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Negative predictive value of drug provocation tests in children

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Abstract

Background: The negative predictive value of the drug provocation test is important for both the patient and the physician. However, in children this predictive value is unresolved.

Methods: The study included patients who had drug provocation test with a suspected drug and was diagnosed as “not allergic to the drug”. Three months after allergy work-up, the patients were contacted and asked for re-exposure to the tested drug. Patients who have reported reactions during re-exposure were re-evaluated with skin tests and drug provocation.

Results: During the study period, 217 provocations were performed to 203 patients. Of these, 163 patients (80.3.%) with 175 negative drug provocation tests could be contacted. Ninety one (52%) of the 175 cases reported to use the tested drug again and 11 (12%) of these cases declared that they had a new reaction. Two of the eleven cases refused re-evaluation. Nine cases were evaluated by drug allergy work-up. Two of the nine cases were classified as allergic after retests. Collectively, the negative predictive value was 95.6% (87 out of 91 cases) for all drug challenges.

Conclusions: The negative predictive value of the drug provocation test is abundant in children, however, negative drug provocation tests do not necessarily predict tolerance for the drug.

Keyword; beta-lactams, drug hypersensitivity, drug provocation tests, negative predictive value, nonsteroidal anti-inflammatory drugs, re-sensitization

Introduction

A drug provocation test (DPT) is considered the gold standard for identifying drug hypersensitivity. Often, provocation tests are negative, and thus drug hypersensitivity is ruled out (1). Studies on the risk of subsequent reactions with the same drug after a negative provocation test are limited. The reason for a hypersensitivity reaction after a negative provocation test may be due to the absence of crucial co-factors during the test procedure such as co-medication, viral infection, and physical exercise. Also re-sensitization may be another contributing element (1,2).

Drug hypersensitivity reactions are a source of anxiety and lead to the avoidance of the drug. The negative predictive value is important for both the patient and the physician. The physician has to know whether the drug can be safely prescribed for patients with a previous negative allergy work-up. Moreover, the patient has to perceive whether a reaction may occur after taking a drug which was tested negatively.

The aim of this study was to evaluate whether children use the drugs after negative drug provocation tests and upon reuse, evaluate whether or not they experience a hypersensitivity reaction. Reported hypersensitivity reactions were re-evaluated to determine whether these reactions are suspected drug related hypersensitivity reactions.

Patients and methods

This study was conducted in the pediatric allergy department of Ankara Children's Hematology Oncology Training and Research Hospital (Turkey). The study included patients who underwent drug provocation test with a suspected drug and have been diagnosed as "not allergic to the drug" between May 2011 and May 2013. Patients were contacted at least 3 months after allergy work-up. The initial drug allergy work-up was initiated with the standardized ENDA questionnaire on drug allergy (3). Reactions occurring within the first hour were labeled as "immediate reactions" and the ones occurring later than an hour were labeled as "non-immediate reactions". Immediate reactions manifested clinically by urticaria, angioedema, rhinitis, bronchospasm and anaphylaxis. Non-immediate reactions manifested clinically by maculopapular eruptions and delayed-appearing urticaria/angioedema.

In the cases where suspected reaction was compatible with drug hypersensitivity, skin tests and oral provocation tests with the suspected drug were proposed. Antihistamine medications and drugs that could affect skin tests or drug provocation outcomes were stopped 1 week before testing (4,5,6).

Exclusion Criteria

Patients with history of severe life threatening drug reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity syndrome or drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, nephritis, pneumonitis, hepatitis, and vasculitis) were excluded as the provocation test is contraindicated (6).

Skin tests

Skin tests (Prick-intradermal):

Patients were subjected to prick and intradermal skin testing with the suspected drugs (beta lactams, macrolides, cephalosporine, sulphonamide, metamizol and paracetamol) (4,5). Beta

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lactams used for skin tests included Penicillin G (10.000 IU/ml), benzylpenicilloyl poly-L-lysine (PPL), minor determinant (sodium benzylpenilloate) (MDM) (Diater Laboratorios S.A., Madrid, Spain), amoxicillin-clavunate (20mg/ml), ampicillin (20mg/ml). If cephalosporine susceptibility existed, skin tests were performed with the culprit drug using the suggested concentration (2 mg/ml). Furthermore, skin tests with trimethoprim-sulfamethoxazole (0.8mg/ml) and clarithromycin (0.5mg/ml), pyrazolone (0.1 mg/ml) were also performed. All of the drugs were initially tested on the volar forearm skin with the prick method, and reactions were accepted as positive when a wheal diameter of 3 mm greater than the negative control, with surrounding erythema, appeared within 20 minutes.

