doi • 10.5578/tt.20229608
Tuberk Toraks 2022;70(4):365-374
Received: 16.06.2022 • Accepted: 15.11.2022

RESEARCH ARTICLE

Which non-steroidal anti-inflammatory drug (NSAID) is safer in patients with Non-steroids Exacerbated Respiratory Disease (N-ERD)? A single-center retrospective study

Mehmet Erdem ÇAKMAK(ID)

Clinic of Allergy and Clinical Immunology, Başakşehir Çam and Sakura City Hospital, İstanbul, Türkiye

ABSTRACT

Which non-steroidal anti-inflammatory drug (NSAID) is safer in patients with Non-steroids Exacerbated Respiratory Disease (N-ERD)? A single-center retrospective study

Introduction: *In patients with NSAID-Exacerbated Respiratory Disease (N-ERD), respiratory symptoms occur as a result of the use of cyclooxygenase (COX)-1 inhibitor non-steroidal anti-inflammatory drugs (NSAIDs). Patients with N-ERD generally tolerate selective COX-2 inhibitor NSAIDs. However, respiratory symptoms may be exacerbated in patients with N-ERD due to the intake of selective COX-2 inhibitor NSAIDs. The aim of this study was to evaluate which selective or partial COX-2 inhibitor NSAID is safer in patients with N-ERD.*

Materials and Methods: *Forty-nine patients with a history of respiratory hypersensitivity reactions to NSAIDs (N-ERD) who underwent a drug challenge test with celecoxib, nimesulide, meloxicam, and paracetamol between January 2021-April 2022 were retrospectively evaluated.*

Results: *Of the 49 patients who underwent the drug challenge tests, 16 (32.7%) were male and 33 (67.3%) were female and the mean age was 37.67 ± 11.62 years. The most common comorbidities were chronic urticaria [n= 21 (42.9%)] and allergic rhinitis [n= 21 (42.9%)]. As a result of drug challenge tests, celecoxib, nimesulide, meloxicam, and paracetamol drug challenge tests were positive in 2 (4.1%), 8 (16.3%), 7 (14.3%) and 11 (22.4) patients, respectively. The rate of allergic reaction to celecoxib was statistically significantly lower than other drugs (p= 0.001). In paired comparisons of the drugs, the allergic reaction rate with celecoxib was statistically significantly lower than with nimesulide (p= 0.031) and paracetamol (p= 0.004).*

Conclusion: *Selective COX-2 inhibitor NSAIDs are safe in patients with N-ERD. NSAIDs should be prescribed to these patients following general medical precautions and drug challenge tests.*

Key words: *Drug hypersensitivity; asthma; aspirin; nonsteroidal anti-inflammatory agents*

Cite this article as: *Çakmak ME. Which non-steroidal anti-inflammatory drug (NSAID) is safer in patients with Non-steroids Exacerbated Respiratory Disease (N-ERD)? A single-center retrospective study. Tuberk Toraks 2022;70(4):365-374.*

Address for Correspondence

Dr. Mehmet Erdem ÇAKMAK
Clinic of Allergy and Clinical Immunology, Başakşehir Çam and Sakura City Hospital
İSTANBUL-TÜRKİYE
e-mail: mehmeterdemcakmak@gmail.com

ÖZ

Non-steroidal anti-enflamatuvar ilaçlarla (NSAIDs) alevlenen hava yolu hastalığı (N-ERD) olan hastalarda hangi NSAID daha güvenlidir? Tek merkezli retrospektif bir çalışma

Giriş: *Non-steroidal anti-enflamatuvar ilaçlarla (NSAID) alevlenen hava yolu hastalığı (N-ERD) olan hastalarda, siklooksijenaz (COX)-1 inhibitörü NSAID kullanımı sonucu solunum semptomları ortaya çıkar. N-ERD'li hastalar genellikle seçici COX-2 inhibitörü NSAID'leri tolere eder. Bununla birlikte, seçici COX-2 inhibitörü NSAID'lerin alımına bağlı olarak N-ERD'li hastalarda solunum semptomları şiddetlenebilir. Bu çalışmanın amacı, N-ERD'li hastalarda hangi selektif veya kısmi COX-2 inhibitörü NSAID'in daha güvenli olduğunu değerlendirmektir.*

Materyal ve Metod: *Ocak 2021-Nisan 2022 döneminde selekoksib, nimesulid, meloksikam ve parasetamol ile ilaç provokasyon testi yapılan N-ERD'li 49 hasta retrospektif olarak incelendi.*

