Evaluation of drug provocation tests in Korean children: a single center experience

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Summary

Background: **Drug provocation tests (DPTs) are difficult to perform in clinical practice, even though they are the gold standard for the diagnosis of adverse drug reactions (ADRs).**

Objective: **The aims of this study were to evaluate the common causative drugs of type B ADRs and to analyze the relationships between host factors and the results of DPTs in Korean children.**

Methods: **We retrospectively reviewed the medical records of all children younger than 19 years of age who underwent a DPT between November 1994 and November 2014. Open provocation tests were performed with non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, aminopenicillins, cephalosporins, non-β-lactam antibiotics, antiepileptic drugs, or other drugs.**

Results: **Overall, 84 DPTs were performed in 56 patients whose median age was 7.5 years (range, 6 months to 18 years). DPTs were positive in 25 (29.8%) of 84 cases, which translated to 18 (32.1%) positive findings in 56 patients. Drugs that provided positive results included NSAIDs (7 cases, 28.0%), aminopenicillins (5 cases, 20.0%), acetaminophen (4 cases, 16.0%), cephalosporins (3 cases, 12.0%), and non-β-lactams (2 cases, 8.0%). Anaphylaxis was noted in 5 (20.0%) of 25 cases. There were no serious complications of DPTs in any of the subjects. The median age was 10.5 years for children who had a positive result following the DPT and 5.0 years for those with negative results (*P* value = 0.019).**

Conclusions: **DPTs can be performed safely in children with suspected ADRs in order to achieve a correct diagnosis. *(Asian Pac J Allergy Immunol 2016;34:130-6)***

Keywords: *adverse drug reaction, allergy, drug provocation test, hypersensitivity, child*

Introduction

An adverse drug reaction (ADR) is defined by the World Health Organization as an unintended and harmful response that occurs at doses normally used for the prevention, diagnosis, or treatment of disease.[1,2] Type A ADRs, which are related to the pharmacological action of drugs, are common, predictable, and dose-dependent.[2] On the other hand, type B ADRs comprise uncommon reactions that occur in susceptible individuals and are both unpredictable and dose-independent.[1-3] Type B ADRs include both immune-mediated drug hypersensitivity and non-immune-mediated reactions.[4] The overall incidence of ADRs accounts for between 3 to 6% of all hospital admissions and 10 to 15% of hospitalized patients.[3,5,6] A previous Korean national survey reported the prevalence of ADRs as 1.5% in children aged 6 to 15 years.[7]

Skin prick tests (SPT) and intradermal tests (IDT) provide evidence of IgE-mediated sensitization, while patch tests or delayed reading of an IDT indicates a T cell-mediated process to a specific drug.[8-10] These tests are widely used to predict ADRs before drug administration, but have some limitations. For example, if the reaction is not IgE-mediated, a negative skin test result cannot exclude the medicine as being responsible for the ADR.[8] Moreover, limitations in the availability of relevant reagents can cause false negative skin tests even if the reaction is IgE-mediated.[11] In addition, false negative results can occur because of poor skin penetration by large drug molecules or a low dose of the drug.[12] Precise identification of the responsible

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drug is important for future treatments because it can result in the assignment of patients as hypersensitive without clear evidence.[13] Therefore, the drug provocation test (DPT) is considered the gold standard for confirming or excluding ADRs, although this procedure is time-consuming and distressing.[14] Indeed, DPTs can reproduce adverse clinical manifestations and allergic symptoms, regardless of the mechanism.[14]

Although ADRs are more commonly associated with a negative effect on medical treatment and are associated with more significant morbidity in children compared to adults, there are relatively few studies on the results of pediatric DPTs.[5,15,16] In particular, ADRs not only affect patient quality of life, but can also lead to delayed treatment and even mortality as a result of the smaller number of medicines that are generally available to children.[2,16] On the other hand, excessive concerns about ADRs may compel the use of less effective and more expensive alternative treatments owing to restrictions on appropriate drug use. In this study, we aimed to evaluate the common causative drugs in Korean children with suspected type B ADRs and analyzed the relationships between host factors and DPT results.

