TOLERABILITY OF NIMESULIDE IN PATIENTS WITH HISTORIES OF ADVERSE REACTIONS TO ACETYLSALICYLIC ACID AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

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ABSTRACT

Objective: *Analgesic and anti-inflammatory treatment in patients with a positive history of ASA (acetyl salicylic acid) /NSAID (non-steroidal anti-inflammatory drugs) intolerance is a significant problem in clinical practice. Therefore, there is a need to identify an alternative drug that is safe and reliable. Our aim was to determine the safety of nimesulide, a preferential COX-2 inhibitor.*

Material and Method: *A single blind, placebo-controlled oral challenge procedure was applied to 95 patients (37 male, 58 female; with a mean age of 40.19±13.94 years) who had suffered from adverse reactions to ASA/NSAIDs.*

Results: *According to patient histories, the majority of intolerance reactions were due to NSAIDs, and isolated cutaneous symptoms were the most common presenting symptom in 43 subjects (45.2%). While isolated respiratory symptoms were experienced in only 6 (6.3%) patients. Nimesulide was well tolerated in 90 out of 95 patients (95.2%) and only 5 of the 95 patients (4.8%) presented an adverse reaction, which was a slight urticaria. Two of the five patients were suffering from chronic urticaria, one patient had asthma and rhinosinusitis, one was atopic and one had a history of allergic reaction to a ß-lactam.*

Conclusion: *Nimesulide can be a good option for NSAID-intolerant patients: it should first be tested in an allergy unit. However, the results of the current study need further clinical studies to evaluate the effects of higher doses or the prolonged use of nimesulide and whether nimesulide could be used in patients with asthma and with a history of chronic urticaria.*

Keywords: *Aspirin, drug allergy, nimesulide* ***Nobel Med 2014; 10(3): 81-87***

ASA/NSAİD İNTOLERANSI OLAN HASTALARDA NİMESULİDİN TOLERABİLİTESİ

ÖZET

Amaç: ASA (Acetyl salicylic acid)/NSAİD (Nonsteroidal anti-inflammatory drug) intoleransı olan hastalarda analjezik ve antiinflamatuar tedavi seçimi klinik pratikte önemli bir sorun oluşturmaktadır. Bu nedenle güvenilir ve uygun bir alternatif ilaç seçimine ihtiyaç vardır. Çalışmamızda ASA/NSAİD intoleransı olan hastalarda kısmi selektif COX-2 inhibitörü olan nimesulidin tolerabilitesini değerlendirmeyi amaçladık.

Materyal ve Metod: ASA/NSAİDs alerji öyküsü olan 95 hastaya (37 erkek, 58 bayan, yaş ortalaması: 40,19±13,94) tek kör plasebo kontrollü oral provakasyon uygulandı.

Bulgular: Hastaların öyküsüne bakıldığında intoleransa neden olan ilaç çoğunlukla NSAİD kullanımıydı ve alerjik reaksiyonların çoğunluğunu cilt bulguları (43 hasta; %45,2) oluştururken, yalnız 6 hastada (%6,3) solunum semptomu öyküsü mevcuttu. 95 hastanın 90 tanesi (%95,2) nimesulidi tolere ederken yalnızca 5 hastada provakasyon sırasında hafif ürtiker gelişti. Nimesulidi tolere edemeyen 5 hastanın 2 tanesinde kronik ürtiker, 1 tanesinde astım ve rhinosinüzit, 1 tanesinde atopi, 1 tanesinde de ß-laktam antibiyotik alerji öyküsü mevcuttu.

