

Rofecoxib, as a safe alternative for acetyl salicylic acid/nonsteroidal anti-inflammatory drug-intolerant patients

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Summary: *Background:* Intolerance to acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) is a crucial problem in medical practice. There is therefore a need for safer NSAIDs in analgesic-intolerant patients.

Objective: To assess the safety of rofecoxib, a selective COX-2 inhibitor, in ASA/NSAID-intolerant patients.

Methods: A single blind, placebo-controlled oral challenge procedure was applied to 94 adult patients (M/F: 30/64, mean age: 39.2 ± 11.9 yrs) with a reliable history of ASA/NSAID intolerance. 1/4 and 3/4 divided doses of placebo and rofecoxib were given with 2-hour intervals on consecutive days. During the challenge procedure, blood pressure, heart rate, nasooocular, pulmonary and cutaneous symptoms were monitored. Erythema, pruritus accompanied by erythema, urticaria/angioedema, rhinorea, nasal obstruction, sneezing, dyspnea or cough associated with a decrease of at least 20% in the FEV₁, and hypotension were considered as positive reactions.

Results: None of the patients reacted to placebo. Only one patient (1.1%) presented urticarial-type cutaneous reaction to rofecoxib challenge. The remaining patients (98.9%) perfectly tolerated the drug challenge.

Conclusion: Rofecoxib can be used as a safe alternative drug for ASA/NSAID intolerant patients.

Key words: Aspirin intolerance, asthma, rofecoxib, urticaria, anaphylactoid reaction

Resumen. La intolerancia al ácido acetilsalicílico (AAS) y a los fármacos antiinflamatorios no esteroideos (AINE) es un problema crucial en la práctica médica, por lo que existe la necesidad de utilizar AINE más seguros en pacientes con intolerancia a los analgésicos.

Objetivo: Evaluar la seguridad de rofecoxib, un inhibidor selectivo de la COX-2, en pacientes con intolerancia a AAS y AINE.

Métodos: Se realizó provocación oral controlada por placebo y simple ciego a 94 pacientes adultos (V/M: 30/64, edad media: $39,2 \pm 11,9$ años) con una historia de intolerancia a AAS/AINE. Se suministraron dosis fraccionadas de 1/4 y 3/4 de placebo y rofecoxib a intervalos de 2 horas en días consecutivos. Durante el procedimiento de provocación, se controlaron la presión arterial, la frecuencia cardíaca y los síntomas nasoooculares, pulmonares y cutáneos. El eritema, prurito acompañado de eritema, urticaria o angioedema, rinorea, obstrucción nasal, estornudos, disnea o tos asociadas con una disminución de al menos un 20% del VEF₁ e hipotensión se consideraron reacciones positivas.

Resultados: Ninguno de los pacientes reaccionó al placebo. Sólo un paciente (1,1%) experimentó una reacción cutánea de tipo urticaria ante la provocación con rofecoxib. El resto de pacientes (98,9%) toleraron perfectamente la provocación con el fármaco.

Conclusión: Rofecoxib puede utilizarse como fármaco alternativo seguro en pacientes con intolerancia a AAS/AINE.

Palabras clave: Intolerancia al ácido acetilsalicílico, asma, rofecoxib, urticaria, reacción anafilactoide.

Introduction

Aspirin (acetylsalicylic acid:ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for the management of acute and chronic pain, most rheumatic conditions, fever and inflammation. However, a variety of adverse reactions including precipitation of asthma attack, rhinitis, urticaria/angioedema and anaphylactoid reaction related to ASA/NSAID intake has been reported. Asthmatic reactions induced by NSAIDs occur in about 5%-20% of adult asthma patients [1]. The mechanism underlying the adverse reactions to ASA/NSAIDs remains unclear. Immunoglobulin E-mediated reaction has been proposed for patients who react to only one NSAID or ASA without showing any cross reactivity between these drugs and especially for anaphylactoid reactions to pyrazolone drugs [1]. 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 [2, 3]. 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 [4]. The antiinflammatory actions of NSAIDs are thought to be due to inhibition of COX-2, whereas the side effects such as gastric damage and aspirin-induced asthma are mediated through inhibition of COX-1 with subsequent release of leukotrienes [5, 6]. Therefore, NSAIDs that inhibit COX-2 but not COX-1 can be a safe alternative in aspirin-intolerant patients.