When prick tests yielded negative results, 0.02 mL of the relevant agent was re-injected intradermally on volar forearm skin. Readings were made 20 minutes after injections and when an increase larger than 3 mm in the wheal diameter accompanied by erythema, was present results were considered positive. Positive controls for prick tests were performed with histamine (10 mg/ml). As a negative control for both prick and intradermal tests, 0.9 % NaCl was used.

The procedure ended when the skin test resulted positively. In patients with a non-immediate reaction or when the time interval with the reaction and exposure to the drug was not exactly known, a late skin tests reading was performed (24–72 h post-exposure).

Drug provocation tests

Drug provocation tests were done on participants where other investigations were inconclusive or the provocation test was not contra-indicated. ENDA guidelines for provocation tests were carefully applied (6). A provocation test involved administering the

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suspected drug at divided doses every 30 minutes, until a cumulative dose close to the age/weight adjusted daily dose of the drug was achieved. The provocation was administered in maximum of 5 doses in order to prevent the possibility of desensitizing the patient. The test was discontinued in the event of any adverse reaction. In most cases, a route of administration was chosen that was identical to the route that the patient had been using during the incidence of allergic reaction. If an oral formulation of an injectable drug was available, we administered the drug orally first and if there was no reaction, we administered the drug with injection. An open drug provocation was done by a physician with full resuscitation back-up.

The drug provocation test result was considered positive if any objective symptoms or signs were documented and negative if no sign of drug hypersensitivity appeared after the usual daily dose was reached. The patients were kept under surveillance for at least 2 hours post provocation test.

For non-immediate reactions and when the time interval between reaction and exposure was not obvious in the history, patients were instructed to take the drug for 5 more days at home (7,8). Patients were asked to contact our department if any reactions occurred in the following days.

Follow-up (Questionnaires and data collection)

Three months after their first visits, patients characterized as “not allergic to the suspected drug” were called and a questionnaire was filled on the phone. The questionnaire included the followings;

Has the patient taken the tested drug after negative provocation test?

If yes, what was (were) the name(s) of the drug and did a reaction occur?

If yes, what happened? (The description of the reaction, and time lapsed between drug use and the reaction)

If no, what were the reasons for not taking a drug?

The patient didn't need the drug

The drug was not prescribed by the doctor

The family was afraid of using the drug

When a patient reported a reaction, he/she was invited to the clinic for a new allergy work-up including detailed clinical history, skin tests and a new provocation test if necessary.

After the latter workup, the patient was classified as true negative (absence of drug allergy) or as false negative (true drug allergy with negative initial work-up). If the patient refused re-evaluation, he/she was classified as false negative.

The local ethical committee approved the entire study design and protocols.

Statistical analysis

Statistical analyses were performed using the SPSS-15 statistical software package (SPSS, Inc., Chicago, IL) for Windows. The definitions were provided as number and percentage for discrete variables and mean and standard deviation for continuous variables. Chi-square test or Fisher's exact test were used to compare groups, where appropriate. Kruskal-Wallis test was conducted to compare continuous variables that are not normally distributed. A p -value of ≤ 0.05 was considered statistically significant. Negative predictive value was calculated.

Results

Throughout the study, 217 provocations were performed on 203 patients. Of these, 163 patients (80.3%) with 175 negative drug provocation tests could be contacted three months after their first visit. Forty patients who had 42 provocation cases could not be reached.

Mean age of the patients was 8.48 ± 4.60 years (4-12.5 year) and (49.1%) were male ($n=80$). The history was compatible with immediate reactions for 75 cases (42.9%). Eight of

these (4.6%) were reportedly anaphylactic reaction, five for antibiotics (3 penicillin, 1 amoxicillin-clavulanate and 1 cefaclor) and three for paracetamol.