Bulgular: *İlaç provokasyon testi yapılan 49 hastanın 16'sı (%32,7) erkek ve 33'ü (%67,3) kadındı ve ortalama yaşları 37,67 ± 11,62 yıldı. En sık görülen komorbiditeler kronik ürtiker [n= 21 (%42,9)] ve alerjik rinit [n= 21 (%42,9)] idi. İlaç provokasyon testleri sonucunda; 2 (%4,1) hastada selekoksib, 8 (%16,3) hastada nimesulid, 7 (%14,3) hastada meloksikam ve 11 (%22,4) hastada parasetamol ile ilaç provokasyon testleri pozitif idi. Selekoksib'e karşı alerjik reaksiyon oranı diğer ilaçlara göre istatistiksel olarak anlamlı derecede düşüktü (p= 0,001). İlaçların ikili karşılaştırmalarında selekoksib ile alerjik reaksiyon oranı, nimesulid (p= 0,031) ve parasetamol (p= 0,004) ile karşılaştırıldığında istatistiksel olarak anlamlı derecede düşüktü.*

Sonuç: *Selektif COX-2 inhibitörü NSAID'ler, N-ERD'li hastalarda güvenlidir. Genel tıbbi önlemler ve ilaç provokasyon testleri sonrasında bu hastalara NSAID'ler reçete edilmelidir.*

Anahtar kelimeler: *İlaç aşırı duyarlılığı; astım; aspirin; nonsteroid anti-enflamatuvar ajanlar*

INTRODUCTION

Intake of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) by patients with asthma/rhinitis/nasal polyps as an underlying disease can cause respiratory complaints such as runny nose, sneezing, nasal congestion, runny eyes, cough, shortness of breath, and severe bronchospasm. In some patients, non-respiratory findings such as urticaria, angioedema, abdominal pain, nausea, vomiting, and low blood pressure may accompany respiratory findings (1,2). This clinical condition has been defined in the past as "aspirin triad (characterized by rhinosinusitis with nasal polyposis, asthma, and increase in nasal and/or respiratory symptoms after NSAID intake), Samter syndrome, Widal syndrome, aspirin-induced asthma or aspirin-sensitive rhinosinusitis/asthma syndrome, aspirin-intolerant asthma, and aspirin-exacerbated respiratory disease". Currently, the most appropriate nomenclature recommended is NSAID-Exacerbated Respiratory Disease (N-ERD) (3).

Respiratory symptoms occur as a result of the use of cyclooxygenase (COX)-1 inhibitor NSAIDs (acetic acids, salicylic acids, propionic acids, enolic acids, and pyrazolone derivatives) in patients with N-ERD. In the pathogenesis, as a result of the imbalance in the lipoxygenase and cyclooxygenase pathways, COX1 inhibition occurs after the use of NSAIDs and it causes an increase in leukotrienes in the airway, which causes bronchospasm (4). Therefore, because selective COX-2 inhibitors are safer in patients with N-ERD, drug challenge tests are recommended with these drugs. However, the degree of COX-2 selectivity may vary. Cross-reactions can occur at high doses of acetaminophen (paracetamol), which weakly inhibits COX-1. Meloxicam and nimesulide predominantly inhibit COX-2 but can also inhibit COX-1 at high doses. Selective COX-2 inhibitors celecoxib and rofecoxib may be safer in patients with N-ERD because they do not inhibit COX-1 and do not cause a decrease in protective prostaglandin (PG) E2 levels (5-8). Therefore, we think that selective COX-2 inhibitor drugs are safer in patients with NERD. The aim of this study was to evaluate which selective or partial COX-2 inhibitor NSAID is safer in patients with N-ERD.

MATERIALS and METHODS

Study Design, Patient Selection, and Data Collection

A retrospective evaluation was made of 49 patients with a history of respiratory hypersensitivity reactions to NSAIDs (N-ERD) who underwent a drug challenge test with celecoxib, nimesulide, meloxicam, and paracetamol between January 2021 and April 2022. Drug challenge tests with celecoxib, nimesulide, meloxicam, and paracetamol are routinely performed in our allergy outpatient clinic to identify safe NSAIDs for patients with N-ERD. The demographic data, comorbidities, laboratory data, and drug challenge test results of the patients were obtained from their medical records.

Atopy was evaluated using the skin prick test (Allergopharma/Germany) or measurement of allergen-specific IgE level (ImmunoCAP). The skin prick test was performed using a panel, consisting of *Dermatophagoides farinae*; *Dermatophagoides pteronyssinus*; grass, tree, and weed pollen; and cat, dog, *Cladosporium*, *Alternaria*, and cockroach allergens. It was performed using histamine (10 mg/mL) as a positive control and saline as a negative control. The skin prick test was performed with the puncture method and test results were evaluated after 20 minutes. A mean wheal diameter of ≥3 mm from the negative control (saline) was described as positive. The skin prick test was not performed in pregnant women, patients who had taken antihistamines in the previous seven days or systemic steroids in the previous 14 days, or patients with dermographism. An allergen-specific IgE level >0.35 kU/L was accepted as positive. Skin prick tests or intradermal tests were not performed with NSAIDs.

Patients who had an early type of hypersensitivity reaction (respiratory symptoms) after NSAID intake were included in the study. Patients with delayed-type hypersensitivity reactions were not included in the study. Patients who had only skin hypersensitivity reactions [NSAIDs-Exacerbated Cutaneous Disease (NECD)] after NSAID use were not included in the study.