Sonuç: NSAİD intoleransı olan hastalarda nimesulid alerji ünitesinde alternatif ilaç seçiminde öncelikli olarak test edilebilir. Ancak nimesulidin uzun süreli ve yüksek doz kullanımı ve kronik ürtiker, astım öyküsü olan hastalarda kullanıp kullanılmayacağına dair çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Aspirin, ilaç alerjisi, nimesulid

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INTRODUCTION

NSAIDs (non-steroidal anti-inflammatory drugs) are widely prescribed drugs for the treatment of pain, fever, arthritis or other inflammatory diseases because of their high safety profile.[1] The use of NSAIDs may be accompanied by intolerance reactions of the skin (urticaria, angio-oedema, pruritus, flush), respiratory symptoms (dyspnea, rhinitis) or eventually even by anaphylactoid reactions.[2,3] (The term 'anaphylactoid,' is changed to 'non-allergic anaphylaxis' which is mediated by a non-immunologic reaction).[4]

The pathogenetic mechanisms underlying hypersensitivity reactions to aspirin and other common nonsteroidal anti-inflammatory drugs (NSAIDs) are not yet fully understood. However, inhibition of the cyclooxygenase (COX) pathway seems to be the most accepted explanation that is responsible for both; the efficacy and side effects of NSAIDs.[5-7] There are at least two isoforms of COX: COX-1 is constitutively expressed in most tissues and in blood platelets and is responsible for the production of prostaglandins (PG), whereas COX-2 is expressed only in response to proinflammatory agents in epithelial cells, fibroblasts, eosinophils, monocytes and macrophages.[8] COX-2 specific inhibitors exert their effect without interfering with the homeostatic functions mediated by COX-1 derived prostanoids, resulting in better tolerance. Moreover, NSAIDs inhibit COX-2 but not COX-1 can be a safe alternative in aspirin-intolerant patients. In recent years, the two preferential COX-2 inhibitors, nimesulide and meloxicam, have been found to be well tolerated at moderate doses in ASA (acetyl salicylic acid)/NSAIDs-intolerant patients.[9,10]

Nimesulide is preferential for COX-2 and displays additional effects on inflammatory mediator synthesis and release. Nimesulide is capable of modulating rather than blocking the inflammatory process by means of scavenging the free radicals important in the determination of tissue damage and thus producing rapid recovery of the important functions of the respiratory mucosa.[11,12] Furthermore, nimesulide has been well tolerated and shown to modulate the skin response to histamine and codeine and to have a synergistic effect on antihistaminic activity with cetrizine.[13,14] This study was performed to evaluate the tolerability of nimesulide in subjects with reliable histories of adverse reactions to ASA/NSAIDs.

MATERIAL AND METHOD

Patient selection

The study was conducted among patients admitted to our outpatient clinic who gave a reliable history of urticaria/angioedema, naso-ocular symptoms, bronchospasm, and/or non-allergic anaphylactic reaction within 2 hours after ingesting a prescribed ASA and/or NSAIDs and/or paracetamol.[15] Before oral challange procedure some drugs (β_2-agonists, ipratropium bromide, tiotropium bromide, theophilline, cromolyn sodium, antihistaminics, nedocromil sodium, leukotriene modifiers, corticosteroids) were withdrawn as in →

recommended EAACI/GA2LEN guideline.[16] None of the patients had episodes of urticaria or angioedema in the week before the challenge. Asthmatic patients were eligible for the study if their asthma had been stable for at least two weeks, and having an FEV1 70% over the predicted value. Patients who were pregnant or breast feeding, who had contraindications to eventual use of epinephrine and psychosomatic disorders were not included in the study. Informed consent was obtained from all patients and the ethical approval from Selçuk University Meram Faculty of Medicine Review Board.

Oral Challenge Tests

In the assessment of nimesulide tolerability, all patients were subjected to an oral drug challenge. The drug challenge was performed by an experienced allergist with emergency equipment available in a clinical setting. The study was designed as a single-blind and placebo controlled oral drug challenge. On the first day, 1/4, 2/4 divided doses and a full dose of placebo and on the second day 25 mg, 50 mg, 100 mg of the active drug nimesulide were given at 60-min intervals. During the challenge procedure, blood pressure and FEV1 values, as well as the skin, ocular, nasal, and bronchial reactions, were monitored every hour after each placebo or active drug dose was given. Patients were followed up to 24 hr to detect any delayed reaction.

