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Original Article

The historical factors associated with the true non-steroidal anti-inflammatory drug hypersensitivity in children

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Abstract

Aim: To determine the frequency of true NSAIDs hypersensitivity in children and whether there were any parameters in the history to predict NSAIDs hypersensitivity.

Material and Methods: Children who applied to outpatient clinic with a history suggesting NSAID hypersensitivity were evaluated by a pediatric allergist. The confirmed NSAID hypersensitivity was found by skin test and/or oral provocation tests.

Results: Fifty patients who were admitted with a suspicion of immediate-type reaction to NSAID were included in the study. The median age of the patients was 6 (1-16) years old and 28 (56%) of the patients were male. We performed skin tests with the suspected NSAID in 28 (56%) patients. Of these, 2 had positive results. Provocation tests were performed on 48 patients whose skin tests were negative or skin tests were not available. During the provocation tests, 11 patients (22%) developed reaction. Clinical parameters in history were evaluated by using univariate analysis; the age of child ≥ 6 years old (p=0.006), family history of NSAIDs hypersensitivity (p=0.039), presence of multiple immediate type NSAIDs hypersensitivity in history (p=0.01), emergence of reaction within an hour (p=0.004) were found as significant factors to predicted true NSAID hypersensitivity in history.

Conclusions: The diagnosis of immediate type NSAIDs hypersensitivity was not done by clinical history, oral provocation tests should be done for true diagnosis. However, the age of child ≥ 6 years old, family history of NSAIDs hypersensitivity, presence of multiple immediate type NSAIDs hypersensitivity in history, emergence of reaction within an hour in history can predict the true NSAIDs hypersensitivity

Keywords: NSAID; Children; Oral Provocation Test.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAID) are frequently used on children due to their antipyretic, analgesic and anti-inflammatory effects (1). In allergic reactions developed against drugs in children, NSAID comes the second after beta lactams (2). While the frequency of NSAID hypersensitivity in children proven with provocation tests is 0.3%, aspirin hypersensitivity in children with asthma is around 5% (3,4). Most of the hypersensitivity reactions caused by these drugs are presented to skin in the form of localized urticaria and/or angioedema (5,6).Non-steroidal anti-inflammatory drugs are used in childhood mostly to decrease fever that develops in the course of infections. However, in the course of infections, especially viral infections, skin localized findings such as urticaria and angioedema can be seen. Thus, it is mostly misleading to diagnose hypersensitivity reactions that develop against NSAIDs with history and physical examination findings and skin tests and/or provocation tests are required to make a definitive diagnosis. Studies conducted show that only 14-68% of patients who describe hypersensitivity reaction to NSAIDs have true NSAID hypersensitivity (5,7,8). However, in first and second line health institutions in which there are no allergic clinics, there is no possibility to make oral provocation tests to make definitive diagnosis.

Thus, to diagnose NSAID hypersensitivity with the history taken from the family will cause over diagnosis.

The objective of this study is to find out the factors which predict NSAID hypersensitivity from the history of child

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patients in clinics which do not have the facilities to make oral provocation tests.

MATERIAL and METHODS

Patients who referred to Pediatric Immunology and Allergy Department with a history of early type NSAID hypersensitivity were included in the study. In our Pediatric Immunology and Allergy Department, the diagnosis of NSAID hypersensitivity is made according to "European Network for Drug Allergy" (ENDA) guideline (9). Drug allergy forms prepared according to "European Network for Drug Allergy" guideline include the following information: the patients' demographic characteristics, the responsible NSAID, reaction type and time of occurrence after drug intake, whether the patient developed reaction previously with the same drug, comorbid atopic diseases of the patients and NSAID hypersensitivity history in the parents, etc. From the patient files, the results of skin tests with the responsible drug, if tests were made, and the results of the provocation test conducted for definitive diagnosis and with which NSAID the provocation was made were recorded.

Patients between the ages of 1 and 18 whose files were complete and who described early type NSAID reactions such as urticaria/angioedema, bronchospasm, larynx edema were included in the study. Patients younger than one and those who had late NSAID reaction diagnosis such as fixed drug eruptions, erythema multiform and Stevens-Johnson / Toxic Epidermal Necrolysis complex were excluded from the study.

Diagnostic approach to patients who have defined early type reaction with NSAID

In our clinic, firstly skin prick /intradermal tests are conducted on patients who describe early type reaction with just one NSAID by using the responsible NSAID; if the result is negative, provocation tests are made with the responsible NSAID. On patients who describe more than one NSAID group, oral provocation tests are conducted with acetyl salicylic acid, which is a strong COX-1 inhibitor, in order to find out the reactions that develop due to a possible COX-1 inhibition.