Drug Challenge Tests

The diagnosis of N-ERD was based on a positive oral aspirin challenge test result or a recorded and significant clinical respiratory hypersensitivity reaction with COX-1 inhibitor NSAIDs (such as aspirin, naproxen, diclofenac, ibuprofen, and metamizole) from at least two different chemical groups. In patients with a history of suspected or a single group NSAID hypersensitivity, a challenge test with the potent COX-1 inhibitor aspirin was performed to confirm or exclude the diagnosis of N-ERD. Drug challenge tests (aspirin or celecoxib, nimesulide, meloxicam, and paracetamol) were not performed in patients who had a history of sensitivity to sulfonamides or lactose, those who had taken systemic corticosteroids, antihistamines, cromolyn, or β-blocker drugs in the previous week, or had an active skin rash. All of the patients had asthma, and the drug challenge tests were performed if their asthma had been under control for at least two weeks and the forced expiratory volume (FEV) 1 value was >60% predicted. The drug challenge tests were not performed in patients who had experienced drug hypersensitivity reactions in the previous 4-6 weeks. If a drug hypersensitivity reaction developed during the drug challenge tests, appropriate medical treatment was administered. The drug challenge tests were performed at intervals of at least four weeks. Written informed consent was obtained from the patients before the drug challenge tests. The drug challenge test flow chart is shown in Figure 1.

Aspirin Challenge Test

The aspirin (acetylsalicylic acid 100, 300, 500 mg, Bayer, Germany) challenge test was performed in our adult allergy outpatient clinic under strict medical surveillance. The aspirin challenge test was performed single-blind and placebo-controlled on two separate days. On the first day, a placebo (lactose) was given, and on the second day, aspirin was given. FEV_1 and basal blood pressure were measured before the aspirin challenge test. In the challenge test, oral aspirin was administered at doses of 25, 50, 100, 300, and 500 mg at one-hour intervals. FEV_1 and blood pressure were measured 30 minutes after each aspirin dose. The patients were carefully observed until six hours after the administration of the last aspirin dose. The aspirin challenge test result was accepted as negative if there was no significant objective change in clinical symptoms. If dyspnea, bronchospasm, cough, wheezing, chest tightness, a significant decrease in FEV_1 (>20% of baseline FEV_1), nasal symptoms (such as nasal congestion and rhinorrhea), cutaneous symptoms (urticaria, angioedema, erythema, and other skin rashes), hypotension (systolic blood pressure measured <90 mmHg or a decrease of more than 30% from baseline), or gastrointestinal symptoms (diarrhea, abdominal pain, vomiting, nausea) were observed, the aspirin challenge test was accepted as positive. If these symptoms developed in patients during the aspirin challenge test, the test was stopped and medications such as systemic steroids, antihistamines, short-acting beta-2 agonists, and epinephrine were administered to treat these symptoms.

Celecoxib, Nimesulide, Meloxicam and Paracetamol Challenge Test

The celecoxib (Celebrex 200 mg, Pfizer, Türkiye), nimesulide (Nimes 100 mg, Sanovel, Türkiye), meloxicam (Melox 15 mg, Nobel, Türkiye), and paracetamol (Parol 500 mg, Atabay, Türkiye) challenge