The oral challenge test was accepted as positive if one of the following symptoms existed: conjunctival reaction; upper and lower respiratory tract reactions such as sneezing, rhinorrhea, nasal blockage, dyspnea, wheezing, and cough with a 20% decrease in FEV1; cutaneous reactions such as erythema, pruritus with erythema, urticaria/angioedema. We defined anaphylaxis as suggested by the change in terminology proposed by Simons which is a severe, life threatening generalized or systemic hypersensitivity reaction.[17]

Evaluation of Atopy

Atopy was defined as a positive skin prick test (SPT) to at least one of the aeroallergens. Glycerinate extracts (Allergopharma) of the following allergenic sources were used in SPTs: Dermatophagides pteronyssinus (der p); Dermatophagoides farinae (der f); grass, tree, weed pollens; cat; dog; Alternaria; and Cladosporium antigens. Positive histamine and negative (saline solution) controls were included. The puncture method with a 1 mm tip disposable lancet was used and a mean wheal diameter of 3 mm or greater than the control solution was considered positive.

Statistical Analysis

Numerical results were expressed as mean ± standard deviation (SD). Nominal variables were expressed as percentage of the patients. A p value of less than 0.05 was considered significant. The Statistical Package for Social Sciences (SPSS) for Windows version 10.0 (Chicago, IL, USA) was used to analyze the data.

Table 1: Characteristic features of the patients

Sex (female/male) n (%)	58/37 (61.1/38.9%)
Age (years) (Mean±SD)	40.19±13.94
Baseline FEV1 (L) (Mean±SD)	2.90±0.77
Rate of positive skin prick test	30/95 (31.6%)
Implicated drugs, n (%)	
ASA	3 (3.2%)
NSAIDs	40 (42.1%)
Paracetamol	16 (16.8%)
ASA + NSAIDs	20 (21.1%)
ASA + paracetamol	6 (6.3%)
NSAIDs + paracetamol	6 (6.3%)
ASA + paracetamol + NSAIDs	4 (4.2%)
Single analgesic intolerance n (%)	59 (62.1%)
Multiple analgesic intolerance n (%)	36 (37.9%)

RESULTS

A-Patient Characteristics

The study comprised 95 patients: 38.9% men and 61.1% women with a mean age of 40.19 years. Demographic data and detailed clinical presentations of ASA/NSAID intolerance of the study group are given in Table 1. A patient reacting to only ASA or any one of NSAIDs or only paracetamol was accepted as single-analgesic intolerant. The combination of at least two of these groups was defined as multiple analgesic intolerant. A total of 36 (37.9%) subjects described intolerance reactions to multiple analgesics.

SPT analysis was performed on 95 subjects and atopy ratio was 31.6% in the study group. This ratio was no different from that of the general adult population of Turkey (31.6% vs 25%, p>0.05).[18] Mite allergens were the most common cause of allergy with a ratio of 16.8% (n=16).

According to patient histories, the majority of intolerance reactions were due to NSAIDs, and isolated cutaneous symptoms were the most common presenting symptom in 43 subjects (45.2%). While isolated respiratory symptoms were experienced in only 6 (6.3%) patients, 40 (41.05%) patients experienced cutaneous and respiratory symptoms. Gastrointestinal symptoms were experienced with multiple organ manifestations. We defined anaphylaxis as suggested by the change in terminology proposed by Simons, so the rate of non allergic anaphylaxis due to ASA/NSAIDs was almost →