Finding a safe NSAID is a difficult task for patients who need an antiinflammatory analgesic drug, and the choice of safe alternative is very restricted. The discovery of two isoforms of COX-isoenzyme, a constitutive COX-1 and an inducible COX-2, led to the development of new NSAID, the selective COX-2 inhibitors, promising minimal NSAID-typical toxicity. In recent years, the two preferential COX-2 inhibitors, nimesulide and meloxicam, were found to be well tolerated at moderate doses in ASA/NSAIDs-intolerant patients [7-9]. However, these drugs are not completely devoid of adverse effects and can cause bronchial obstruction or skin reaction at higher doses [10-12].

Rofecoxib was recently introduced as a very selective COX-2 inhibitor on the basis of *in vivo* and *in vitro* data from animal and humans, and may be considered a valid choice in patients with ASA/NSAID intolerance [13]. Thus, we performed this study to evaluate the tolerability of rofecoxib in subjects with reliable histories of adverse reactions to ASA/NSAIDs. Since rofecoxib is usually recommended at doses of 12.5 and 25 mg, this study aimed to assess the tolerability of 25 mg of rofecoxib. An initial part of the study was previously reported with a subset of the subjects [11]. In the present study, we report all data from 94 patients who were challenged with rofecoxib.

Materials and methods

Patient selection

The study was conducted among patients admitted to our outpatient clinic located in Ankara, the capital city of Turkey. All patients gave reliable histories of urticaria/angioedema episodes, skin rashes of any type, naso-ocular symptoms, mild to severe bronchospasm and/or anaphylactoid reaction within 2 hours after ingesting a prescribed ASA and/or NSAIDs and/or paracetamol. NSAIDs are accepted as chemically unrelated compounds that have COX-1 and COX-2 inhibitory activity and thus crossreact with ASA. Aminophenazone, diclofenac, diflunisal, etodolac, fenoprofen, ibuprofen, indomethacin, ketoprofen, naproxen, metamizol, and piroxicam are available drugs amongst this group in our country.

Patients taking systemic antihistamines, systemic corticosteroids, cromolyn, oral sympathomimetics or β -blocker drugs for the last week were not included in the study. 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 was in stable period for at least two weeks, and having an FEV₁ 70% over the predicted value. All asthmatics were free of respiratory infection for at least 6 weeks. They were allowed to continue their maintenance therapy with inhaled corticosteroids and inhaled albuterol as needed, but inhaled albuterol was not allowed 6 h before the challenge procedure. Aminophylline and long acting β -₂ agonists were withheld for 48 h before the study procedure.

After inclusion in the study, age, sex, duration of analgesic intolerance, implicated analgesic(s), reaction patterns, number of the drug(s) inducing reactions, were recorded. Duration of drug allergy was defined as the time period between the first reaction to ASA and/or NSAIDs and hospital admission for an alternative analgesic.

Presence of comorbid disorders such as asthma, rhinitis, chronic rhinosinusitis and chronic urticaria were also evaluated. Asthma was diagnosed by the presence of recurrent symptoms of wheezing, shortness of breath, cough and demonstration of objective sign of reversible airway obstruction as stated by the American Thoracic Society [14]. Sensitivity to other drugs was diagnosed by the reliable history of IgE-mediated reactions (urticaria/angioedema, bronchospasm, laryngeal edema, rhinitis, and systemic anaphylactoid reactions involving hypotension, laryngeal edema, bronchospasm and/or shock and presence of non-IgE-mediated reactions (maculopapular eruption, fixed drug eruption, photosensitivity, contact dermatitis, and other reactions) to a prescribed drug. All patients gave written informed consent to participate in the drug challenge.

Oral Challenge Tests

An experienced allergist in the hospital setting performed an oral challenge test where emergency

equipment was available. The challenge protocol consisted of oral administration of the drug with increasing doses as described by our previous studies [8, 11]. The study was designed as a single-blind and placebo controlled oral drug challenge. On two consecutive days, 1/4 and 3/4 divided doses of placebo and the active drug rofecoxib (Vioxx 25 mg, Merck-Sharp Dohme/Turkey), were given with 2-hour intervals. During the challenge procedure, blood pressure and forced expiratory volume in 1 s (FEV₁) values, as well as 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 h to detect a delayed reaction. In case of no reaction at the end of 24 hours, patients were accepted as rofecoxib-tolerant.