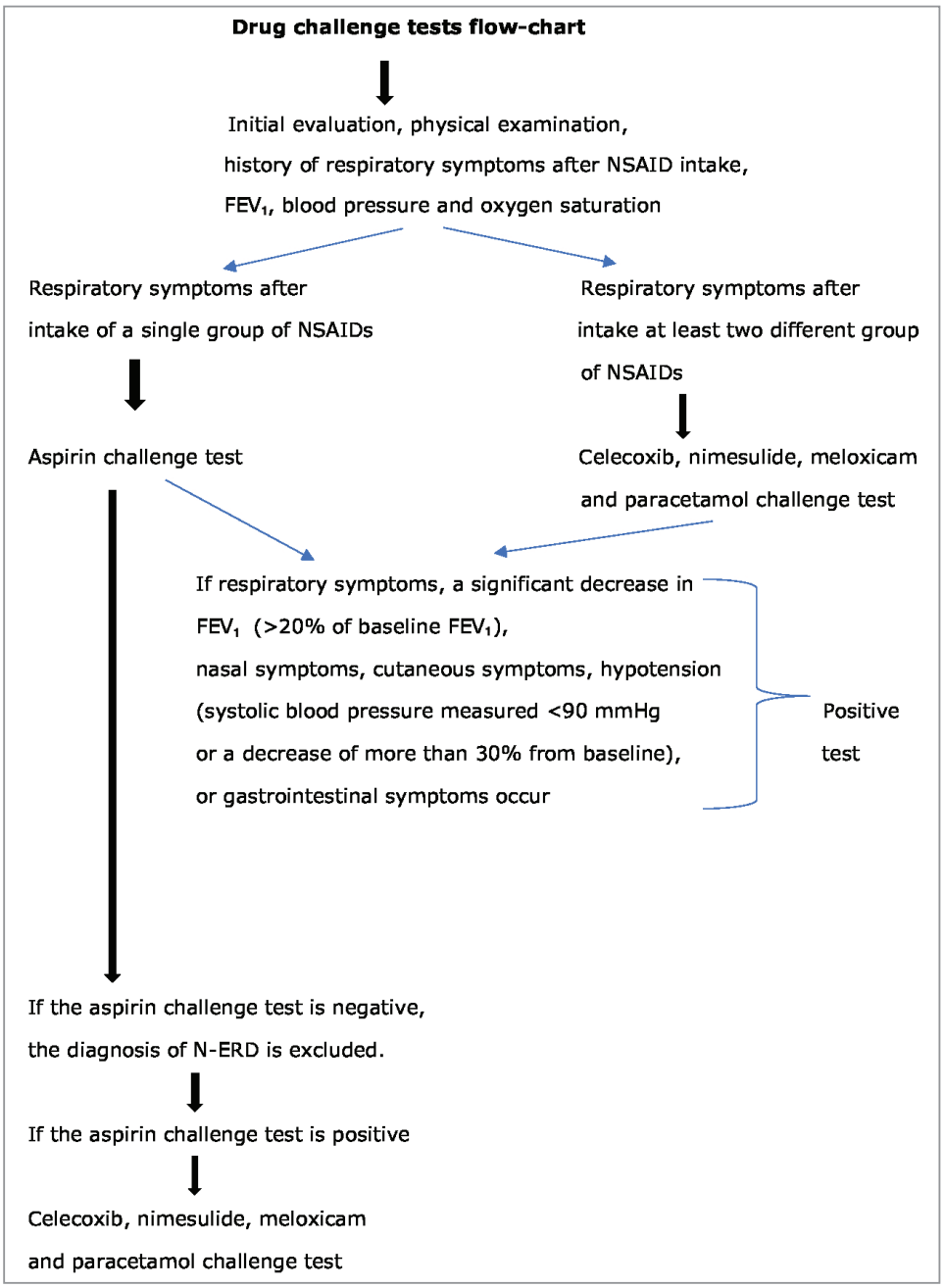

Figure 1. Drug challenge tests flow chart.

tests were performed under strict medical surveillance in our adult allergy outpatient clinic. The drug challenge tests with celecoxib, nimesulide, meloxicam, and paracetamol were performed on separate days, with an interval of at least two days. If an allergic reaction occurred, the drug challenge tests were postponed for at least four weeks. On the first day, a placebo (lactose) was given. On the second day, the active drug as 1/4 and 3/4 divided doses of celecoxib, nimesulide, meloxicam, or paracetamol was given, also at two-hour intervals. FEV_1 and basal blood pressure were measured before the drug challenge tests. FEV_1 and blood pressure were measured 30 minutes after each dose was administered. The patients were carefully observed until six hours after the administration of the last drug dose.

Table 1. Demographics and general characteristics of the patients (n= 49)

Age (years) (mean ± SD)	37.67 ± 11.62
Body mass index (BMI)	27.67 ± 3.73
Sex male, n (%)	16 (32.7)
Total IgE (kU/L), median (min-max)	120 (18-3976)
Eosinophil (cells/mcL), median (min-max)	310 (100-1205)
Atopy (skin prick test or sIgE +) n (%)	24 (49)
FEV_1 (%) (mean ± SD)	89.57 ± 14.45
Current smoker, n (%)	6 (12.2)
Ex-smoker, n (%)	15 (30.6)
Non-smoker, n (%)	28 (57.1)
ESS number, median (min-max)	1 (0-6)
Comorbidities, n (%)	
Hypertension	4 (8.2)
Diabetes mellitus	4 (8.2)
Coronary artery disease	1 (2)
Autoimmune disease	5 (10.2)
Psychiatric disease	6 (12.2)
Thyroid disease	7 (14.3)
Chronic urticaria	21 (42.9)
Allergic rhinitis	21 (42.9)
Other drug allergies	15 (30.6)
Atopic dermatitis	3 (6.1)
Food allergy	4 (8.2)
Bee allergy	3 (6.1)
Culprit drug groups in history, n (%)	
Acetic acids	36 (73.5)
Salicylic acids	33 (67.3)
Propionic acids	42 (85.7)
Enolic acids	14 (28.6)
Pyrazolone derivatives	27 (55.1)
Cross-reactivity between NSAIDs, n (%)	
Acetic acids-Salicylic acids	26 (53)
Acetic acids-Propionic acids	30 (61.2)
Acetic acids-Enolic acids	13 (26.5)
Acetic acids-Pyrazolone derivatives	19 (38.8)
Salicylic acids-Propionic acids	28 (57.1)
Salicylic acids-Enolic acids	12 (24.4)
Salicylic acids-Pyrazolone derivatives	18 (36.7)
Propionic acids-Enolic acids	13 (26.5)
Propionic acids-Pyrazolone derivatives	23 (46.9)
Enolic acids-Pyrazolone derivatives	12 (24.4)
Reaction patterns in history, n (%)	
Nasal and respiratory symptoms	49 (100)
Gastrointestinal symptoms (abdominal pain, diarrhea, nausea, vomiting, etc.)	7 (14.3)
Cutaneous reactions	21 (42.9)
Cardiovascular system involvement (hypotension)	4 (8.2)
Anaphylaxis	5 (10.2)

*ESS: Endoscopic sinus surgery, NSAIDs: Non-steroidal anti-inflammatory drugs.

