test results were negative, or if there were no available forms for skin tests,patients would undergo drug provocation tests in which gradually increasing doses of the suspected drug were given[9]. The target dose was the patient's daily therapeutic dose. A maximum of four to five incremental doses was applied, doses were incremented sequentially in 15- to 60-minute intervals, depending on the severity of the reaction in the patient's history. Patients were observed in the hospital for positive immediate reactions at least 2 hours after the provocation tests. In order to evaluate delayed reactions type, provocative drug testing was monitored at least 72 hours. If the patient did not show any reactions after those periods, the provocation test was considered negative. Provocation test was considered positive when the patient had any reaction to the provocative drug.

Statistical analysis

Statistical analysis was performed using SPSS software version 18. Descriptive statistical methods [percent, median (min-max) and frequency] were applied. Analysis of the differences between the confirmed true drug allergy and no drug allergy groups were performed using Fisher's exact test. P-Value < 0.05 were considered statistical significance.

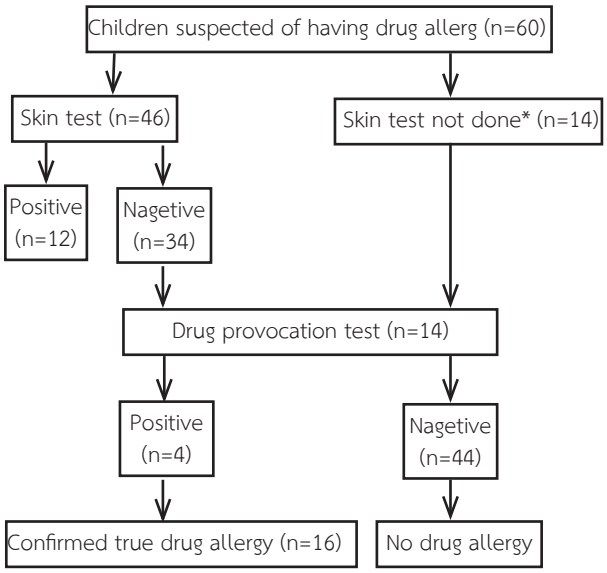
Results

Patients

Sixty patients were evaluated for drug allergy. 61.7% of them were male. The median age was 7.17 years (min 0.5 -max 19.16). The majority of the patients (66.7%) reported a delayed reaction (> 2 hours, Table 1). Forty-eight out of 60 patients underwent drug provocation tests. Sixteen patients (26.7%) were confirmed allergic to the suspected drugs (Table 2). Twelve patients were confirmed by skin test and 4 patients by drug provocation test (Figure 1).

The suspected and culprit drugs causing allergy

Among the 60 patients evaluated for drug allergy, the most common suspected group of drugs was antibiotics (43 patients, 71.7%), followed anti-pyretic/ anti-inflammatory (7 patients, 11.7%) and respiratory drugs (4 patients, 6.7%) (Table2). Out of 43 patients whom suspected of having antibiotics allergy, 36 of them were evaluated for Beta-lactam allergy. Only



*non-irritating concentration or intravenous form were unavailable

Figure 1 Protocol and results of pediatric patients undergoing evaluation for drug allergy

12 (33.3%) of them were confirmed to have Beta-lactam allergy among which amoxicillin was the most common.

Clinical characteristics of patients with and without true drug allergy

Skin and mucocutaneous reactions were the most common presentation (95%) particularly urticaria and angioedema (66.7%). These clinical presentations were not significantly different between confirmed the true drug allergy and no drug allergy groups. There were no differences in age, and onset of drug allergy between the two groups. However, patients with true drug allergy had a significantly lower prevalence of allergic disease than those with no drug allergy The true drug allergy and no drug allergy groups included 3 and 6 patients with autoimmune disease or malignancy, respectively. However, there were no statistically significant differences between the two groups. (Table 1). Five patients presented with multiple symptoms and were diagnosed with anaphylaxis. Three of these patients were confirmed to have a true drug allergy by skin test.