Negative oral provocation tests have been performed with antibiotics in 128 (73.4% penicillin and 10.9% cephalosporin), analgesic anti-inflammatory medication in 38 (21.7%) and other drugs in nine (5.1%) of the cases.

The suspected drugs are listed below:

Antibiotics (128 cases): 94 penicillin (49 amoxicillin-clavulanate, 33 penicillin, 2 amoxicillin, 10 ampicillin-sulbactam) 14 cephalosporine (1 cefaclor, 8 cefixime, 1 cefdinir, 1 cefprozil, 3 cefuroxime), 6 trimethoprim-sulfamethoxazole, 1 azithromycin, 12 clarithromycin, 1 isoniazid.

Analgesic-NSAID (38 cases): 15 ibuprofen, 4 acetylsalicylic acid, 16 paracetamol, 1 ketoprofen, 1 metamizol, 1 meloxicam.

Other drugs (9 cases): 5 decongestant, 1 multi-vitamin suspension, 1 lactulose, 1 cholchicine, 1 prednisolone.

One hundred sixty three patients with 175 negative drug provocation tests could be contacted. In 84 (48%) of these cases, the culprit drug was not used after the provocation. In thirty eight (45.2%) of the cases, the drug has not been used because they or their doctor were afraid of a drug reaction and in 46 (54.8%) cases the drug was not needed. Frequency of drug use after provocation and demographic parameters were not different between groups of patients with antibiotics, NSAID/analgesics and other drug reactions (Table 1).

Ninety one (52%) of the 175 tested drugs were used and a reaction was reported in 11 (12%) of these cases (10 patients). Sixty five of the used drugs were antibiotics and reaction occurred in 10 (15.4%) of them. Sixty of the reactions caused by antibiotics were due to beta lactam class and the reaction frequency was 16.6% (10 of 60). Five percent of the used

NSAIDs (1 of 20) were reported to cause a reaction. Cutaneous reactions, specifically urticaria, angioedema and macular/maculopapular exanthema, were the most frequently reported reactions. While six had an immediate reaction, 5 displayed non-immediate reaction. One of the patients who had used amoxicillin-clavulanate was reported to have urticaria, dispnea and gastrointestinal symptoms after 1 hour of drug ingestion and he was designated to have anaphylaxis (Table 2).

Nine of the 11 cases were re-evaluated. Results of re-evaluation are presented in Table 2. Two patients (no:1, no:5), who were initially diagnosed as non-allergic to amoxicillin-clavunate with skin tests and provocation tests, had positive results with intradermal test (amoxicillin-clavunate). One of these patients developed anaphylaxis both before and after the negative challenge. Thus, 2 patients were diagnosed as allergic to the suspected drug after re-evaluation (2 of all 91 drugs, 2.2% and 2 of 60 beta-lactamase group 3.3%).

Negative predictive value

A reaction was reported in 11 of 91 cases. Nine of these cases were re-evaluated and two of them were classified as allergic to the tested drug. Two cases refused re-evaluations and they were considered as allergic to the tested drug. Therefore, the negative predictive value was 95.6% (87out of 91cases). Only one of the patients having NSAID had a reaction but skin test and provocation tests were negative during re-evaluation; thus the negative predictive value was 100% for analgesic-NSAID. Four of the patients having a reaction after antibiotic use were considered to have a real allergic reaction. Two of them had positive intradermal tests during re-evaluation and two had a history compatible with drug allergy but their parents refused to give consent for re-evaluation; NPV was 93.8% (61out of 65 cases) for antibiotics. All antibiotics diagnosed as allergic were beta-lactams and NPV for beta-lactams were calculated as 93.3% (56 out of 60 cases).

Discussion

To our knowledge, our study is the first report evaluating drug use after negative drug provocation tests and reaction rates following re-exposure with beta-lactam antibiotics and other drugs among children. This study included 163 patients with 175 negative drug provocation tests. Ninety one (52%) of the 175 tested drugs were reported to be used and a reaction was reported in 11 (12%) of these. Eight patients (9 cases) were re-evaluated and two of them were diagnosed to have hypersensitivity. The negative predictive value was calculated as 95.6% (87 out of 91 cases). An anaphylactic reaction was diagnosed in one patient after negative challenge.