Methods

Patients

We retrospectively reviewed the medical records of all children younger than 19 years of age who visited Samsung Medical Center and underwent a DPT between November 1994 and November 2014. Medical records included demographic information, medical history and family history of allergic disease, detailed history of ADRs, manifestations after ingestion of drugs, and results of DPTs with suspected drugs. Allergic disease was defined as atopic dermatitis, allergic rhinitis, or asthma as diagnosed by a physician. This study was approved by the institutional review board at Samsung Medical Center (SMC 2014-08-089).

Drug provocation tests

Patients who were suspected to have an ADR underwent an open provocation test according to established protocols.[14,17-19] Patients were excluded from DPTs if they had an obvious history of Stevens-Johnson syndrome or toxic epidermal necrolysis. The DPT was conducted when at least five times the half-life of the suspected drug had passed since the most recent ADR. It was carried out under the supervision of a pediatric allergist who was competent to perform resuscitation. If the patients had ingested more than one drug during the ADR episode or wanted to receive additional testing using an alternative drug, DPTs were conducted for each drug at 1-4 week intervals. DPTs consisted of administering the suspected drug at divided doses ever 30-60 minutes until a cumulative dose close to the daily dose of the drug was achieved. The test was discontinued upon observation of any drug reaction. In most cases, we used the same route of administration as that used by the patient when the ADR was noted, except in one case of hypersensitivity to topically applied sodium fusidate. In this case, we performed an oral provocation test using a fusidic acid tablet because we suspected the ADR was caused by systemic absorption of fusidic acid through abraded skin.[20] The administrated drugs were classified as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), aminopenicillins, cephalosporins, non-beta lactam antibiotics, antiepileptic drugs, or other medicines.

DPT results were considered positive if any signs or symptoms were documented. We classified symptoms according to the affected organ: (i) skin reactions, such as urticaria, rash, and itching; (ii) isolated angioedema; (iii) respiratory symptoms such as cough, dyspnea, or wheezing; and (iv) anaphylaxis. Anaphylaxis was defined as symptoms that occurred rapidly after exposure and affected at least two major organ systems according to the established guidelines.[21] Oral antihistamine, inhaled beta-2 agonist, or intramuscular epinephrine was given to patients who exhibited a positive DPT result based on their symptoms. Patients were monitored for at least 2 hours after the last dose had been administered without an ADR. In cases with negative DPT results on the initial day of testing, patients were instructed to observe clinical symptoms for 2 days in order to identify delayed reactions.[2]

Laboratory tests

Measurements of eosinophil count, serum total IgE level, and specific IgE (sIgE) to *Dermatophagoides pteronyssinus*, *D. farinae*, egg white, cow's milk, soy, wheat, and peanut were performed. Serum IgE level was determined by ImmunoCAP (Thermo Fisher Scientific Inc., Waltham, MA, USA) assay. SPTs were performed on the backs of patients using the following allergens (Allergopharma, Reinbek, Germany): *D. pteronyssinus*, *D. farinae*, egg white, cow's milk,

soy, wheat, and peanut. Histamine was used as a positive control, and normal saline was used as a negative control. Sensitization was defined as an sIgE level ≥ 0.35 IU/ml or the formation of a wheal with a diameter at least 3 mm larger than the negative control.

Statistical analysis

Data were analyzed using SPSS for Windows (version 21.0; Chicago, IL). The Chi-squared test was applied to examine the associations between the occurrence of ADRs in DPTs and categorical variables such as gender, medical history of allergic diseases, allergic diseases of the parents, sensitization to common allergens, and drug groups. Age, total IgE level, and eosinophil count were compared between children who showed positive and negative DPTs using the Mann-Whitney U test. Total IgE was analyzed on a logarithmic scale. *P* values < 0.05 were considered significant.

Results

Overall, 84 DPTs were performed in 56 patients (33 boys and 23 girls) over a period of 20 years. The median age of subjects was 7.5 years (range, 6 months to 18 years). A total of 21 (37.5%) patients had a personal history of allergic disease, and 9 (16.1%) patients had a parental history of allergic disease. With respect to underlying disease, 14 (25.0%) patients had atopic dermatitis, 7 (12.5%) had allergic rhinitis, and 2 (3.6%) had asthma (Table 1). The most frequent suspected drugs were NSAIDs in 24 cases (28.6%), followed by aminopenicillins in 17 cases (20.2%), cephalosporins in 14 cases (16.7%), acetaminophen in 12 cases (14.3%), other drugs in 9 cases (10.7%), antiepileptic drugs in 5 cases (6.0%), and non-β-lactams in 3 cases (3.6%). Other drugs included antihistamines, mucolytics, decongestants, corticosteroids, gastrointestinal tract regulators, and antispasmodics. There were no differences in the occurrence of ADRs among the drug groups (*P* value = 0.836).