Correlation between the onset of reaction from history-taking and onset of reaction from drug provocation tests in patients with true drug allergy

Most of the patients in the true drug allergy group (81.2%) reported onset of reaction more than 2 hours. There were 7 patients who presented with symptoms

Table 1 Characteristics, clinical presentation and outcomes of the patients

Characteristic	All patients	True drug allergy	No drug allergy	P-value[#]
N	60	16	44	-
Male, n (%)$	37 (61.7)	10 (62.5)	28 (63)	0.936
Age in years, median (min-max)	7.17 (0.58-19.17)	7.31 (2.42-17.08)	7.17 (0.58-19.17)	0.783
Onset, hours (median/ min-max)	4.5 (0.08-168)	5 (0.25-72)	3.75 (0.08-168)	0.331
- Onset ≤ 2 hours, n (%)	20 (33.3)	3 (18.8)	17 (38.6)	0.218
- Onset >2 hours, n (%)	40 (66.7)	13 (81.2)	27 (61.4)	
Clinical presentation, n (%)				
- Skin and mucocutaneous tissue	57 (95)	15 (93.8)	42 (95.5)	1.000
• Angioedema and urticaria	40 (66.7)	12 (75)	28 (63.6)	0.212
• Maculopapular rash	20 (33.3)	3 (20)	17 (38.6)	0.794
- Respiratory (wheezing, respiratory discomfort, desaturation)	6 (10)	2 (12.5)	4 (9.1)	0.627
- Gastrointestinal (nausea/vomit)	3 (5)	1 (6.3)	2 (4.5)	1.000
- Cardiovascular (hypotension)	1 (1.7)	1 (6.3)	0 (0)	0.267
Underlying diseases				
- Allergy	32 (53.3)	3 (18.8)	29 (65.9)	0.002*
• Asthma	7 (11.7)	0 (0)	7 (15.9)	0.173
• Allergic rhinitis/allergic rhinoconjunctivitis	19 (31.7)	3 (1.9)	16 (36.4)	0.229
• Atopic skin diseases (atopic dermatitis, dermographism &chronic idiopathic urticaria	2 (3.3)	0 (0)	2 (4.5)	1.000
• Food allergy	3 (5)	0 (0)	3 (6.8)	0.558
• Insect allergy	1 (1.7)	0 (0)	1 (2.3)	1.000
- Autoimmune disease	7 (11.7)	2 (12.5)	5 (11.4)	1.000
- Malignancy	2 (3.3)	1 (6.3)	1 (2.3)	0.466

[#]P- value compared between true drug and no drug allergy groups
[$]Percentage of the patients in the same group
[*]p-value <0.05

compatible with an immediate reaction (urticaria and/ or angioedema) but reported onset of reaction more than 2 hours. None of the patients who presented with symptoms of delayed reaction (maculopapular rash) had onset of symptoms less than 2 hours.

Correlation between presenting symptoms and provocation test reaction

Among the 4 patients who were confirmed to have a true drug allergy by drug provocation test, their initial presenting symptoms did not correlate with reactions to the provocation test (Table 3). In contrast, patients who presented with urticaria developed maculopapular rash after a provocation test or vice versa.

Safety of patients undergoing drug allergy evaluations

Forty-eight out of the 60 patients underwent drug provocation tests. There were only minor reactions in those patients. Only skin reactions which responded immediately to antihistamine were found (Table 3). There were no serious systemic reactions.

Table 2 Suspected and culprit drugs causing allergy

Characteristic	All patients	True drug allergy (%)*	No drug allergy (%)*
All	60	16 (26.7)	44 (73.3)
Antibiotic	43	14 (32.6)	29 (67.4)
- Beta-lactam	36	12	24
• Amoxicillin	19	8	11
• Amoxicillin/ clavulanic acid	6	2	4
• Cloxacillin	2	1	1
• Piperacillin/tazobactam	1	1	0
• Cefaclor	2	0	2
• Cefazolin	1	0	1
• Cefditoren	2	0	2
• Ceftiaxone	3	0	3
- Macrolide	3	1	2
- Clindamycin	1	0	1
- Gentamicin	1	0	1
- Cotrimoxazone	1	0	1
- Ciprofloxacin	1	1	0
Antipyretic/anti-inflammatory	7	1 (14.3)	6 (85.7)
- Paracetamol	4	1	3
- Ibuprofen	1	0	1
- Naproxen	1	0	1
- Prednisolone	1	0	1
Respiratory drug	4	0 (0)	4 (100)
- Bromhexine	1	0	1
- Montelukast	1	0	1
- Pseudoephridine	1	0	1
- Salbutalmol	1	0	1
Local anesthesia	2	0 (0)	2 (100)
- Merpivarcaine	1	0	1
- Lidocaine	1	0	1
Others	4	1 (25)	3 (75)
- Cisatracuronium	1	1	0
- Cyclosphosphamide	1	0	1
- Derferaxirox	1	0	1
- Dimercaptosuccinic acid (DMSA)	1	0	1