The negative drug provocation tests have not always been convincing for the physicians and the patients. Although patients were informed that they were not allergic to the suspected drug, only some of them use the tested drug. In studies conducted among adults, only 25.8% of the patients tested with beta-lactam antibiotics and 53.5% of patients tested with NSAIDs were reported to use the tested drug after negative provocation test (9, 10). Ponvert et al (11) reported that 66% of children with negative allergy tests for beta-lactam antibiotics have used the tested drug. Patients with antibiotic reactions reported that they did not need the drug or their physician refused to prescribe the tested drug (9). Patients with NSAID reactions did not use the drug because they or their physicians feared that a new reaction could occur (10). In this study, 48% of our patients with negative oral provocation tests did not use the drug; 54.8% of the patients did not use the drugs because they revealed that there was no need to use the drug and 45.2% of the patients were afraid of a new reaction and/or their physician did not want to prescribe the tested drug.

The reason for a hypersensitivity reaction after a negative provocation test may be the absent crucial co-factors during the test procedure. Thus, a reaction after a negative allergy tests may imply a false negative test or re-sensitization (1,2). Studies on the re-occurrence of a

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reaction with the tested drug after negative drug provocation tests are limited, especially among children. In some of the studies, 4.5-10% of the patients who were only skin tested with beta-lactams during the initial evaluation were reported to have a reaction after re-exposure (12-14). In studies that followed up patients after negative provocation tests with beta-lactams, an IgE mediated reaction was reported in 1.8% (15) and an IgE mediated and/or non-immediate reaction was reported in 7.5 % (11) of children. For adults, 7.6% had a reaction after re-use of beta lactam antibiotics (9) and 3.1% had a reaction after re-use of NSAIDs (10). In another study evaluating patients that have undergone a wide variety of reactions including fix drug eruptions, AGEP, etc., caused by a wide range of drugs (vaccines, chemotherapeutics, radio contrast agents, proton pump inhibitors, etc), 7.5% of the patients reported a reaction after re-exposure (16). In our study, 11 (12%) of the 91 cases were reported to have a reaction: 15.4% caused by antibiotics, 16.6% by betalactams and 5% by NSAID's.

Re-sensitization rates gave a wide range in studies performing re-test procedures after negative allergy testing. Studies reported re-sensitization rates of 0-16% (17-19) in adult and 1-2% in children for betalactam antibiotics (20,21). In the present study, 2 of 8 cases had positive reaction with intradermal test for beta-lactams. One of them had anaphylaxis and other had urticaria after using the drug. In our study, re-sensitization rate of beta-lactams was found to be 3.4% (2 of 58).

Only a limited number of studies reported reactions to the negatively tested drug after re-exposure and performed a second allergy workup including provocation tests. Ponvert et al (11) reported a reaction with beta lactam antibiotics in 7 of 93 children with previous negative provocation tests; oral provocation test was negative in 5 of 6 patients and one had a non-immediate reaction. Other studies were conducted among adults. In their multicenter study,

Demoly et al (9) reported that 9 of 118 adults (7.6%) who were re-exposed to the negatively tested beta-lactam antibiotics had a reaction. They performed provocation test on 4 of these patients and 2 were positive with a NPV of 94.1%. Defrance et al (10) studied adult patients with suspected NSAID allergy and reported that 5 of 260 adults who had taken the negatively tested drug had a suspected hypersensitivity reaction. Three of these patients were re-challenged and only one of them had a positive result and the NPV was reported to be 96.4%. In our study, 11 (10 beta-lactams, 1 paracetamol) (12%) of the 91 cases reported that they had a reaction after using the negatively tested drug. Eight patients (9 cases) were re-evaluated and two patients were diagnosed to have hypersensitivity. The negative predictive value was calculated to be 95.6%. The negative predictive value was 100% for analgesic-NSAID and 93.8% for antibiotics.

To date, no anaphylactic reaction has been reported after re-exposure to the tested drug in patients who have had negative drug provocation test in the literature. However, one of our patients had anaphylaxis after using the negatively tested drug and during re-evaluation, intradermal skin test was positive. The significance of this finding is that although the frequency of re-sensitization after negative oral provocation tests is low, severe allergic reactions can occur.