Table 2: Type of reactions according to the specific drugs

Specific drug	Type of reaction					
	Cutaneous			Respiratory		C+R
	Urticaria	Angioedema	U+A	Dyspnea	Rc/ D+Rc	
ASA	0	0	1	0	0	2
NSAIDs	11	4	8	0	0	14
Paracetamol	3	2	2	2	0	7
ASA + NSAIDs	4	1	3	1	0	10
ASA + paracetamol	1	0	0	1	0	4
NSAIDs + paracetamol	1	1	0	0	2	1
ASA + paracetamol+ NSAIDs	1	0	0	0	0	2
TOTAL	21 (22.1%)	8 (8.4%)	14 (14.7%)	4 (4.2%)	2 (2.1%)	40 (42.1%)

U: Urticaria, **A:** Angioedema, **D:** Dyspnea, **Rc:** Rhinitis and/or conjunctivitis, **C:** Cutaneus, **R:** Respiratory
Note: 6 patients have gastrointestinal symptoms with multiple organ manifestations.

Table 3: Type of reactions according to co-morbid disorders

Co-morbid disorders (n=37)	Cutaneous	Dyspnea	C+D	C+D+Rc
Chronic urticaria (n=7)	5	0	1	1
Asthma (n=16)	7	3	4	2
Chronic rhinosinusitis (n=6)	3	0	0	3
Asthma + rhinosinusitis (n=8)	3	1	3	1

D: Dyspnea, **Rc:** Rhinitis and/or conjunctivitis, **C:** Cutaneus

equal to the rate of the patients with cutaneous and respiratory and/or gastrointestinal symptoms. The types of reactions according to the specific drugs with single and multiple organ manifestations are given in Tables 2.

Among these patients, 16 patients (16.8%) exhibited clinical evidence of asthma only, 6 patients (6.3%) had rhinosinusitis only, 8 patients (8.4%) had rhinosinusitis and asthma together and 7 patients (7.3%) were suffering from chronic urticaria. 58 patients did not have any co-morbid disorders. Of the 24 asthmatic patients, 14 (58.3%) developed mostly respiratory reactions, including upper and lower respiratory tract (Table 3). All patients with chronic urticaria reported a cutaneous reaction (100%). Furthermore, 36 (37.8%) patients reported adverse reactions after the intake of other drugs: 31 with antimicrobials (23 β-lactams, 2 macrolides, 4 quinolones, 2 metronidazoles), 3 with muscle relaxants.

B-Nimesulide Tolerability

Nimesulide was well tolerated by 90 out of 95 patients (95.2%) and only 5 of the 95 patients (4.8%) presented an adverse reaction, which was a slight urticaria in all cases. The urticaria was an immediate reaction seen after the cumulative dose of 50 to 100 mg. All subjects had a FEV1 of greater than 80% of the predicted value. None of the patients experienced any reaction to the placebo challenge. In two of the five patients suffering from chronic urticaria, one patient had asthma and rhinosinusitis. 23 ASA/NSAID-intolerant asthmatic patients tolerated nimesulide well, and only 1 patient developed urticaria after 100 mg of the drug. Of the five patients that reacted to nimesulide, one had a positive SPT reaction and four were nonatopic. Five nimesulide intolerant subjects tolerated oral challenges with meloxicam.

Detailed information about these five reactive patients is given in Table 4.

DISCUSSION

Analgesic and anti-inflammatory treatment in patients with a positive case history of NSAID intolerance is a significant problem in clinical practice. Oral challenge procedures are the only way to confirm ASA/NSAID-intolerance.[19] However, as we did not perform the oral challenge with the implicated drug due to the convincing history of patients and ethical limitations. Moreover, a significant correlation between history of intolerance and the results of oral challenge in aspirin-intolerant patients has previously been demonstrated.[20] In keeping with this suggestion, we performed the oral challenge test with nimesulide. However, since we did not challenge the patients with aspirin or other NSAIDS in order to exclude cross-reactive type of hypersensitivity and did not corroborate the diagnosis of propyphenazone diagnosis with the combination of skin prick tests and intradermal skin tests, we could not use the classification of the review EAACI/ENDA and GA2LEN/HANNA which was not yet published when we started the study; instead we based our study on the classification of Bavbek et al.[15,21] So these patients with single drug allergy formed the majority in our classification. N:59 (62.1%): another reason for this may be that our patients may have avoided other NSAIDs after experiencing drug reaction once.