Table 2. Regular medications and drug challenge test results of the patients

Regular medications	**n (%)**	
Inhaled corticosteroid	46 (93.3)	
Long-acting beta agonist	43 (87.8)	
Long-acting antimuscarinic	20 (40.8)	
Short-acting beta-agonist	30 (61.2)	
Short-acting antimuscarinic	19 (38.8)	
Leukotriene receptor antagonist	36 (73.5)	
Intranasal corticosteroid	34 (69.4)	
Oral antihistamine	37 (75.5)	
Omalizumab	9 (18.4)	
Mepolizumab	9 (18.4)	
GINA step		
Step 1	2 (4.1)	
Step 2	5 (10.2)	
Step 3	8 (16.3)	
Step 4	13 (26.5)	
Step 5	21 (42.9)	
Drug challenge test results		
Celecoxib (positive)	2 (4.1)	
Nimesulide (positive)	8 (16.3)	**p= 0.001***
Meloxicam (positive)	7 (14.3)	
Paracetamol (positive)	11 (22.4)	

* Cochran's Q test.

Similar to the aspirin challenge test, the test was accepted as positive if nasal, respiratory, skin, or gastrointestinal symptoms or hypotension developed. If the patient developed these symptoms during the drug challenge test, appropriate treatment was given as in the aspirin challenge test.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Windows v. 20.0 software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to evaluate the distribution of numerical data. Numerical data were presented as mean ± standard deviation (SD) or median (minimum-maximum) values. Frequency distributions (%) were used for categorical variables. Cochran's Q test was used to compare the proportions of more than two dependent groups, and the McNemar test to compare the proportions of two dependent groups. A p-value< 0.05 was accepted as statistically significant.

Ethics Statement

The study protocol was approved by the Ethics Committee (Approval no: 2022-170). The study was conducted in accordance with the principles of the Declaration of Helsinki. All participants were informed about the nature of the study and written informed consent was obtained.

RESULTS

Forty-nine patients [16 (32.7%) males and 33 (67.3%) females, with a mean age of 37.67 ± 11.62 years] who underwent drug challenge tests were evaluated. The most common comorbidities were chronic urticaria [n= 21 (42.9%)] and allergic rhinitis [n= 21 (42.9%)]. Atopy was identified in 24 (49%) patients. The demographic data, general characteristics of the patients, culprit drugs in history, and cross-reactivity rates are shown in Table 1.

According to the Global Initiative for Asthma (GINA) (9), 13 (26.5%) patients had step four treatment, 21 (42.9%) had step five treatment, and many of these patients had severe asthma. Celecoxib, nimesulide, meloxicam, and paracetamol drug challenge tests were positive in 2 (4.1%), 8 (16.3%), 7 (14.3%), and 11 (22.4) patients, respectively. The rate of allergic reaction to celecoxib was statistically significantly lower than other drugs (p= 0.001). The regular medications and drug challenge test results of the patients are shown in Table 2 and the characteristics of patients with positive drug challenge tests are shown in Table 3.

Paired comparisons were made of the allergic reaction rates of the drugs. The allergic reaction rate with celecoxib was statistically significantly lower than with nimesulide (p= 0.031) and paracetamol (p= 0.004) (between celecoxib-meloxicam: p= 0.063, nimesulide-meloxicam: p= 1.000, nimesulide-paracetamol: p= 0.375, meloxicam-paracetamol: p= 0.219).

