ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.019
Asthma Allergy Immunol 2022;20:172-178

RESEARCH ARTICLE

Received: 04.06.2022 • Accepted: 21.06.2022
Online Published: 05.07.2022

Visual Analogue Scale is A Simple and Quick Tool to Evaluate Drug Reaction Severity

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ABSTRACT

Objective: Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) is among the most common drug hypersensitivities. NSAID hypersensitivity (NH) may affect 1-2% of the general population and it is an important public health problem that affects medical prescriptions, practices, and interventions. It also has an influence on the quality of the patients' daily lives.

The primary aim was to understand to what extent a patient feels or perceives the symptoms and complaints during an NH reaction and to grade it with the visual analogue scale (VAS). The secondary aim was to investigate whether there was a difference between the NSAID groups causing the reactions in terms of reaction type and severity.

Materials and Methods: A total of 174 patients with a diagnosis of NH were evaluated in our outpatient allergy clinic. NH reactions were classified as asthma/rhinitis, urticaria/angioedema (u/ae), mixed reaction (asthma/rhinitis and u/ae together), anaphylaxis, and delayed hypersensitivity reaction. Patients were asked to evaluate the severity of each drug reaction by using VAS.

Results: Among 174 patients (115 females, mean age 39.12±12.34 years) the propionic acid group was the leading cause of hypersensitivity reactions. Only 3% of the reactions were reported to be mild and all of those mild reactions were u/ae whereas 92% of the anaphylactic reactions were severe. Most of the reactions were of the u/ae type. The acetic acid group was the leading cause of anaphylactic reactions.

Conclusion: NSAIDs cause reactions of various types with various levels of severity. These reactions are perceived by patients at different severity levels. VAS can provide a simple and quick assessment to evaluate NH reaction severity quantitatively.

Keywords: Drug hypersensitivity reactions, nonsteroidal anti-inflammatory drugs, visual analogue scale

INTRODUCTION

Several classification systems, such as that by Ring and Messmer, are used to classify the severity of allergic reactions. However, these classifications are not practical as they require more than one system evaluation, and the severity of the reaction is determined by the physician (1). To have a more global and coherent vision about the patient, physicians have recognized the importance of the subjective dimension of diseases (2). Patient-reported outcomes have recently been considered and used more often by the scientific community, and these must be evaluated by validated tools exploring the patients' perceptions related to the outcome (3). Specifically developed instruments such as questionnaires, composite scores, and the visual analogue scale (VAS) are necessary to understand how patients perceive and evaluate their disease experience and the therapy effects (3,4). However, there is no universally accepted scale for describing or measuring the severity of a drug hypersensitivity reaction.

VAS is simple and has been used to measure pain, depression, cough severity, disease activity, fatigue, headache, and sleep impairment (5-9). It is easy to administer, not burdensome for the patients, and results in high response rates. Subjects only need to make a mark on a 10 centimeter horizontal line to indicate the degree of the symptoms they are experiencing; the left end of the line is 0 millimeter (mm), which indicates a lack of symptoms, and the right end is 100 mm, which indicates that the symptoms are serious. Intermediate points along the line represent varying degrees of severity of the symptoms (10).

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Nonsteroidal anti-inflammatory drugs (NSAIDs) represent a very large class of widely prescribed drugs comprising more than 30 different compounds from several different chemically unrelated subclasses. NSAID hypersensitivity (NH) is among the most common drug hypersensitivities, and manifests with the whole variety of symptoms involving the skin (rash, urticaria, and angioedema) and respiratory tract (rhinorrhea, nasal congestion, and bronchospasm), and systemic anaphylaxis may develop in some patients (11,12).

NH affects 1-2% of the general population and this issue is an important public health problem with an impact on medical prescriptions, practices and interventions. It influences the quality of the patients' daily lives as much as the increase in health expenditures. Some patients avoid using NSAIDs for a long time because they are worried, while some choose postponing surgical procedures with the fear of developing an allergic reaction, and some patients even experience repeated anaphylactic reactions with repeated exposure to the same drug. Anamnesis and physical examination usually reveal the type of reaction. However, the patients' judgement about the severity of the reactions is also important.

In the present study, the aim was to understand to what extent a patient feels or perceives the symptoms and complaints during a NH reaction and to grade it with VAS. Our secondary aim was to investigate whether there was a difference between the NSAID groups causing the reaction in terms of reaction type and severity.