Considering the risk factors in ASA/NSAIDs intolerance, asthmatic patients particularly those with nasal polyps and chronic sinusitis, are at risk →

Table 4: Findings of the patients demonstrating reaction to nimesulide

NO	AGE (YEARS)	SEX	ASA/NSAIDS	REACTION TYPE	COMORBID DISORDER	PRICK	NIMESULID DOSE (mg)
1	31	M	Naproksen	U/A/Rc	-	Negative	100
2	33	M	Naproksen, parasetemol	U/A	-	D. pteronissinus D. faine	100
3	52	F	ASA, parasetemol, flurbiprofen	U/D/Rc	Asthma + rhinosinusitis + nasal polip	Negative	100
4	22	M	Metamizol, parasetemol, ibuprofen	U/A/D	Chronic urticaria	Negative	50
5	21	F	Parasetemol, flurbiprofen	U/A	Chronic urticaria	Negative	100

U: Urticaria, **A:** Angioedema, **D:** Dyspnea, **Rc:** Rhinitis and/or conjunctivitis

of developing respiratory reactions, and patients with chronic urticaria/angioedema experience urticaria/angioedema-type skin reactions following ingestion of ASA/NSAIDs.[22] In contrast to previous data, in the current study, all patients with chronic urticaria reported cutaneous reaction but the rate was not different from that in asthmatic patients (100% vs. 83.3%, p>0.05). The majority of patients with asthma experienced respiratory reactions but respiratory reactions were experienced in 2 patients with chronic urticaria (58.3% vs. 28.6%, p>0.05). In a study to detect risk factors for intolerance to alternative drugs such as acetaminophen and nimesulide, a history of skin reactions induced by ASA/NSAIDs but without a history of chronic urticaria represented a risk factor for urticaria/angioedema after the ingestion of the alternative study drugs.[23] However, in the study conducted by Quarantino et al. all patients who failed to tolerate nimesulide had histories of chronic urticaria.[24] In our nimesulide intolerant group, two patients had chronic urticaria and all of the five patients had a history of skin reactions induced by ASA/NSAIDs. Although we could not confirm NSAID reactions in the history, it was thought that of patients who had nimesulide intolerance according to the review EAACI/ENDA and GA2LEN/HANNA; 2 with chronic urticary history were NSAIDs-exacerbated urticaria/angioedema, one with asthma, rhinosinusitis and nasal polyp history was NSAID-induced rhinitis/asthma, and the other two patients who did not have chronic skin and/or respiratory disorders history and reacted to NSAIDs with different chemical structures, was multible NSAID induced allergy.[21]

In the present study, 95 patients with a positive case history of NSAID intolerance were investigated, 90 patients successfully completed the challenge protocol without any adverse reactions, and only 5 patients (4.8%) had an immediate adverse reaction to nimesulide which was a slight urticaria. Similar results were reported by Andri et al., with a ratio of 3.3% having adverse reactions to nimesulide. Nimesulide was also found to be the safest available drug with no adverse reactions in 30 patients intolerant to NSAIDs by Ispano et al.[9,20] In another study with nimesulide, 5 (8.3%) of a total of 60 patients developed adverse reactions following ingestion of the drug.[25] Confirming these findings, in this study nimesulide showed good tolerability.

In the last decade, the two selective COX-2 inhibitors, nimesulide and meloxicam, have been the subject of several studies. In a recent study conducted by Senna et al. nimesulide and meloxicam were challenged and they demonstrated that the two tested drugs are safe and reliable alternatives for ASA/NSAID-intolerant patients.[26] However, whereas nimesulide intolerant patients can sometimes tolerate meloxicam, the reverse is unlikely. In this study, the oral challenge test was performed only with nimesulide. The five nimesulide intolerant subjects had tolerated oral challenges with meloxicam.