DPTs were positive in 25 (29.8%) of 84 cases and 18 (32.1%) of 56 patients. Drugs causing positive results were NSAIDs in 7 (28.0 %), aminopenicillins in 5 (20.0%), acetaminophen in 4 (16.0%), cephalosporins in 3 (12.0%), non-β-lactams in 2 (8.0%), antihistamines in 2 (8.0%), antiepileptic drugs in 1 (4.0%), and antispasmodic in 1 (4.0%). The ratio of suspected and proven reactions was highest for non-β-lactams (2/3, 66.7%), followed by acetaminophen (4/12, 33.3%), aminopenicillins (5/17, 29.4%), NSAIDs (7/24, 29.2%), cephalosporins (3/14, 21.4%), antiepileptic drugs (1/5, 20.0%), and other medicines (2 antihistamines and 1 antispasmodic) (3/9, 33.3%) (Figure 1).

Table 1. Clinical characteristics of patients

Characteristics	Number (%)
Sex	
Male	33 (58.9%)
Female	23 (41.1%)
Age, (yr)	
<2	9 (16.1%)
2~5	15 (26.8%)
≥6	32 (57.1%)
Symptoms	
Mucocutaneous (urticaria, angioedema)	55 (98.2%)
Anaphylaxis	15 (26.8%)
Personal history of allergic diseases	
Atopic dermatitis	14 (25.0%)
Allergic rhinitis	7 (12.5%)
Asthma	2 (3.6%)
Time interval between reaction and provocation test (mo)*	
< 2	29 (38.7%)
2 – 6	19 (25.3%)
≥ 6	27 (36.0%)

*75 drug provocation tests were included in this analysis

Five (8.8%) children exhibited positive results for more than one drug. Notably, one patient had positive reactions to acetaminophen, ibuprofen, naproxen, and celecoxib. Sixteen (64.0%) of 25 positive cases showed skin reactions without the involvement of other organs, while 4 cases (16.0%) presented with isolated angioedema during the DPT. Onset time was less than 1 hour in 8 cases (32.0%), 1-2 hours in 6 cases (24.0%), 2-3 hours in 3 cases (12.0%), 3-4 hours in 3 cases (12.0%), and more than 4 hours in 5 cases (20.0%).

Anaphylaxis occurred in 5 (20.0%) of 25 cases, indicating only 31.3% of self-reported anaphylaxis. Detailed results of the patients who developed anaphylaxis during the DPT are provided in Table 2. The drugs that were found to cause anaphylaxis during DPTs consisted of aminopenicillins in 2 cases (40.0%), followed by cephalosporin, non-β-lactams, and NSAIDs in 1 case each (20.0%).

