

# Provocation proven drug allergy in Thai children with adverse drug reactions

Somying Indradat, Jittima Veskitkul, Punchama Pacharn, Orathai Jirapongsananuruk, Nualanong Visitsunthorn

## Summary

**Background:** Adverse drug reactions (ADRs) are a common healthcare problem. The drug provocation test (DPT) is a gold standard for ADR diagnosis.

**Objectives:** To evaluate a correlation between history of ADRs, skin prick test (SPT), intradermal test (ID) and DPT in Thai children.

**Methods:** This was a retrospective review of 211 children under 16 years of age who had a history of ADRs and underwent DPT from January 2006 to December 2012.

**Results:** Two hundred and thirty six (236) DPTs were performed in 211 children with a history of ADRs. The median age at which DPTs were performed was 4 years. Thirty-four children (14.4%) had positive DPT. The positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, likelihood ratio (LR) + and LR- of SPT were 50, 85.7, 6.9, 98.8%, 5.8 and 0.9, respectively. The PPV, NPV, sensitivity, specificity, LR+ and LR- of ID were 33.3, 84.6, 20, 91.7%, 2.4 and 0.9, respectively. Different presentation of symptoms (maculopapular rashes, urticaria, angioedema and anaphylaxis) did not predict SPT, ID and DPT results. Positive human immunodeficiency virus (HIV), but not atopy, was a risk in the present scope of evaluation for drug allergy (odds ratio 11.44, 95% confidence interval 2.60-50.41).

**Conclusion:** Drug allergy, denoted by positive DPT, was present in 14.4% of Thai children with a history of ADRs. Antibiotics were the most common cause of ADRs. Both SPT and ID had high NPV and specificity but did not predict DPT results. HIV positivity is a risk factor of drug allergy in Thai children. (*Asian Pac J Allergy Immunol* 2016;34:59-64)

**Keywords:** adverse drug reaction, drug allergy, drug provocation, skin prick test, intradermal test

## Introduction

Adverse drug reactions (ADRs) describe undesired effects from the use of drugs. ADRs are classified into types A or B.<sup>1</sup> Type A reactions are predictable while type B reactions are unpredictable and include immunological-mediated drug hypersensitivity (drug allergy). The overall incidence of ADRs in outpatient children was 1.5%.<sup>2</sup> In hospitalised children, the overall incidence of ADRs was 9.5% and severe reactions accounted for 12.3% of the total ADRs. The overall rate of paediatric hospital admissions due to ADRs was 2.1% and life-threatening reactions were found in 39.3% of ADRs causing hospital admission.<sup>2</sup> Previous studies showed that 2% of children with ADRs were hospitalised<sup>3</sup> and that 0.1% had severe ADRs.<sup>4</sup>

Drug allergy was present in 15–20% of ADRs.<sup>5</sup> In Spain, the prevalence of drug allergy denoted by the positive provocation test was 26.6%. Of these patients, 75% had skin manifestations and 10% had anaphylaxis.<sup>6</sup> Forty-seven percent of reactions were caused by beta-lactams (63% of which were due to amoxicillin) and 29% by non-steroidal anti-inflammatory drugs (NSAIDs).<sup>6</sup> However, only 6% of paediatric self-reporting cases had true drug allergy according to allergologist criteria.<sup>7</sup> The most common drug allergies in Singaporean children are caused by beta-lactam antibiotics (45%) and NSAIDs (19%).<sup>8</sup> It is important to determine which specific drugs cause allergic reactions in patients to decrease unnecessary drug avoidance.