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 and/or anaphylactoid reaction with urticaria and/or angioedema and hypotension (a 30-mmHg drop in systolic blood pressure) and/or laryngeal edema (with at least skin and respiratory or skin and hypotension or skin or gastrointestinal and one of the above).

Evaluation of Atopy

Atopy was defined as a positive skin prick test (SPT) to at least one of the aeroallergens. Glycerinate extracts (Stallergenes, France) of the following allergenic sources were used in SPTs: *Dermatophagoides pteronyssinus*, *D farinae*, 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

Numeric results were expressed as mean \pm 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.

Results

Patients

A total of 94 subjects were included in the study. Demographic data and detailed clinical presentations of ASA/NSAID intolerance of the study group are given in Table 1. Female gender was prominent in the study group since 68% of patients were female. Baseline FEV₁ had a mean of 2.49 ± 0.65 L in the whole group. NSAIDs and ASA+NSAIDs were the most common drugs involved in intolerance reactions with a frequency of 29.8% and 31.2%, respectively. 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 55 (58.5%) subjects described intolerance reactions to multiple analgesics and 71% of these patients were female.

As far as co-morbid disorders are concerned, 54 subjects (57.4%) appeared to be otherwise normal, 27 (28.7%) and 5 subjects (5.3%), had asthma and chronic

Table 1. Characteristics features and co-morbid disorders of the patients.

| VARIABLE | |
|--|-----------------|
| Sex (female/male) n (%) | 64/30 (68/32%) |
| Age (years) (Mean \pm SD) | 39.2 \pm 11.9 |
| Baseline FEV1 (L) (Mean \pm SD) | 2.49 \pm 0.65 |
| Duration of co-morbid disorders* (years) (Mean \pm SD) | 7.08 \pm 7.54 |
| Duration of drug allergy (years) (Mean \pm SD) | 7.1 \pm 7.54 |
| Single analgesic intolerance n (%) | 39 (41.5%) |
| Multiple analgesic intolerance n (%) | 55 (58.5%) |
| Drug allergy other than ASA/NSAID intolerance n (%) | 26 (27.6%) |
| Co-morbid disorders n (%) | |
| None | 54 (57.4%) |
| Chronic urticaria | 5 (5.3%) |
| Asthma | 8 (8.6%) |
| Asthma + rhinosinusitis | 18 (19.2%) |
| Asthma + Chronic urticaria | 1 (1%) |
| Chronic rhinosinusitis | 5 (5.3%) |
| Other | 3 (3.2%) |

* Asthma, rhinitis, urticaria/angioedema.

Table 2. Type of reactions according to the specific drugs.

| Specific drug | Type of reaction | | | | Total n (%) | Challenge results with rofecoxib |
|-------------------------------|----------------------|----------------------|--------------------|----------------------|----------------|-------------------------------------|
| | Cutaneous (C)* | Respiratory (R)** | C + R | Anaphylactoid | | |
| ASA | 4 | 3 | 1 | 1 | 9 (9.6%) | Negative |
| NSAIDs | 16 | 2 | 5 | 4 | 27 (28.8%) | Negative |
| ASA + NSAIDs | 11 | 8 | 7 | 3 | 29 (30.9%) | Negative |
| Paracetamol | 2 | 0 | 0 | 1 | 3 (3.2%) | Negative |
| ASA + Paracetamol | 1 | 1 | 0 | 2 | 4 (4.2%) | Negative |
| ASA + Paracetamol + NSAIDs | 6 | 1 | 1 | 3 | 12 (12.7%) | Positive in 1 |
| NSAIDs + Paracetamol | 3 | 2 | 1 | 4 | 10 (10.6%) | Negative |
| TOTAL | 43 (45.7%) | 17 (18.1%) | 15 (16%) | 19 (20.2%) | 94 | |

* Urticaria, angioedema and fix drug eruption. ** Asthma, rhinitis.

urticaria, respectively. Among the asthmatic group, 18 subjects (19.2%) had been diagnosed having ASA triad.