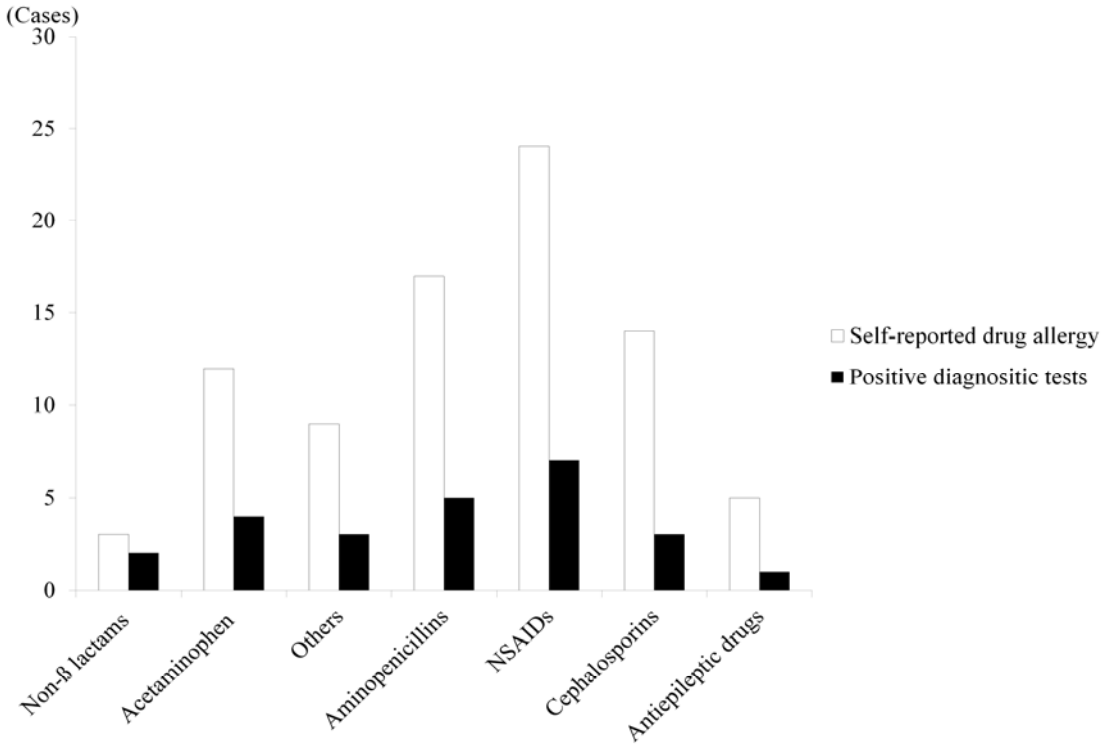

Figure 1. Number of suspected and proven adverse drug reactions

The reaction time of anaphylaxis was less than 30 minutes. There were no complications following DPTs in any of the subjects in this study.

The median age for children who had a positive DPT was 10.5 years, and that for those with negative results was 5.0 years (P value = 0.019) (Table 3). There were no statistical differences between children who had positive and negative DPT results with respect to gender, personal history of allergic disease, parental history of allergic disease, eosinophil count, total IgE level, and proportions of allergic sensitization.

Discussion

Precise identification of the responsible drug using DPTs is important because of the difficulties of the choice of medication for children with suspected ADRs.[8] However, there is a scarcity of data with respect to DPTs in Korean children.[7,15] Thus, we analyzed all of the DPTs performed in our pediatric allergy clinic over the course of 20 years. Importantly, this is the largest and most extensive pediatric DPT study conducted in Korea to date. Positive findings were noted in 18 (32.1%) of 56 patients and 25 (29.8%) of 84 cases in this study. The positive rate was higher than reported rates in other countries. Indeed, the prevalence of positive tests was 10.6% (70/658 cases) in the largest European cohort study conducted to date.[22] In addition, Turkish and Brazilian studies reported positive rates of 6.8% (13/191 cases) and 4.1% (10/243 cases), respectively.[23,24] A previous Korean study also reported a lower positive rate of 23.9% (17/71 cases) compared to that of our study.[15] We postulated that the number of patients included in this study and the background factors of study subjects were the cause of differences in the prevalence of positive DPT findings.

We found that NSAIDs were the most frequent culprits of ADRs, followed by aminopenicillins, acetaminophen, cephalosporins, non-β-lactam antibiotics, and antiepileptic drugs. Even though their order varies, NSAIDs, acetaminophen, and antibiotics are the most common causative drugs related to positive ADRs in all ages worldwide.[22-24] A previous Korean study also reported that the most common drugs associated with ADRs are acetaminophen, NSAIDs, penicillin, and cephalosporins.[15] Common causative drugs are known to have similar characteristics such