From Division of Allergy and Immunology, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Corresponding author: Nualanong Visitsunthorn

E-mail: nualanongv@yahoo.com

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Drug hypersensitivity reactions are classified as immediate reaction (19.5%), non-immediate reaction (18.3%) and unknown classification (62.2%).<sup>9</sup> The reported risk factors of drug allergy include asthma, allergic rhinitis, eczema, food allergy, human immunodeficiency virus (HIV) infection and chronic diseases such as systemic lupus erythematosus (SLE), malignancy and immunodeficiency.<sup>10-12</sup>

The diagnosis of ADR is usually based on clinical history, skin testing and, to a lesser extent, *in vitro* testing.<sup>13</sup> Clinical history is often not reliable and the reagents used in skin tests and *in vitro* tests are seldom standardised.<sup>14</sup> Skin prick test (SPT) and intradermal test (ID) are used to assess immediate type of drug hypersensitivity reactions.<sup>15</sup> The drug provocation test (DPT) is the gold standard for the diagnosis of drug allergy.<sup>12</sup> If a DPT result is positive and the patient has a very severe allergic reaction, the patient must avoid the drug. If alternative drugs are not available and the patient has to use the allergy-inducing drug, desensitisation should be used. This is performed by initially giving the suspected drug in very small amounts and progressively increasing the dose to induce non-responsive mast cells, basophils and cellular mediators of allergic reactions.<sup>12,15,16</sup>

The aim of this study was to evaluate the correlation between a history of ADRs, SPT, ID and DPT in Thai children.

## Methods

This study was approved by the Institutional Ethics Committee of Siriraj Hospital. The retrospective chart review was performed over a seven-year period (January 2006 to December 2012) in paediatric patients (under 16 years of age) from the Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand. All cases had a clinical history of allergic reactions to drugs and underwent DPTs.

Clinical data including demographic data, clinical presentation of drug allergy, onset of drug reaction, allergy clinical history, risk factors of drug allergy, duration from ADR to the drug test, and results of SPT, ID and DPT were recorded. All tests were performed after receiving written informed consent from the patients and/or parents.

Skin tests were performed on the upper back or volar side of the arm. Reagents used for the skin test were 50% glycerine in normal saline solution as a negative control, histamine 10 mg/ml as a positive

control and non-irritating concentrations of suspected drugs. SPT was considered positive when the wheal diameter was at least 3 mm larger than the negative control at 15 minutes after the test. If SPT was negative, ID was performed with non-irritating concentrations of the same drug. An ID was considered positive when the wheal size was  $\geq 3$  mm in diameter greater than the negative control at 15 minutes after the test.

DPTs were performed at the hospital using an open challenge protocol. The starting dose was 1:1,000, 1:100 or 1:10 of the therapeutic dose, dependent on the severity of the reaction. The drug doses were increased every 30 minutes until the cumulative dose reached the therapeutic dose. The vital signs, as well as signs and symptoms of drug allergy were evaluated by a paediatrician and paediatric nurse every 15 minutes for the 2-hour period of testing. The DPT was considered positive when signs or symptoms of test drug allergy such as anaphylaxis, urticaria, angioedema, maculopapular rashes, repeated vomiting, wheezing, dyspnoea or rhino-conjunctivitis were observed between DPT and 72 hours after testing. Anaphylaxis was treated immediately with an intramuscular injection of adrenaline. Symptomatic treatment such as antihistamines and bronchodilators was administered for the treatment of urticaria and wheezing, respectively.

## Statistical analysis

The data were analysed using SPSS software version 16. The frequency was used for general characteristics such as sex, type of drug allergy, signs and symptoms of drug allergy, and percentage of positive drug provocation test. The Mann-Whitney *U*-test was used for the determination of age and risk factors of drug allergy. These results were presented as median (min, max), *P* value, odds ratio (OR) and 95% confidence interval (CI). The negative predictive value (NPV), positive predictive value (PPV), sensitivity, specificity, likelihood ratio (LR) + and LR- were used to evaluate the association between the results of SPT/ID and DPT.