Skin prick and intradermal tests: In our clinic, skin prick and intradermal tests are carry out according to EAACI/GA2LEN guideline (9) for the hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) and conducted with acetaminophen, metamizole sodium and diclofenac sodium, the ampoule forms of which are available. Skin prick test is conducted with acetaminophen (Perfalgane, 10 mg / ml; Bristol-Myers Squibb, Itxassou, French) in 10 mg / ml concentration, with metamizole sodium (Novalgin, 1 g / 2 mi; Sanofi-Aventis, Milano, Italy) in 0.4 mg / ml concentration and with diclofenac sodium (Voltaren, 75 mg/3 ml, Novartis Pharma AG, Basel, Switzerland) in 25 mg/ml concentration. Intradermal tests are conducted in 1/10 dilutions. In the skin test, if the diameter of wheal is ≥3 mm when compared with the negative control and if there is also erythema 15 minutes after the test is conducted, it is accepted as positive.

Oral provocation tests: Oral provocation tests are conducted in hospital and under medical supervision within a period of time when the children have a good health condition. Oral provocation tests carried out according to EAACI/GA2LEN guideline (9) for the hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) and the single blind method was used in our clinic. Antihistaminic should be discontinued 7 days before the test. Prior to oral provocation, all the patients are examined and their vital findings are checked. Vital findings are recorded before each dose increase. All the patients get an IV access and oral provocation tests are started after all anaphylaxis precautions are taken. Oral provocation tests are not conducted on patients who use drugs that can influence the result of oral provocation tests such as antihistaminic and oral steroid; in individuals who have urticaria, uncontrolled asthma, underlying severe cardiac, renal or liver disease or those who have upper respiratory tract infection. During OPT, NSAID is divided into four or five in increasing doses of 45 minutes until the daily maximum dose of the drug is reached. In cases with negative results, the patient is kept under medical observation for two hours. During this process, they are advised to take the child back to the clinic in case of a suspicious situation. If no reaction develops at the end of the follow-up period, the result of the oral provocation test is accepted to be negative. If urticaria, angioedema, laryngeal edema, hypotension, shortness of breath, nasal symptoms, anaphylaxis or other rashes are observed in patients receiving oral provocation test with NSAID during the test or within the first 24 hours after the test, NSAID early type reaction is accepted to be positive. In case of a positive reaction, tests are stopped and the patient is given symptomatic treatment. The patients are kept under observation until the symptoms recover completely.

Inonu University local ethical committee approved the study (approval number: 2015/5-3) and also written informed consent was obtained from all patients and/or their parents if age of patient was ≤ 12 years old.

Data analysis was conducted with SPSS for Windows 15.0 program. Descriptive statistics were given in mean (minimum-maximum) since the continuous variables did not show normal distributions and categorical variables were given as observation number and (%). In the comparison of categorical variables, Pearson's Chi-square or Fisher's exact test Chi-square tests were used. The results were accepted as statistically significant in case of $p<0.05$.

RESULTS

Fifty patients whose file records were complete were included in the study. The median age of the patients was 6 (1-16) and 28 patients (56%) were male. In the history, 8 patients (16%) had early type reaction for two or more NSAID groups. Nine patients (18%) defined ≥ 2 early type reaction history to NSAID. In patients who developed early type reaction to NSAID, ibuprofen (46%) was the drug which caused the most frequent reaction. This drug was followed by acetaminophen (40%); the most frequently

developed reaction was urticaria (66%), followed by pruritus (56%) and angioedema (48%). Forty-four (88%) of the NSAIDs which caused reaction were given orally. Fifty percent of the early type reactions which developed against NSAID occurred within the first one hour. When the comorbid allergic diseases were examined, 7 (14%) patients were found to have asthma, 7 (14%) patients were found to have allergic rhinitis and 8 (16%) patients were found to have food allergy. Seven (14%) of the parents had NSAID hypersensitivity history.

Skin prick/intradermal tests were conducted on 28 of the patients who referred with a history of early type reaction to NSAIDs. Intradermal test was found to be positive in two patients (acetaminophen and metizamole sodium). Oral provocation tests were conducted on 48 patients since the ampoule form of the drug was not found for skin test or since their skin tests had negative results. Early type hypersensitivity to NSAID was proven in 13 (26%) patients (2 as a result of intradermal tests and 11 as a result of oral provocation test). In patients included in the study, the algorithm from history to diagnosis was shown in figure 1.