Table 2. Patients showing anaphylaxis in drug provocation tests

Age (yr)	Sex	Personal history of allergic diseases	Drug	Eosinophil count (/mm^3)	Total IgE (IU/ml)	Symptoms during provocation tests	Time to reaction after administration (min)	Cumulative dose to elicit reaction (mg)
16	M	None	Fusidate sodium	None	None	Cough, dyspnea, chest discomfort, urticaria, itching	30	125
8	M	None	Amoxicillin	6890	27.8	Urticaria, abdominal pain, vomiting	20	50
8	F	Atopic dermatitis	Cefaclor	6830	121	Urticaria, itching, dyspnea	18	150
14	F	None	Amoxicillin	6650	None	Urticaria, decreased aeration, dyspnea	30	156.3
18	F	None	Aspirin	6410	73.1	Angioedema, chest discomfort	5	150

as high molecular weight and the ability to act as a hapten.[2] Such ADRs may also be due to the fact that these are the most commonly prescribed drugs during childhood. Nevertheless, the ratio of suspected and proven reactions in this study was highest for non-β-lactams (67%), followed by acetaminophen (33%), aminopenicillin (29%), NSAIDs (29%), cephalosporin (21%), and antiepileptic drugs (20%), which is similar to their frequency of use among children.

In the present study, skin and/or mucosal symptoms were the most frequent reactions, similar to previous studies that reported mucocutaneous reactions in more than 90% of cases.[17,23,24] Anaphylaxis was observed in 20% of all reactions, which corresponded with the 10-20% noted in other studies.[15,23,24] There were no serious complications of DPTs in any of the subjects evaluated in this study, supporting the idea that DPTs can be performed safely under a doctor's supervision. However, sustained and careful attention is required, because positive reactions were observed in about 40% of patients more than 2 hours after the provocation test.

An important finding of our study is that the rate of positive challenge results was higher in older children than in younger ones. These results are in agreement with those of a recent large cohort study that compared the prevalence of positive DPTs between childhood and adulthood.[22] This previous cohort study reported positive rates of 10.6% in patients whose index reaction and DPT occurred during childhood and 16.5% in patients whose index reaction and DPT occurred during adulthood. This observation can be explained by the phenomenon that older people are more likely to come into contact with drugs.[22] A second possibility is that most of the skin reactions in younger children may be caused by infectious diseases or interactions between drugs and infectious organisms rather than an ADR itself.[22,25,26] Indeed, skin rashes related to antibiotics in children are rarely reproducible in subsequent challenges, and viral infections are thought to be an important factor in these cases, as they can alter the immune response or drug metabolism.[26] These results suggest that DPTs should be performed in children with suspected ADRs, even if they are young. In these children, a negative result is also important because it can prevent meaningless avoidance of suspicious drugs in the future.

Our study has some limitations, mostly stemming from the small sample size and selection bias. Specifically, we only included 84 DPTs conducted in 56 patients despite including 20 years of patient data. The smaller sample size and higher positive rates than studies from other countries might be related to selection bias. It is difficult to perform a provocation test with suspected drugs in children because many Korean parents do not want to subject their children to such risks. Therefore, our cases might have included more severe reactions and drugs that were more likely to cause reactions compared with previous studies. In addition, most of patients did not undergo SPTs or IDTs using suspected drugs prior to the DPT. Despite these limitations, our results provide useful information

Table 3. Characteristics of patients with positive and negative test results

Variables	Drug provocation test results		*P* value
	Positive	Negative	
Gender (male, %)	9/18 (50.0)	24/38 (63.2)	0.350
Age (median, range)	10.5 (1 – 18.0)	5.0 (0-14)	0.019
Personal history of allergic diseases (%)	7/18 (38.9)	14/38 (36.8)	0.883
Parental history of allergic diseases (%)	5/17 (29.4)	4/36 (11.1)	0.098
Eosinophil count (/mm^3) (median, range)	211.7 (0 - 630.7)	126.0 (0 – 944.3)	0.452
Logarithm of total IgE (IU/ml) (median, range)	2.1 (1.3 – 3.9)	1.9 (0.9 – 3.1)	0.286
Allergic sensitization (%)	8/15 (53.3)	20/35 (57.1)	0.804

regarding ADRs and DPTs in childhood and also reveal age-related factors associated with ADRs.

In conclusion, the positive rate of DPTs in our study was 29.8%, with a lower rate noted in younger children. The most common causative drugs were NSAIDs, followed by β-lactam antibiotics and acetaminophen. DPTs can be performed safely as long as careful and sustained attention is given to children with a suspected ADR, because a positive clinical history alone is not sufficient for the diagnosis of an ADR.

Conflict of interest

The authors have no conflicts of interest to declare.

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