In terms of the reaction pattern as to ASA/NSAIDs, cutaneous reactions were the most common presentation in 44 subjects (46.8%) followed by respiratory reactions in 19 subjects (20.2%). Twenty-six subjects (27.6%) described reactions to other drugs in addition to ASA/NSAID intolerance. Sensitivity to anti-microbial drugs such as penicillins and sulphonamides was prominent since it was reported in 77% of these patients.

As far as reaction patterns according to co-morbid diseases are concerned, asthmatic subjects developed mostly respiratory reactions, including upper and lower respiratory tract, in 17 (62.9%) patients, followed by isolated cutaneous reaction, cutaneous plus asthmatic reaction and anaphylactoid reaction in 11.1%, 14.8% and 11.1% of these patients, respectively. Patients with urticaria or without any history of allergic diseases except drug allergy reported mostly cutaneous reaction (80% and 55.7%, respectively).

Atopy status

SPT analysis was performed in 83 subjects and atopy ratio was 24.1% in the study group. This ratio was similar to the general adult population of Turkey [15] (24.1% vs 25%, $p > 0.05$).

Rofecoxib provocation

No reaction against placebo was observed. Rofecoxib, 1/4 of 25 mg, triggered urticarial-type reaction within 2 hours in only one patient who had been presented with anaphylaxis to ASA/NSAIDs and paracetamol, the remaining patients tolerated the rofecoxib challenge perfectly. The 38-year-old patient who reacted to rofecoxib was suffering from chronic irritant hand dermatitis and had also reacted to both nimesulide and

meloxicam challenges with urticarial-type reaction. The patient denied previous exposure to these three drugs and the present reaction responded to the treatment with hydroxyzine 25 mg per oral. As far as the reaction patterns according to comorbid disorder are concerned, patients with asthma and/or rhinosinusitis and/or chronic urticaria did not show any adverse reaction to the drug challenge.

Discussion

In the present study, only one otherwise healthy subject with a history of ASA/NSAID-induced anaphylactoid reaction, developed urticaria with 1/4 of 25 mg of rofecoxib challenge. The remaining 93 subjects tolerated the rofecoxib challenge perfectly without showing any sign of intolerance reaction. Although controlled oral challenge is the only way to confirm ASA/NSAID intolerance, which is the major methodological limitation of our study, we did not carry out confirmatory oral challenges with the implicated drugs [16]. Instead, we used oral challenge to identify a safe alternative drug for ASA/NSAID intolerant-patients. This approach has been proved to be safe, rapid and reliable and meets the ethical considerations in clinical practice [9, 17]. Moreover, a significant correlation between history of intolerance and the result of oral challenge in aspirin-intolerant patients was demonstrated previously [18]. Moreover, in our study, the relatively high percentage of patients (58.5%) reacting to multiple NSAIDs suggesting the presence of cross-reactivity may support a diagnosis of true NSAID-intolerance.

Considering that the COX-1 inhibition is the main reason of ASA/NSAID-related adverse reactions, it is expected that selective COX-2 inhibitors will be safe alternatives for ASA/NSAID-intolerant patients. New, very selective COX-2 inhibitors, rofecoxib, celecoxib and valdecoxib, have been marketed in many countries [13, 19, 20]. Studies have shown that rofecoxib is at least 1000-fold more selective for COX-2. It is an effective analgesic in patients with primary dysmenorrhea and postoperative

dental pain and also has antipyretic activity similar to ibuprofen in patients with upper respiratory tract infection [13, 21]. As a selective COX-2 inhibitor, rofecoxib has been the subject of several studies in NSAID intolerant patients [22-25]. In a double-blind, placebo-controlled, crossover study by Szczeklik et al, 25 mg rofecoxib was tolerated in 12 aspirin-intolerant asthma patients in each of whom aspirin sensitivity was proven through the use of oral aspirin challenges [24]. In these patients, supporting the role of COX-1 inhibition in precipitation of respiratory reactions in aspirin-intolerant asthma, rofecoxib challenge was free of aspirin-triggered signs such as rising urinary LTE₄ and PGD₂. Similarly, Stevenson and Simon investigated the tolerability of rofecoxib in a larger sample, 60 patients with aspirin-induced asthma, using a double-blind, placebo-controlled oral challenge procedure. None of the patients experienced respiratory, cutaneous or systemic reaction to rofecoxib challenges [25]. Recently, similar results were reported with 40 aspirin-induced asthma patients whose diagnosis had been based on a detailed clinical history and emergency department report. At the end of the challenge procedure with rofecoxib, 100% of asthma patients tolerated 25 mg of the drug without any sign of immediate or delayed reactions [26]. Our findings are consistent with these observations, since none of our asthma patients did react to rofecoxib challenge. Thus, we may suggest that rofecoxib can be safely taken by aspirin-intolerant patients with asthma.