* Percentage of true or no drug allergy/total drug of the same group

Table 3 Correlation between presenting symptoms and reaction from provocation tests

Patient	Culprit drug	Presenting symptoms	Onset after drug exposure from history	Provocation test reaction	Onset after provoked*
1	Amoxycillin/ clavulanic acid	Urticaria	2.5 hours	Maculopapular rash	30 minutes
2	Cloxacillin	Maculopapular rash	5 hours	Urticaria	30 minutes
3	Piperacilllin/ tazobactam	Urticaria	1 hour	Erythramatous papule	60 minutes
4	Paracetamol	Maculopapular rash	4.5 hours	Urticaria	5 minutes

* Onset of reaction after the target dose

Discussion

True prevalence of drug allergy is uncertain and reports vary according to different methodology, population or drug allergy definition. One systematic review and meta-analysis of prospective studies estimated an overall incidence of adverse drug reactions in pediatric in-patients and out-patients at 9.53 and 1.46%, respectively[1]. However, most studies assessed drug allergy according to clinical history and without proper confirmation. Our study confirmed drug allergy by skin tests and/or drug provocation tests and found that only the minority of children had a true drug allergy. There were similar findings in previous studies. Gomes et al.[3] found that of the 39 children who reported drug allergy from a plausible clinical history, only 3 had a true drug allergy. Aun et al.[10] performed 243 drug provocation tests and among these, only 4.1% revealed were positive. Therefore, clinical history or reports of drug allergy are unreliable and must be confirmed by drug provocation tests in order to avoid overdiagnosis.

There are 2 main types of drug reaction: immediate and delayed. Immediate reaction is mediated by Immunoglobulin E (IgE) with acute onset of less than 2 hours after exposure to the culprit drugs[9]. Patients with immediate type reaction often present with urticaria, angioedema or wheezing which were the clinical presentation most commonly observed in our patients. Interestingly, there were no significant differences in clinical presentation or onset of reaction between the true drug allergy and no drug allergy groups. This included presentation of angioedema or urticaria which are clearly mediated by IgE reaction and potentially related to a drug reaction. In addition, a number of patients who presented with clinical of immediate reaction but had onset of reaction more than 2 hours and vice versa for delayed reactions. Moreover, our study found that presenting symptoms did not correlate with provoked reactions. Our results contrast wit h previous studies[8, 11] that have found the culprit drugs provoked similar reactions as those reported in clinical history. This may be due to unreliability of clinical history in our patients. Therefore, clinical presentation and onset could not be used to predict whether the patients had true drug allergy.

Previous study had demonstrated that while atopy itself does not appear to be a major risk factor for most drug allergy, an atopic background is a substantial risk factor for severe drug allergy reaction[12]. In contrast, our study found that the patients in the no drug allergy group had more atopic disease. A plausible explanation for this could be that the number of patients in no drug allergy group was much higher than the true drug allergy group and most of the patients were enrolled from our allergy clinic.

Autoimmune disease and malignancy can lower the threshold of T cell activation by immune dysregulation and may predispose an individual to the development of a drug allergy[13-15]. Our study, however, did not find this association, most likely due to the sample's small number of patients with these underlying diseases.

There are limitations of the present study. First, the sample size is small and the fact that only a minority of the patients were confirmed to have a true drug allergy. This may explain non-statistical significances when comparing the differences between the true drug allergy and no drug allergy groups. Second the retrospective study design, creates inherent risks for incomplete information and

unavoidable recall bias especially, in reporting the precise onset of symptoms after drug exposure and the exact symptoms causing suspicion of having a drug allergy. Nevertheless, our study was conducted in children as young as six months old. In addition, our patients underwent complete evaluation including drug provocation tests if indicated.

Conclusions

Drug allergy is commonly reported but only a minority of children have a true drug allergy. We found that only 26.7 percent of pediatric patients were confirmed allergic to the culprit drugs. Antibiotics were the most common suspected and culprit drug. Of the antibiotics, Beta-lactam was the most common drug causing reactions. There were no precise clinical predictors for drug allergy. Skin tests were able to diagnose a majority but not all of true drug allergy patients. The provoked reaction may differ from reported history. Thus, drug provocation test remains the gold standard for diagnosis.

Acknowledgments

The authors would like to thank current and past fellows, staffs and attendings of the Division of Allergy and Immunology, Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University. We also express our gratitude to the patients and their parents who participated in this study. This study was supported by a research grant from the Faculty of Medicine Ramathibodi Hospital, Mahidol University.

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