There are several contributors affecting false negative results other than co-factors and re-sensitization (1,2,6). One of them is too short or too long a time interval of reaction. Time interval of reaction was not too short for any of our patients but some of our patients had long time interval of reaction. Another factor is desensitization by testing. However, since we have performed the provocation in a maximum of 5 doses. Indicating that it is highly unlikely that the study will our patients were not desensitized by provocation test. Finishing the test with a low dose is another factor but we completed the test at high dose close to the cumulative dose.

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It was argued that too short exposure or observation time can also lead to false negative results. The exposure and observation time for DPT lacks consensus. It was suggested that the drug should be given for 2-10 more days at home after DPT when testing non immediate or non-severe reactions. Similar to other authors (8), we have administered the drug for 5 extra days after DPT but lower re-sensitization rates were reported in some studies that administered the drug for a longer duration after the test (19,20). For these work, the study methods and study groups were different than the one we report here. Longer duration of exposure may be related with lower false negative results. However, a multicenter study that had given the drug for only one day and did not continue the drug at home, reported a NPV similar to our results (94.1% vs 93.3%) (9). More studies are needed to determine the most useful duration of drug exposure after DPT.

Conclusion

The NPV of drug provocation tests in children is high and very useful for reliable diagnosis of drug hypersensitivity. However, a negative Drug Provocation Test does not always predict tolerance to the drug in their later stages of life. It must be kept in mind that although very rare, severe allergic reactions can arise even after negative provocation tests.

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Table 1. Frequency of drug use after provocation and demographic parameters of the patients

	Antibiotics	Analgesic-NSAID	Others	<i>p</i>
	128 cases/ 117 patients	38 cases/ 37 patients	9 cases/9 patients	
	n (%)	n (%)	n (%)	
Age (year)	8.23±4.75	9.55±3.97	7.29±4.71	0.203
Min-max	(0.5-14.5)	(0.5-15.0)	(1.5-12.8)	
Gender (male)	61 (52.1)	15 (40.5)	4 (44.4)	0.219
Immediate reaction	49 (38.3)	21 (55.3)	5 (55.6)	0.063
Used drug	65 (50.8)	20 (52.6)	6 (66.7)	0.841
Afraid of reaction	29 (22.6)	9 (23.6)	0	0.976
Did not need drug	34 (26.5)	9 (23.6)	3 (33.3)	
Reaction after use	10 (7.8)	1 (2.6)	0	0.139

Table 2. Characteristics of the cases who had a hypersensitivity reaction with the tested drug after negative challenge

Cases No	1	2	3	4	5	6	7	8	9	10	11
Age (year)	10	12.1	11	4	3	8	7.5	2	6	7.5	7
Gender (M/F)	M	M	F	M	F	M	M	M	F	M	F
Drug	Amox-Clav	Amox-Clav	Amox-Clav	Cefixime	Amox-Clav	Amox-Clav	Paracetamol	Amox-Clav	Amox-Clav	Amoxicillin	Penicilline
First Reaction	Urticaria Angioedema a Vomiting Dispnea	MPE	Urticaria	Urticaria Angioedema	Urticaria	Urticaria Itching	Urticaria Angioedema	MPE Itching	MPE Itching	Urticaria	MPE
First Reaction Type	Anaphylaxis	Immediate	Immediate	Immediate	Non-immediate	Non-immediate	Non-immediate	Non-immediate	Non-immediate	Non-immediate	Non-immediate
Time between history and first evaluation (month)	24	8	6	5	6	2	45	5	6	30	6
Reaction due to the use of tested drug after negative challenge	Urticaria Angioedema a Dyspnea Hypotension	MPE	MPE	Urticaria Angioedema	Urticaria	MPE	Urticaria Angioedema	Urticaria	MPE Itching	Urticaria	Urticaria

Second Reaction Type	Anaphylaxis	Non-immediate	Non-immediate	Immediate	Non-immediate	Non-immediate	Immediate	Immediate	Non-immediate	Immediate	Immediate
Second allergy work-up	Positive ID test with Amox-Clav	Negative	Negative	ND	Positive ID test with Amox-Clav	Negative	Negative	Negative	Negative	Negative	ND
Time between second reaction and second work-up (month)	22	12	13	ND	12	12	12	12	8	6	ND

MPE: Maculopapularexanthema , Amox-Clav: Amoxicillin-Clavunate, ID:intradermal test, ND:not done