Table 3. Characteristics of patients with positive drug challenge tests

	Age	Sex	Culprit drug groups in history	Reaction patterns in history	Drug challenge test results	Reaction patterns after drug challenge test
Patient 1	39	f	Acetic acids Salicylic acids Propionic acids Enolic acids Pyrazolone derivatives	Nasal and respiratory symptoms	Celecoxib: (+) Nimesulide: (+) Meloxicam: (+) Paracetamol: (+)	Celecoxib: Rhinitis Nimesulide: Dyspnea Meloxicam: Dyspnea, decrease in FEV_1>20% Paracetamol: Dyspnea
Patient 2	43	m	Acetic acids Salicylic acids Propionic acids Enolic acids Pyrazolone derivatives	Nasal, respiratory, gastrointestinal and cutaneous symptoms, hypotension, anaphylaxis	Celecoxib: (+) Nimesulide: (+) Meloxicam: (+) Paracetamol: (+)	Celecoxib: Dyspnea Nimesulide: Urticaria Meloxicam: Urticaria Paracetamol: Dyspnea, decrease in FEV_1>20%
Patient 3	36	f	Acetic acids Salicylic acids Propionic acids Enolic acids Pyrazolone derivatives	Nasal, respiratory and cutaneous symptoms	Celecoxib: (-) Nimesulide: (+) Meloxicam: (+) Paracetamol: (+)	Nimesulide: Dyspnea Meloxicam: Dyspnea Paracetamol: Dyspnea
Patient 4	36	f	Acetic acids Salicylic acids Propionic acids Enolic acids Pyrazolone derivatives	Nasal, respiratory and cutaneous symptoms	Celecoxib: (-) Nimesulide: (+) Meloxicam: (-) Paracetamol: (+)	Nimesulide: Urticaria Paracetamol: Rhinitis
Patient 5	47	f	Propionic acids Enolic acids Pyrazolone derivatives	Nasal, respiratory and cutaneous symptoms	Celecoxib: (-) Nimesulide: (+) Meloxicam: (+) Paracetamol: (+)	Nimesulide: Rhinitis Meloxicam: Dyspnea Paracetamol: Dyspnea
Patient 6	29	f	Propionic acids Pyrazolone derivatives	Nasal, respiratory, gastrointestinal and cutaneous symptoms, hypotension, anaphylaxis	Celecoxib: (-) Nimesulide: (+) Meloxicam: (+) Paracetamol: (+)	Nimesulide: Nasal congestion Meloxicam: Rhinitis Paracetamol: Nasal congestion
Patient 7	47	m	Acetic acids Propionic acids Enolic acids	Nasal, respiratory and cutaneous symptoms	Celecoxib: (-) Nimesulide: (+) Meloxicam: (+) Paracetamol: (-)	Nimesulide: Dyspnea Meloxicam: Dyspnea
Patient 8	32	m	Acetic acids Salicylic acids Enolic acids	Nasal and respiratory symptoms	Celecoxib: (-) Nimesulide: (+) Meloxicam: (+) Paracetamol: (+)	Nimesulide: Dyspnea Meloxicam: Dyspnea Paracetamol: Rhinitis, Nasal congestion

Table 3. Characteristics of patients with positive drug challenge tests (continued)

	Age	Sex	Culprit drug groups in history	Reaction patterns in history	Drug challenge test results	Reaction patterns after drug challenge test
Patient 9	29	f	Acetic acids Propionic acids Pyrazolone derivatives	Nasal, respiratory and cutaneous symptoms	Celecoxib: (-) Nimesulide: (-) Meloxicam: (-) Paracetamol: (+)	Paracetamol: Urticaria
Patient 10	39	f	Acetic acids Salicylic acids Pyrazolone derivatives	Nasal and respiratory symptoms Meloxicam: (-)	Celecoxib: (-) Nimesulide: (-) Meloxicam: (-) Paracetamol: (+)	Paracetamol: Rhinitis
Patient 11	25	f	Acetic acids Pyrazolone derivatives	Nasal and respiratory symptoms	Celecoxib: (-) Nimesulide: (-) Meloxicam: (-) Paracetamol: (+)	Paracetamol: Dyspnea
Patient 12	48	f	Salicylic acids Propionic acids	Nasal, respiratory and cutaneous symptoms	Celecoxib: (-) Nimesulide: (-) Meloxicam: (-) Paracetamol: (+)	Paracetamol: Rhinitis, dyspnea

(+): Positive, (-): Negative, m: Male, f: Female.

DISCUSSION

The aim of this study was to investigate which COX-2 inhibitor NSAID is safer in patients with N-ERD, and the results demonstrated that the rate of allergic reaction to celecoxib was lower than other drugs. The safety of celecoxib in patients with N-ERD was 95.9%. In a study by Roll et al. (10), of patients with a history of hypersensitivity to NSAIDs, the allergic reaction rates were determined 4.7% with celecoxib, 15.6% with paracetamol, and 17.6% with nimesulide. The authors emphasized that celecoxib is well tolerated by most patients with NSAID intolerance, and cumulatively up to 175 mg is a safe alternative treatment option. However, they stated that an oral challenge test should be performed before prescribing celecoxib to NSAID-intolerant patients. Martín-García et al. (11) reported that 30 (90.9%) of 33 patients with N-ERD tolerated celecoxib well. Various studies in the literature have shown that COX-2 inhibitors are well tolerated in patients with a history of hypersensitivity to NSAIDs (7,12,13).