Despite these findings regarding the safety of rofecoxib in aspirin-intolerant asthma patients, some adverse events including cutaneous and systemic reactions developed by selective COX-2 inhibitors have been reported [27-29]. One subject without asthma but with a history of NSAID-induced anaphylactoid reaction developed the same type of reaction with celecoxib [30]. Moreover, a first case of a celecoxib-specific anaphylactoid reaction in a patient who was tolerant to both naprosyn and rofecoxib has been reported recently [31]. These reactions may be related to the mechanisms underlying the isolated skin reactions or may suggest the role of IgE-mediated reaction in selective COX-2 inhibitor-induced adverse reactions [16, 32]. Additionally, increased cardiovascular toxicity associated with coxibs has been a current topic of interest. However, it seems mandatory to conduct a trial specifically assessing the cardiovascular risk and benefit of these agents to achieve the final conclusion to this issue [33].

In contrast to these data, some recent studies showed that rofecoxib was perfectly tolerated by almost all patients with a history of cutaneous reactions [23, 34, 35]. As a first report in the literature, Pacor et al [34] demonstrated that rofecoxib did not have cross-reactivity in 104 subjects with histories of urticaria/angioedema reaction to NSAIDs and suggested that rofecoxib was a safe alternative in these patient groups. Quiralte et al reported safety of rofecoxib in 15 patients with NSAID-induced skin reactions as well [36]. Similarly, in our study group, 6 patients with chronic urticaria and 54 otherwise healthy subjects with histories of urticaria/angioedema or anaphylactoid reaction after taking NSAIDs did not react to rofecoxib challenge. Only

one of our patients with a history of anaphylactoid-type reactions to ASA/NSAIDs and paracetamol reacted to rofecoxib challenge with urticaria. We did not rechallenge the patient with rofecoxib to exclude the possibility of coincidental hives; however, nimesulide and meloxicam challenge resulted in urticarial-type reaction in the same patient. Nevertheless, further challenge studies with rofecoxib or other selective COX-2 inhibitors on larger series of patients and higher doses of the drugs will clearly be welcome for this distinct subgroup of patients with analgesic intolerance. Surprisingly, a recent trial showed that the addition of rofecoxib to the treatment regimen seems to help some patients with chronic urticaria [37]. However, these are preliminary data and double blind, placebo-controlled trials should be designed to evaluate the role of selective COX-2 inhibitors in the treatment of chronic urticaria.

There are some controversial data regarding the status of atopy as a risk factor for allergic drug reactions. Contrary to the common belief that atopy is not a risk factor in ASA/NSAID intolerance [38], recent studies demonstrated an increased prevalence of atopy in patients with ASA/NSAID intolerance [39]. Although in this trial the atopy rate of whole group was not different from that of the general adult population in Turkey (24.1% vs 25%, $p > 0.05$), our previous study showed that SPT reactivity was significantly higher in patients with analgesic intolerance than that reported in healthy adult population of our country (41.7% vs 25% $p < 0.05$) [8, 15]. Besides the presence of atopy, the presence of reaction to antimicrobial drugs or anaphylactoid reactions to ASA was shown to increase the likelihood of intolerance to alternative drugs such as nimesulide and acetaminophen [40]. In the present study, the only patient reacting to rofecoxib had a history of anaphylactoid reaction to ASA, paracetamol, metamizole and antibiotics, but he was nonatopic. However, these very limited data prevent us drawing any conclusion on this issue.

In summary, rofecoxib can be used as a safe alternative for ASA/NSAID intolerant patients. However, considering its potential for adverse reactions, we suggest that the drug be prescribed after consulting with cardiology and neurology specialists and tested by an experienced allergist with oral challenge in equipped settings.

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