## Results

In this study, 211 children were suspected as having ADRs and underwent 236 DPTs from January 2006 to December 2012. The median age at which ADRs were diagnosed was 3 years (range 0.1–16.0 years). One hundred and twenty six cases (59.7%) were male. DPTs were performed at a

**Table 1.** General characteristics of 211 Thai children who underwent 236 drug provocation tests

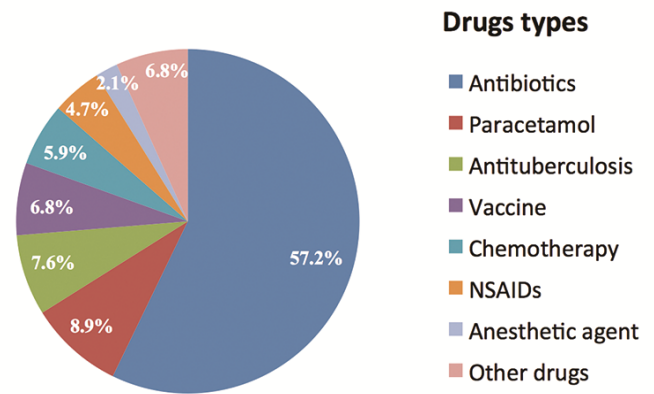
Factors	N (%)
Sex: male	126 (59.7)
Age at DPT performed (yr) (median, min-max)	4 (0.3-16.0)
<b>Drugs with DPT performed*</b>	
Penicillin	61 (25.8)
Cephalosporin	34 (14.4)
Macrolides	19 (8.1)
Other antibiotics	21 (8.9)
Non-antibiotic drugs	101 (42.7)
<b>Symptoms of adverse drug reactions*</b>	
Urticaria/angioedema	118 (50)
Maculopapular rashes	77 (32.6)
Anaphylaxis	18 (7.6)
Other	8 (3.4)
Missing data	15 (6.4)

\*One case may have more than one DPT and more than one symptom.  
DPT: drug provocation test.

median age of 4 years (range 0.3–16.0 years). Symptoms of ADRs were urticaria/angioedema (50%), maculopapular rashes (32.6%) and anaphylaxis (7.6%), as shown in Table 1. The most common drugs associated with ADRs in children were antibiotics (57.2%) followed by paracetamol (8.9%), anti-tuberculosis drugs (7.6%), vaccines (6.8%) and chemotherapeutic drugs (5.9%) (Figure 1).

Positive DPTs were observed in 34 of 236 tests (14.4%). Two hundred and forty-one tests of SPT and 44 tests of ID were performed. Among antibiotic allergies proven by positive DPTs, penicillin was the most common cause (45.2%) followed by cephalosporin (25.2%) and macrolides (14.1%). When using DPT as the gold standard, SPT had high NPV (85.7%) and specificity (98.8%). If drugs were categorised by antibiotic drugs, the specificity was 100% and LR+ was infinity (Table 2). ID also showed high NPV (84.6%) and specificity (91.7%) (Table 3).

Thirteen of 34 children with positive DPT (38.2%) developed anaphylaxis during the DPT procedure. None of the 13 cases had a previous history of anaphylaxis. Among these 13 patients, 2 had negative SPT and ID (1 to piperacillin and 1 to cotrimoxazole), 7 had negative SPT but ID was not performed (3 to paracetamol, 1 to cephalixin, 1 to

**Figure 1.** Types of drugs associated with adverse drug reactions in studied Thai children.

NSAIDs: nonsteroidal anti-inflammatory drugs.

dapsone, 2 to mepivacaine), and SPT and ID were not performed in 4 patients (1 to carboplatin, 1 to cefdinir, 1 to cyclosporine, 1 to meropenem). In 18 cases with a history of anaphylaxis from drugs, 24 drug allergy episodes were observed. In this group, only 3 children had positive IDs while 21 had negative SPT and DPT. None of the cases with a history of anaphylaxis to drugs developed anaphylaxis during DPT. The different presenting symptoms observed (maculopapular rashes, urticaria, angioedema and anaphylaxis) did not predict the results of SPT, ID and DPT. In 33 patients who had negative SPT and ID, none of them had DPT reactions which were more severe than the previous allergic reactions.