In the current study, we found that the rate of allergic reactions with nimesulide, meloxicam, and paracetamol was higher after the drug challenge tests compared to some studies in the literature. In a study by Senna et al. (14) evaluating the tolerability of meloxicam, celecoxib, and rofecoxib in NSAID-intolerant patients, they observed that all patients with a history of respiratory drug hypersensitivity reaction tolerated these three drugs well. In a meta-analysis involving randomized placebo-controlled trials evaluating selective NSAID or COX-2 inhibitor exposure in patients with N-ERD, exposure to selective NSAID or COX-2 inhibitor caused respiratory symptoms in one of 13 patients with N-ERD (15). In the current study, most of the patients who underwent drug challenge tests had severe asthma. Therefore, the high rates of allergic reactions to nimesulide, meloxicam, and paracetamol may be related to these patients having severe asthma.

In this study, the tolerability of celecoxib was significantly higher than that of other COX-2 inhibitors. Celecoxib is a selective COX-2 inhibitor, nimesulide and meloxicam are partially selective COX-2 inhibitors, and paracetamol is a weak COX-1 inhibitor at high doses (2). We think that the tolerability of celecoxib is higher because it inhibits only COX-2. Drug challenge tests with celecoxib were positive in two patients and we observed mild nasal and respiratory symptoms. Drug challenge tests were also positive with nimesulide, meloxicam, and

paracetamol in these patients. These patients tolerated codeine as an alternative analgesic. In general, we observed mild nasal, respiratory, and skin reactions after drug challenge tests. We did not observe any severe allergic reactions (anaphylaxis).

Most N-ERD patients have moderate to severe asthma, although some have mild asthma. The prevalence of severe asthma in patients with N-ERD is twice that of the general asthma population (3). One study demonstrated a history of aspirin hypersensitivity as an independent risk factor for severe asthma (16). In another cohort study, 30% of severe asthmatic patients with NSAID hypersensitivity were receiving high-dose inhaled corticosteroids (17). In a multicenter study, it was shown that patients with N-ERD were hospitalized more frequently, had more respiratory symptoms, and were taking medications more frequently compared to other asthma phenotypes (18). It has been reported that N-ERD patients have a higher risk of uncontrolled and severe asthma, an increased frequency of asthma attacks, and a worse quality of life (17,19). Of the patients with N-ERD in the current study, 42.9% were severe asthmatic patients who received step 5 treatment according to GINA, and of these patients, 18 (36.8%) were receiving biological agents (omalizumab= 9, mepolizumab= 9).

Upper airway disease of chronic rhinosinusitis with nasal polyps (CRSwNP) is frequently observed in N-ERD. Symptoms such as nasal congestion, runny nose, facial pain or pressure, and postnasal drip are often present. Partial loss of smell and anosmia are also common in N-ERD, and loss of smell can be used as a clinical marker to identify N-ERD (20). Upper respiratory tract symptoms are worse in N-ERD than in NSAID-tolerant CRSwNP patients, and recurrence of nasal polyps is more frequent after endoscopic sinus surgery (ESS) (21). Poor control of nasal symptoms also affects asthma control in patients with N-ERD. Most of the patients in the current study had a history of recurrent ESS due to CRSwNP.

This study had some limitations, primarily that it was retrospective in design. Second, the aspirin challenge was not performed on all patients to confirm the diagnosis of N-ERD, which in some patients was based on a medical record of allergic reaction with at least two different groups of COX-1 inhibitor NSAIDs. Despite these limitations, this study can be considered important in terms of comparing the safety of four different groups of NSAIDs in patients with N-ERD.

CONCLUSION

In conclusion, selective COX-2 inhibitor NSAIDs were observed to be safe in patients with N-ERD. However, NSAIDs should be prescribed to these patients after taking general medical precautions and performing drug challenge tests.

Ethical Committee Approval: This study approval was obtained from Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (Decision No: 2022.05.170, Date: 26.05.2022).

CONFLICT of INTEREST

The author declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: MEÇ

Analysis/Interpretation: MEÇ

Data acqusition: MEÇ

Writing: MEÇ

Clinical Revision: MEÇ

Final Approval: MEÇ

REFERENCES

1. *Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal antiinflammatory drugs. Allergy 2013; 68(10): 1219-32. https://doi.org/10.1111/all.12260*

2. *Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs)-classification, diagnosis and management: Review of the EAACI/ENDA and GA2LEN/HANNA. Allergy 2011; 66(7): 818-29. https://doi.org/10.1111/j.1398-9995.2011.02557.x*

3. *Kowalski ML, Agache I, Bavbek S, Bakirtas A, Blanca M, Bochenek G, et al. Diagnosis and management of NSAID-exacerbated respiratory disease (N-ERD)-a EAACI position paper. Allergy 2019; 74(1): 28-39. https://doi.org/10.1111/all.13599*

4. *Woo SD, Luu QQ, Park HS. NSAID-exacerbated respiratory disease (NERD): From pathogenesis to improved care. Front Pharmacol 2020; 11: 1147. https://doi.org/10.3389/fphar.2020.01147*