MATERIALS and METHODS

The study was conducted at the Hacettepe University Hospital, Department of Chest Diseases, Division of Allergy and Clinical Immunology. We included all adult patients with a diagnosis of NH seen in our outpatient clinic between September 2014 and September 2015. Patients who described a reaction to drugs other than NH were not included in the study. Demographic features, type of reactions, and the total number of reactions a patient experienced were recorded. The patients were asked to evaluate the severity of each drug reaction they had experienced by using VAS, ranging from 0 to 10 (0 means no symptoms, 10 means the worst imaginable, serious symptoms; Figure 1). The results of the VAS were categorized into three groups as 1-3: mild, 4-7: moderate, and 8-10: severe. The symptoms of the reaction that was evaluated by VAS were queried. The reaction types were classified as asthma/rhinitis, urticaria/angioedema (u/ae), mixed reaction (asthma/rhinitis and u/ae together), anaphylaxis, and delayed hypersensitivity reaction. NH reaction severity was also classified according to the Ring and Messmer classification by allergy fellows (1).

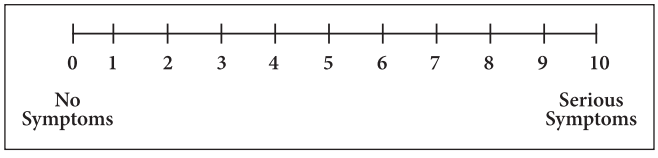

Figure 1. Visual analogue scale.

Patients were classified and defined according to the European Network for Drug Allergy (ENDA) interest group (12). Symptoms that occur beyond 24 hours are considered delayed reactions. This classification includes NSAID-exacerbated cutaneous disease (NECD), NSAID-exacerbated respiratory disease (NERD), NSAID-induced u/ae (NIUA), single NSAID-induced u/ae and/or anaphylaxis (SNIUAA), and single NSAID-induced delayed reactions (SNIDR). The first three groups include cross reactor patients (patients that have hypersensitivity to all potent COX enzyme inhibitors), while the last two are selective reactor patients (patients that have hypersensitivity to a single NSAID.

This study was approved by the ethical committee of the Hacettepe University, and written informed consent was received from all patients (GO 14/494-19).

Statistical Analysis

All statistical analyses were performed using SPSS for Windows, version 21.0 (IBM Corp., Armonk, N.Y., USA). The results for continuous variables were expressed as mean±SD. The comparisons of some variables in selected sub-groups were carried out by the Binomial test. A p value <0.05 was considered statistically significant.

RESULTS

During the study period, 174 patients presented to our clinic with the diagnosis of NH. The mean age of the patients was 39.12±12.34 years. One hundred fifteen (66.1%) of the patients were female. In total, 105 (60%) patients had at least one accompanying atopic disease (Table I).

A total of 786 reactions were experienced by 174 patients. Eight patients (4.6%) had gastrointestinal symptoms accompanying other reactions. Only 3% of the reactions were reported to be mild (VAS:1-3) and all of those mild reactions were of the u/ae type whereas, 92% of the anaphylactic reactions were severe (VAS:8-10) (Table II). According to the Ring and Messmer classification, most of the reactions (59.4%) were classified as grade I (generalized skin symptoms) and only 4.8% of the reactions were grade III (anaphylactic shock, loss of consciousness) (Table III). Thirty-five patients had a single reaction while 139 patients had more than one reaction. VAS scores were not different when patients with single and multiple reactions, and male and female patients were compared (data not shown).

Almost half of the reactions were experienced with the use of propionic acid derivatives (37.91%) and none of them were mild (VAS>3). While most of the reactions caused by propionic acid derivatives were severe (66.8%), reactions caused by salicylic acid derivatives, pyrazolones, paracetamol, and acetic acid derivatives were mostly moderate or severe (Table IV). Reactions were less frequent with oxicams, sulfonanilides, and fenamic acid derivatives. Five patients experienced 7 reactions with oxicams and none of them were mild (VAS>3). Reactions to sulfonanilides and fenamic acid derivatives were detected in one patient from each group, and both patients described the severity of their reaction as moderate (VAS: 4-7) (Table IV).

Table I. Demographic features and clinical characteristics of the patients

Female, n (%)	115 (66.1)
Age (mean±SD)	39.12±12.34
Ever smokers, n (%)	92 (53.2)
Antibiotic allergy, n (%)	34 (19.5)
Accompanying diseases, n (%)	
Asthma	64 (36.8)
Chronic urticaria	28 (16.1)
Persistent rhinitis	73 (42)
Nasal polyposis	34 (19.5)
Distribution of patients according to the ENDA classification, n (%)	
NSAID-induced u/ae (NIUA)	61 (35.1)
NSAID-exacerbated respiratory disease (NERD)	47 (27)
Single NSAID-induced u/ae and/or anaphylaxis (SNIUAA)	37 (21.3)
NSAID-exacerbated cutaneous disease (NECD)	24 (13.8)
Single NSAID-induced delayed reactions (SNIDR)	3 (1.7)
Unclassified #	2 (1.1)
Age of onset of NH* (mean±SD)	34.17±12.54
NH* duration [months, median (min-max)]	36 (1-432)