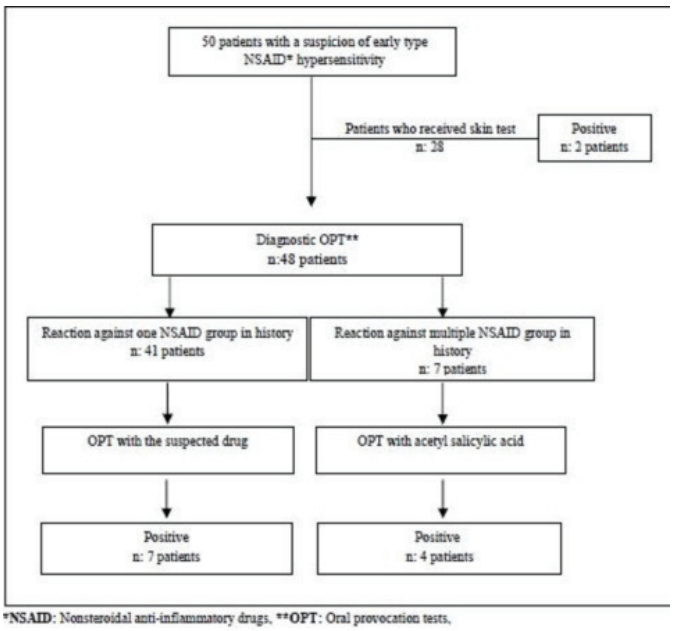

Figure 1. The algorithm of the study from history to diagnosis

When the patient group which was proven to have early type hypersensitivity to NSAID as a result of the oral provocation test or skin prick test was compared with the patient group which was proven not to have hypersensitivity, the factors which predicted early type hypersensitivity to NSAIDs were patients' being older than 6 (p=0.006), NSAID hypersensitivity history in the family (p=0.039), history of early type reaction to more than one NSAID group (p=0.01) and the reaction occurring within the first hour after drug intake (p=0.004). There were no differences between two groups in terms of gender (p=0.174), previous early type reaction history to NSAIDs (p=0.458), comorbid allergic diseases (p=0.720) and the way the drug was given (p=0.221) (table 1)

Table 1. Comparison of groups with (+) and (-) oral provocation test results with NSAID in terms of factors with clinical significance in history

	Oral provocation test with NSAID (+) group n (%)	Oral provocation test with NSAID (-) group n (%)	p-value
Gender, male	4 (36.4)	23 (62.2)	0.174
Age ≥ 6, years	9 (81.9)	12(32.4)	0.006
Previous NSAID hypersensitivity history	4 (36.4)	9 (24.3)	0.458
Parental NSAID hypersensitivity history	4 (36.4)	3 (8.1)	0.039
Comorbid allergic disease	4 (36.4)	11 (29.7)	0.720
Multiple NSAID hypersensitivity history	5 (45.5)	3 (8.1)	0.010
Reaction development within the first hour	10 (90.9)	13 (35.1)	0.004
Drug administration, oral	9 (81.8	35 (94.6)	0.221

DISCUSSION

It is most of the time misleading to make or exclude NSAID diagnosis according to history and/or skin test results. Because COX-1 inhibition rather than IgE mediated hypersensitivity reaction is held responsible for hypersensitivity to NSAID. Thus, skin prick/intradermal tests have negative results in most of the patients and provocation tests are needed for diagnosis. In few studies conducted on children, it was shown that 14-68.2% of the patients who described NSAID hypersensitivity in their history had true NSAID hypersensitivity (5,8). In our study, it was shown that there was true NSAID hypersensitivity in approximately one fourth of the patients who described early type reaction with NSAID. Thus, the diagnosis of NSAID hypersensitivity in children should not be based on history and the results of skin tests, provocation tests should be made in patients who require them and the diagnosis should be made definitive. In our study, the diagnosis was made with the positive results of skin tests only in two patients. In the other patients, the diagnosis was made according to oral provocation test results.

Oral provocation tests are generally needed to make the definitive diagnosis of NSAID hypersensitivity (10,11). However, these tests can be made only in tertiary medical center. Thus, in health institutions in which it is not possible to make oral provocation tests, the factors which predict that the NSAID hypersensitivity described with history is true NSAID hypersensitivity or not. Within this context, few studies conducted so far have researched factors which can predict true NSAID hypersensitivity from clinical history (5,6). In their study conducted on adults, Balance-Lopez et al. (6) reported that being female, the reaction occurring within the first hour after drug intake and history of multiple NSAID hypersensitivity are factors which predicted true NSAID hypersensitivity. Yılmaz et al. conducted a study on children (5) and they reported that NSAID hypersensitivity in the family was

a factor which predicted true NSAID hypersensitivity in children. Univariate analysis was conducted in our study showed that the patient's being older than 6, NSAID hypersensitivity history in the family, history of early type reaction to more than one NSAID group and the reaction occurring within the first hour after drug intake increase the possibility of true early type reaction.

Our study had a few limitations. First, it was not researched whether there was cross reaction with the other NSAIDs in patients who described reaction to only one NSAID. Oral provocation test was made only with the suspected drug. Secondly, it may not be correct to generalize the results since we had a few number of patients. Wider series are needed to do this. Thirdly, if we had sufficient number of patients, conducting logistic regression analysis besides univariate analysis to find out independent risk factors would yield more correct results.

CONCLUSION

As a conclusion, the patient's being older than 6, NSAID hypersensitivity history in the family, history of early type reaction to more than one NSAID group and the reaction occurring within the first hour after drug intake increase the possibility of true early type reaction.

Competing interests: The authors declare that they have no competing interest.

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