5. *Bavbek S, Dursun AB, Dursun E, Eryilmaz A, Misirligil Z. Safety of meloxicam in aspirin-hypersensitive patients with asthma and/or nasal polyps. A challenge-proven study. Int Arch Allergy Immunol 2007; 142(1): 64-9. https://doi.org/10.1159/000096000*

6. *Bavbek S, Celik G, Pasaoglu G, Misirligil Z. Rofecoxib, as a safe alternative for acetyl salicylic acid/nonsteroidal anti-inflammatory drug-intolerant patients. J Investig Allergol Clin Immunol 2006; 16(1): 57-62.*

7. *Celik G, Paşaoğlu G, Bavbek S, Abadoğlu O, Dursun B, Mungan D, et al. Tolerability of selective cyclooxygenase inhibitor, celecoxib, in patients with analgesic intolerance. J Asthma 2005; 42(2): 127-31. https://doi.org/10.1081/JAS-51326*

8. *Bavbek S, Celik G, Ozer F, Mungan D, Misirligil Z. Safety of selective COX-2 inhibitors in aspirin/nonsteroidal anti-inflammatory drug-intolerant patients: Comparison of nimesulide, meloxicam, and rofecoxib. J Asthma 2004; 41(1): 67-75. https://doi.org/10.1081/JAS-120026063*

9. *Global Initiative for Asthma (GINA). Available from: http://www.ginasthma.org. (Accessed date: 12.04.2022).*

10. *Roll A, Wüthrich B, Schmid-Grendelmeier P, Hofbauer G, Ballmer-Weber BK. Tolerance to celecoxib in patients with a history of adverse reactions to nonsteroidal anti-inflammatory drugs. Swiss Med Wkly 2006; 136(43-44): 684-90. https://doi.org/10.4414/smw.2006.11358*

11. *Martín-García C, Hinojosa M, Berges P, Camacho E, García-Rodriguez R, Alfaya T. Celecoxib, a highly selective COX-2 inhibitor, is safe in aspirin-induced asthma patients. J Investig Allergol Clin Immunol 2003; 13(1): 20-5.*

12. *Çelik GE, Erkekol FÖ, Aydın Ö, Demirel YS, Mısırlıgil Z. Are drug provocation tests still necessary to test the safety of COX-2 inhibitors in patients with cross-reactive NSAID hypersensitivity? Allergol Immunopathol (Madr) 2013; 41(3): 181-8. https://doi.org/10.1016/j.aller.2012.03.006*

13. *Li L, Laidlaw T. Cross-reactivity and tolerability of celecoxib in adult patients with NSAID hypersensitivity. J Allergy Clin Immunol Pract 2019; 7(8): 2891-3. https://doi.org/10.1016/j.jaip.2019.04.042*

14. *Senna G, Bilò MB, Antonicelli L, Schiappoli M, Crivellaro MA, Bonadonna P, et al. Tolerability of three selective cyclo-oxygenase-2 inhibitors, meloxicam, celecoxib and rofecoxib in NSAID-sensitive patients. Eur Ann Allergy Clin Immunol 2004; 36(6): 215-8.*

15. *Morales DR, Lipworth BJ, Guthrie B, Jackson C, Donnan PT, Santiago VH. Safety risks for patients with aspirin-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: Meta-analysis of controlled clinical trials. J Allergy Clin Immunol 2014; 134(1): 40-5. https://doi.org/10.1016/j.jaci.2013.10.057*

16. *The ENFUMOSA Study Group. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. Eur Respir J 2003; 22(3): 470-7. https://doi.org/10.1183/09031936.03.00261903*

17. *Schatz M, Hsu JW, Zeiger RS, Chen W, Dorenbaum A, Chipps BE, et al. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. J Allergy Clin Immunol 2014; 133(6): 1549-56. https://doi.org/10.1016/j.jaci.2013.10.006*

18. *Makowska JS, Burney P, Jarvis D, Keil T, Tomassen P, Bislimovska J, et al. Respiratory hypersensitivity reactions to NSAIDs in Europe: The global allergy and asthma network (GA(2) LEN). Allergy 2016; 71(11): 1603-11. https://doi.org/10.1111/all.12941*

19. *Morales DR, Guthrie B, Lipworth BJ, Jackson C, Donnan PT, Santiago VH. NSAID-exacerbated respiratory disease: A meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. Allergy 2015; 70(7): 828-35. https://doi.org/10.1111/all.12629*

20. *Mullol J, Picado C. Rhinosinusitis and nasal polyps in aspirin-exacerbated respiratory disease. Immunol Allergy Clin North Am 2013; 33(2): 163-76. https://doi.org/10.1016/j.iac.2012.11.002*

21. *Stevens WW, Peters AT, Hirsch AG, Nordberg CM, Schwartz BS, Mercer DG, et al. Clinical characteristics of patients with chronic rhinosinusitis with nasal polyps, asthma, and aspirin-exacerbated respiratory disease. J Allergy Clin Immunol Pract 2017; 5(4): 1061-70. https://doi.org/10.1016/j.jaip.2016.12.027*