In this study, HIV positive infection was the risk factor for drug allergy (OR 11.4, 95%CI 2.6-50.4,  $P < 0.001$ ), while atopic diseases, epilepsy, malignancy and primary immunodeficiency were not risk factors (Table 4). Five of eight HIV positive patients with ADRs had positive DPT. Three HIV positive patients had positive DPT to sulpha group antibiotics (2 to cotrimoxazole and 1 to dapsone) and two had positive DPT to  $\beta$ -lactam antibiotics (1 to cefotaxime and 1 to piperacillin + tazobactam).

## Discussion

Positive DPT was observed in 14.4% (34/236) of children and adolescents with a history of drug allergy who underwent DPT. This was supported by a previous study where 13% of children (median age 5 years) with self-reported drug allergy had positive DPT.<sup>7</sup> Our study showed that the most common

**Table 2.** Comparison between skin prick test and drug provocation test

Positive SPT	Sensitivity %	Specificity %	PPV %	NPV %	LR+	LR-
All drugs (n=193)	6.9	98.8	50.0	85.7	5.8	0.9
Antibiotic drugs (n=120)	6.7	100	100	88.2	∞	0.9
Non-antibiotic drugs (n=73)	7.1	96.6	33.3	81.2	2.1	1.0

SPT: skin prick test; PPV: positive predictive value; NPV: negative predictive value;  
LR: likelihood ratio.

cause of drug allergy was antibiotics (57.2%). This confirmed findings of a study in Spain where antibiotics was the most common drug allergy, accounting for 47% of allergic reactions.<sup>6</sup>

In our study, the PPV, NPV and specificity of SPT to antibiotics were high. Evaluation between SPT and DPT for all drugs, LR+ 5.8, showed a moderate post-test probability while the evaluation between SPT and DPT for antibiotic drugs, LR+ infinity, showed high post-test probability. ID for antibiotic drugs had a lower sensitivity than SPT, but the sample size was too small to make a definite conclusion. If the result of SPT was negative, ID could be performed before that drugs were administered by the parenteral route (intravenous, subcutaneous or intramuscular). Furthermore, the results of positive SPT and/or ID did not predict the severity of reactions from DPT. The SPT and ID were not useful for diagnosis of patients with drug allergies because of low sensitivity in patients who were allergic to both antibiotic drugs and non-antibiotic drugs, but the SPT and ID did have a high specificity. DPT is the gold standard procedure to confirm diagnosis of drug allergy. However, false-negative DPT can occur and does not exclude a drug as the culprit for a reaction since crucial co-factors

might be absent during the test procedure, such as anxiety or an associated inflammatory disease (e.g. latent asthma, urticaria or viral infections).<sup>17</sup>

There was no significant difference in the results of DPTs among patients who had different symptoms (maculopapular rashes, urticaria, angioedema and anaphylaxis). This was supported by previous studies showing that positive DPT could be found for all of these symptoms<sup>18</sup> and delayed-onset urticarial or maculopapular rashes were frequently observed in children treated with  $\beta$ -lactams.<sup>19</sup> Our study showed that a history of anaphylaxis from drugs neither predicts recent drug allergy (proven by DPTs) nor anaphylaxis reactions by DPT. None of the cases with drug anaphylaxis history had anaphylaxis proven by DPT and none of the cases that had anaphylaxis proven by DPT had a history of drug anaphylaxis. This might be lack of the crucial co-factors. Our study showed that 38.2% of children with ADRs without a previous history of anaphylaxis developed anaphylaxis during the DPT procedure. Therefore, we suggest that DPT should be performed with caution in an intensive care unit with full facilities for resuscitation.