For almost a decade now, very selective COX-2 inhibitors-rofecoxib, celecoxib, and valdecoxib-have been marketed in many countries. Studies have shown that rofecoxib is at least 1000-fold more selective for COX-2.[27,28] In a recent study conducted by Bavbek et al. tolerances to nimesulide, meloxicam, and rofecoxib were assessed by single-blind placebo controlled oral challenges.[29] They indicated that rofecoxib seems to have the most favorable tolerability. The study made by Andri et al. to determine the clinical tolerance of celecoxib proves its safety too.[30] However, some studies have indicated possible adverse effects of coxibs on the cardiovascular system, especially in patients with osteoarthritis requiring a prolonged use of these drugs.[31-32]

It is also important to emphasize that a prolonged use of all NSAIDs is not recommended in patients suffering from NSAID hypersensitivity because of the higher risk of inducing cutaneous/respiratory reactions after the intake of previously well-tolerated anti-inflammatory agents. In the current study, patients who tolerated oral challenges with nimesulide were not followed-up. However in a previous study, where follow-up interviews were conducted with 248 NSAID-intolerant subjects who had tolerated oral challenges with nimesulide and/or acetaminophen 1 to 3 years earlier, nimesulide was tolerated by →

115/122 (94.2%) of the patients who had tried it and acetaminophen by 71/75 (94.6%). Intolerance was unrelated to the nature of the condition treated or the number of doses administered.[24]

Although nimesulide, with tolerance percentages between 71% and 100%, is one of the most widely studied drugs in ASA sensitive patients we have to consider that only a few of these studies have included patients with asthma attacks after NSAID-intake.[20] In a double blind placebo controlled study, efficacy and tolerability in acute bronchial asthma were assesed by Gulsan et al.[33] No side effects were reported and all the outcome measures showed a significant improvement over time in the nimesulide group indicating the efficacy of nimesulide in patients with moderate to severe acute exacerbation of bronchial asthma. Therefore, it was thought that nimesulide could be administered to asthmatic patients whenever there is a need for such therapy. In another study, 100 mg of oral nimesulide was given without any adverse effects to 20 ASA-intolerant patients with asthma, but a mild asthmatic reaction was observed in 3 patients after 400 mg of oral nimesulide.[22] In the current study, 23 ASA/NSAID-intolerant asthmatic patients tolerated nimesulide well. Only 1 patient developed urticaria after 100 mg of the drug.

Recent studies have demonstrated an increased prevalence of atopy in patients with ASA/NSAID intolerance.[34] However, in this trial the atopy rate of the whole group was no different from that of the general adult population in Turkey (31.6% vs 25%, p>0.05), Furthermore, it was shown that atopy and reaction to antimicrobial drugs increase the likelihood of intolerance of nimesulide and acetaminophen.[23,35] In the current study, the presence of atopy and reaction to antimicrobial drugs did not seem to influence the reactions to nimesulide, since only one case from a total of 5 patients reacting to nimesulide was atopic and one had a history of allergic reaction to an antimicrobial drug, which was a β-lactam.

The results of this study show that nimesulide can be a good option for NSAID-intolerant patients: it was safe for these patients and is easier to purchase than coxibs, although it should first be tested in an allergy unit before it is prescribed for an individual. However, the results of the current study need further clinical studies to evaluate the effects of higher doses or the prolonged use of nimesulide and whether nimesulide could be used in patients with asthma attacks and with a history of chronic urticaria.

CONCLUSION

Nimesulide can be a good option for NSAID-intolerant patients: it should first be tested in an allergy unit. However, the results of the current study need further clinical studies to evaluate the effects of higher doses or the prolonged use of nimesulide and whether nimesulide could be used in patients with asthma attacks and with a history of chronic urticaria.

* The authors declare that there are no conflicts of interest.

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