ENDA: The European Network for Drug Allergy, **#:** Patients without accompanying disease but with a respiratory type NH reaction, ***NH:** Nonsteroidal anti-inflammatory drug hypersensitivity

Table II. Assessment of reactions by VAS

Reaction types	Severe (VAS: 8-10) n (%)	Moderate (VAS: 4-7) n (%)	Mild (VAS: 1-3) n (%)	Total n
u/ae*	232 (50)	217 (47)	14 (3)	463
asthma/rhinitis	126 (62)	78 (38)	-	204
anaphylaxis	35 (92)	3 (8)	-	38
mixed reaction	48 (62)	29 (38)	-	77
delayed reaction	2 (50)	2 (50)	-	4

***u/ae:** urticaria/angioedema.

Among the 38 anaphylactic reactions, 22 (57.89%) were caused by acetic acid derivatives. The prevalence of a delayed type reaction (1 Stevens-Johnson syndrome, 1 exanthema, 2 fixed drug eruption) was 0.5% (n=4), and the most common reaction type among all drug groups (except fenamic acid derivatives) was u/ae at 58.9% (n=463) (Table V).

DISCUSSION

Although VAS is a simple tool for measuring symptom perception quantitatively, no studies have used it to assess the degree of subjective NH reactions. The present study was the first to evaluate the severity of NH reaction by using VAS.

Table III. Distribution of the severity of drug reactions by VAS and the Ring and Messmer classification.

VAS	n (%)	Ring and Messmer classification	n (%)
mild **VAS: 1-3**	14 (1.8)	**Grade I** (generalized skin symptoms)	467 (59.4)
moderate **VAS: 4-7**	329 (41.8)	**Grade II** (mild to moderate pulmonary, cardiovascular, and/or gastrointestinal symptoms)	281 (35.8)
severe **VAS: 8-10**	443 (56.4)	**Grade III** (anaphylactic shock, loss of consciousness)	38 (4.8)

Table IV. Distribution of NSAID groups and severity of drug reactions according to VAS

NSAID groups	n (%)	Severe (VAS:8-10) n (%)	Moderate (VAS:4-7) n (%)	Mild (VAS:1-3) n (%)	p value
Propionic acid derivatives	298 (37.9)	199 (66.8)	99 (33.2)	-	**<0.0001**
Salicylic acid derivatives	131 (16.7)	69 (52.7)	60 (45.8)	2 (1.5)	0.481
Pyrazolones	120 (15.3)	55 (45.8)	64 (53.3)	1 (0.8)	0.463
Paracetamol	115 (14.6)	49 (42.6)	56 (48.7)	10 (8.7)	0.558
Acetic acid derivatives	112 (14.2)	66 (58.9)	45 (40.2)	1 (0.9)	0.057
Oxicams	7 (0.9)	5 (71.4)	2 (28.6)	-	
Fenamic acid derivatives	2 (0.3)	-	2 (100)	-	
Sulfonanilides	1 (0.1)	-	1 (100)	-	

n: Number of reactions, **p:** For the comparison between drug reactions with severe or moderate severity

Table V. Distribution of NSAID groups and reaction types

NSAID groups	n (%)	u/ae* n (%)	Asthma/rhinitis n (%)	Anaphylaxis n (%)	Mixed n (%)	Delayed reaction n (%)
Propionic acid derivatives	298 (37.9)	173 (58.1)	98 (32.9)	5 (1.7)	21 (7)	1 (0.3)
Salicylic acid derivatives	131 (16.7)	83 (63.4)	33 (25.2)	-	15 (11.5)	-
Pyrazolones	120 (15.3)	64 (53.3)	37 (30.8)	1 (0.8)	18 (15)	-
Paracetamol	115 (14.6)	72 (62.6)	21 (18.3)	9 (7.8)	12 (10.4)	1 (0.9)
Acetic acid derivatives	112 (14.2)	65(58)	15 (13.4)	22 (19.6)	10 (8.9)	-
Oxicams	7 (0.9)	5 (71.4)	-	1 (14.3)	1 (14.3)	-
Fenamic acid derivatives	2 (0.3)	-	-	-	-	2 (100)
Sulfonanilides	1 (0.1)	1 (100)	-	-	-	-
Total number of reactions	786 (100)	463 (58.9)	204 (26)	38 (4.8)	77 (9.8)	4 (0.5)

n: Number of reactions ***u/ae:** Urticaria/angioedema

A growing number of clinical trials for allergic diseases have assessed patient-reported outcomes and most of them are about asthma (13-17). A specific tool measuring health-related quality of life (HRQoL) in patients with drug hypersensitivity was developed by an Italian group. (DrHy-Q: Drug Hypersensitivity Quality of Life Questionnaire) (4). However, this questionnaire does not evaluate drug reaction severity. In this respect, VAS can be a simple, easy, and quick alternative measure to evaluate the severity of NH reactions.