Beta-lactam antibiotic was the most common cause of drug allergy (40.2%) in our study. The

**Table 3.** Comparison between intradermal test and drug provocation test

Positive ID	Sensitivity %	Specificity %	PPV %	NPV %	LR+	LR-
All drugs (n=29)	20.0	91.7	33.3	84.6	2.4	0.9
Antibiotic drugs (n=7)	0.0	100	0.0	71.4	0.0	1.0
Non-antibiotic drugs (n=22)	33.3	89.5	33.3	89.5	3.2	0.6

ID: intradermal test; PPV: positive predictive value; NPV: negative predictive value;  
LR: likelihood ratio.

**Table 4.** Risk factors associated with drug allergy.

Factors	Positive DPT n=34	Negative DPT n=202	OR	95%CI	P value
<b>Sex</b>					
Male	22	124	0.87	0.41–1.85	0.712
Female	12	78			
<b>Any atopic diseases</b>					
Yes	11	60	1.13	0.52–2.47	0.755
No	23	142			
<b>Allergic rhinitis</b>					
Yes	10	48	1.34	0.60–3.00	0.479
No	24	154			
<b>Asthma</b>					
Yes	7	23	2.02	0.79–5.15	0.136
No	27	179			
<b>Food allergy</b>					
Yes	1	10	0.58	0.07–4.70	0.607
No	33	192			
<b>Atopic dermatitis</b>					
Yes	3	7	2.70	0.66–10.98	0.151
No	31	195			
<b>Chronic urticaria</b>					
Yes	3	11	1.68	0.44–6.36	0.432
No	31	191			
<b>Epilepsy</b>					
Yes	1	2	3.03	0.27–34.37	0.374
No	33	200			
<b>Malignancy</b>					
Yes	4	23	1.04	0.34–3.21	0.949
No	30	179			
<b>HIV infection</b>					
Yes	5	3	<b>11.44</b>	<b>2.60–50.41</b>	<b>&lt;0.001</b>
No	29	199			
<b>Primary immunodeficiency</b>					
Yes	1	8	0.74	0.09–6.07	0.774
No	33	194			

DPT: drug provocation test; OR: odds ratio; CI: confidence interval.

previous study of 247 children with paediatrician-diagnosed allergy reactions to penicillin, amoxicillin, and oral cephalosporins showed that 84 cases (34.0%) had IgE-type reactions by skin testing.<sup>20</sup> In cases with negative skin testing to beta-lactam antibiotics, 1.8% had mild IgE-type reactions.<sup>20</sup> The previous study in adult patients showed that NSAIDs were the most common drugs that caused drug hypersensitivity (37%), followed by beta-lactam antibiotics (29.4%), and that a diagnosis of drug allergy required DPT in 30.8% of cases.<sup>21</sup>

Our study showed that if SPT and ID were negative, no DPT reactions were more severe than the previous allergic reactions, confirming previous studies.<sup>14,19,20</sup>

We found that HIV infection was a risk factor for drug allergy, particularly cotrimoxazole. Five of the eight patients (62.5%) with HIV infection had positive DPT. Atopic disease, epilepsy, malignancy and primary immunodeficiency were not major risk factors for drug allergy. Previous studies showed that the presence of a specific IgE against common

aeroallergens was not associated with the occurrence of severe reactions to drugs in atopic patients.<sup>22,23</sup>

This study used a high number of cases in whom DPTs were performed. A limitation was that this was a retrospective study, thus, in some cases, DPT was performed without SPT or ID. Furthermore, the number of HIV patients was low. In addition, there might be selective bias for performing DPT because some anaphylaxis cases were chosen to receive alternative drugs without undergoing DPTs.

## Conclusion

Drug allergy, denoted by a positive DPT, was present in 14.4% of Thai children with a history of ADRs. Antibiotics were the most common cause of ADRs. Both SPT and ID had high NPV and specificity but did not predict the result of DPT. Positivity for HIV infection is a risk factor for drug allergy in Thai children.

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