We may assume that a patient with more than one reaction can make a more rational self evaluation. However, in our study population the VAS scores were similar among those with single or multiple drug reactions. Although our study population with a single drug reaction is small, we think that VAS is a consistent measure to evaluate reaction severity among patients with single or multiple drug reactions.

Consistent with the existing literature, most of the reactions were of the u/ae type in our study population (58.9%). In two previous studies, the prevalence of a u/ae type reaction was reported to be 56% and 51%, respectively (18,19).

When the VAS and Ring and Messmer classification results were compared, most of the reactions were reported as severe (56.4%) with VAS, while most of the reactions (59.4%) were classified as mild (grade I) with the Ring and Messmer classification. Accompanying urticaria with ae, the presence of ae reactions in the face and near the throat, and generalized and prolonged u/ae reactions may have caused the patients to perceive their reactions as severe.

In the present study, most of the reactions and most of the severe ones were caused by propionic acid derivatives, and more than two thirds of the mild reactions were caused by paracetamol. As a consequence of the chemical features of the drug, different groups of NSAIDs have variable COX-1 and COX-2 selectivity (20-23). Propionic acid derivatives (e.g., ibuprofen and ketoprofen) inhibit COX-1 and COX-2 with comparable potency, while nimesulide and meloxicam have intermediate COX-2 selectivity (24). However, it is commonly stated that paracetamol is at best a weak inhibitor of COX-1 and COX-2 (25). As weak COX-1 inhibitors, paracetamol, oxicams (meloxicam, piroxicam), and sulfonanilides (nimesulide) cause reactions less frequently and they are the preferred alternative drugs to be tested in patients with cross-reactive NH.

Drugs most commonly implicated in single NSAID anaphylaxis include NSAIDs of the pyrazolone class, diclofenac, and ibuprofen (26,27). In the present study, most of the anaphylactic reactions were caused by acetic acid derivatives (e.g., diclofenac).

In the present study, it was found out that almost half of the reactions were caused by propionic acid derivatives followed by salicylic acid derivatives. It was reported that among 149 patients with NH, the clinical history revealed acetylsalicylic acid and ibuprofen (propionic acid derivative) to be the most common cause of a reaction (40%, and 32%, respectively), and in that study u/ae was the most common reaction type (51%) (19). Demir et al. noted that the leading cause of NH reactions was metamizole (30.5%) followed by aspirin (30.2%) (28). This difference in prevalance rates may be due to differences in prescription and consumption patterns. In a previous study, high amounts of cumulative analgesic consumption was reported among patients with NH (29). We recommend that drugs including NSAIDs should not be used unnecessarily to prevent sensitization.

A limitation of the present study was that we did not confirm each drug reaction with an oral provocation test. In patients who experience NH reactions with different NSAID groups (cross-reactive), we performed an oral provocation test with alternative drugs. Another limitation of the study was that we were unable to determine the exact time between the reaction and visit because it was conducted retrospectively. Nevertheless, our findings provide important information about the reaction the patient experienced and we believe that a higher VAS result will alert the treating physician.

In conclusion, NSAIDs cause reactions of various types with various levels of severity. These reactions are perceived by patients at different severity levels. Most of the patients perceived reactions as moderate/severe. There was no significant difference in the levels of perception between patients who experienced one or more than one reaction. Our study has shown that hypersensitivity reactions caused by different NSAID groups may generate different perceptions at the patient level. VAS might be beneficial for assessing the NH reaction severity quantitatively, providing a simple and quick evaluation that does not require excessive training.

Funding

No financial support was provided.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Authorship Contributions

Concept: **A. Fuat Kalyoncu,** Design: **Ebru Özdemir, Ebru Damadoğlu, Gül Karakaya, A. Fuat Kalyoncu,** Data collection or processing: **Ebru Özdemir, Esra Karabiber,** Analysis or Interpretation: **Ebru Özdemir, Ebru Damadoğlu,** Literature search: **Ebru Özdemir, Esra Karabiber,** Writing: **Ebru Özdemir, Ebru Damadoğlu,** Approval: **Ebru Damadoğlu, Gül Karakaya, A. Fuat Kalyoncu.**

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