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Meloxicam and/or Etoricoxib Could Be Administered Safely in Two Equal Doses during an Open Oral Challenge in Patients with Nonsteroidal Anti-Inflammatory Drug Hypersensitivity

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Keywords
Nonsteroidal anti-inflammatory drug · Hypersensitivity · Cyclooxygenase-2 inhibitors · Oral provocation test · Safety

Abstract
Background: Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) are common. These patients require an effective and safe analgesic alternative. ***Objective:*** The aim of the study was to demonstrate the safety of meloxicam and etoricoxib administered by open oral challenge in 2 equal steps in patients with NSAID hypersensitivity. ***Methods:*** A cross-sectional, descriptive study of patients with a diagnosis of NSAID hypersensitivity who underwent an oral drug provocation test (DPT) with meloxicam or etoricoxib between January 2011 and August 2017 was conducted. The analysis was performed from a database in BD Clinic. ***Results:*** Two hundred and twenty-eight oral provocations were performed with an alternative NSAID (203 with meloxicam and 25 with etoricoxib) in 217 patients with hypersensitivity to NSAIDs. The median age was 38 years. Ninety-eight percent of meloxicam and 100% of etoricoxib DPTs were performed in 2 steps (without previous placebo), and 52% and 64% of meloxicam and etoricoxib DPTs, respectively, were performed with 50% of the therapeutic dose in each step. Tolerance to meloxicam was demonstrated in 192 patients (94.5%) and in 100% of patients receiving etoricoxib. ***Conclusions:*** Open oral provocation with meloxicam and etoricoxib carried out in 2 steps without placebo seems to be safe and implies less costs and less time expenditure. Also, it could be performed with 2 equal doses.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in clinical practice. However, they are one of the most frequent drugs to cause hypersensitivity reactions [1, 2], becoming a great problem for patients and their families and a real challenge to the allergist. The prevalence of NSAID hypersensitivity reactions has been reported as being between 0.6 and 5.7% in the general population, depending on the geographic zone, type of reaction, and criteria used for diagnosis [2, 3]. These reactions can be classified into 5 categories, based on clinical

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manifestations, the number of NSAIDs involved, and the presence or absence of underlying diseases according to the panel of experts from the European Academy of Allergy and Immunology (EAACI). These categories are (a) NSAID-exacerbated respiratory disease (NERD), (b) NSAID-exacerbated cutaneous disease (NECD), (c) NSAID-induced urticaria/angioedema (NIUA), (d) single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA), and (e) single NSAID-induced delayed reactions (SNIDRs) [4]. The first 3 groups are nonimmunologically mediated (cross-reactive) hypersensitivity reactions to NSAIDs related to cyclooxygenase-1 (COX-1) enzyme inhibition and, therefore, involving unrelated chemical groups of NSAIDs, and the last 2 groups are immunologically mediated hypersensitivity reactions to a single NSAID, with no cross-reactivity between groups [4, 5] The diagnosis of NSAID hypersensitivity is based on a well-documented history of repeated previous reactions to aspirin or another NSAID [4]; however, in many patients, this is not enough, so an OPT with aspirin is the most sensitive method (sensitivity ranges from 89 to 90%) to confirm the presence of hypersensitivity to aspirin and other cross-reactive NSAIDs [6]. A bronchial or nasal provocation test with aspirin lysine (L-ASA) is safer and faster to perform than the oral, but they are less sensitive (77–90% for the bronchial test and 80–86.7% for the nasal test) [7]. Although several in vitro tests have been proposed, none has been proven to be sensitive, specific, and reproducible enough to be recommended for routine practice [8, 9]. NSAIDs are the main medications used for pain management and other conditions including fever, rheumatologic diseases, and trauma pain. If NSAID hypersensitivity is diagnosed, it is important to evaluate tolerance to other analgesics as an alternative therapeutic option [10]. In this sense, COX-2-preferential inhibitors (nimesulide and meloxicam) or COX-2-selective inhibitors (recognized by the acronym "coxib") have been used [11–15].

However, in most of these studies, provocation protocols have been carried out in more than 2 steps and even performed on several days, increasing time and costs to carry them out. This turns out to be a major limitation, especially in low-income countries such as Colombia.

Methods

Patients

A descriptive cross-sectional study was designed to study patients with suspected NSAID hypersensitivity attended in Allergy Service of Fundación Valle del Lili, Cali, Colombia, from January 2011 to August 2017. Patients of all ages with a history of skin, respiratory, and/or anaphylaxis reactions related to NSAID intake were included. Patients with a history of delayed severe reaction (Stevens Johnson syndrome, toxic epidermal necrolysis, and DRESS/DiHS), pregnant women, or patients with serious comorbidities (uncontrolled asthma, severe infection, and decompensated heart, liver, or kidney disease) were excluded. All patients signed the informed consent before the OPT. This study was approved by Ethics Committee of Fundación Valle del Lili.

According to Dona et al. [2], the history of 3 or more episodes of reaction to 2 different NSAIDs is predictive for the cross-reactive type of hypersensitivity, while 2 or more reactions to the same NSAID with concomitant history of good tolerance to another NSAID with strong potency speak for the selective type. In the present study, diagnosis of cross hypersensitivity was based on the clinical history and was defined as the history of skin, respiratory, and/or anaphylactic reactions to 2 or more NSAIDs of different chemical groups. In those with no conclusive medical history, an OPT with aspirin or with the suspected culprit drug was carried out first, taking those who were positive as NSAID hypersensitive (Fig. 1).

OPT with Meloxicam or Etoricoxib

A meloxicam or etoricoxib OPT was performed openly, without previous placebo, mostly in 2 steps, at 30-min intervals, under medical surveillance in the Allergy Unit of Fundación Valle del Lili, where there is complete equipment for severe reaction management and blue code availability. Before each step, 60 and 180 min after the last dose was given, vital signs (blood pressure, heart rate, respiratory rate, and oxygen saturation) and spirometry were monitored; also, the presence of skin, ocular, nasal, bronchial, and/or gastrointestinal manifestations were evaluated every hour during the challenge procedure. At the time of discharge, warning signs were indicated, and patients were followed up to 48 h to detect a delayed reaction. The OPT was considered positive if one or more of the following signs/symptoms appeared: (a) cutaneous: urticaria, angioedema, rash, and pruritus; (b) respiratory: rhinorrhea, nasal blockage, conjunctivitis, dyspnea, and wheezing; (c) a ≥20% decrease in FEV_1; and (d) anaphylaxis, according to the EAACI/GA2LEN guideline [6].

Statistical Analysis

A univariate analysis was carried out to determine the numeric variable distribution. The variable normality was contrasted through the Shapiro-Wilk test considering a p value of 0.05. The normal distribution variables were summarized using central and dispersion tendency measures as the average and the standard deviation and were summarized with the median and interquartile range. The data analysis was carried out using the STATA v.14 statistical software.

Results

Demographic and Clinical Data

A total of 326 patients with suspected NSAID hypersensitivity were studied, and diagnosis was confirmed by reliable clinical history in 211 (64.7%), while 115 (35.3%)

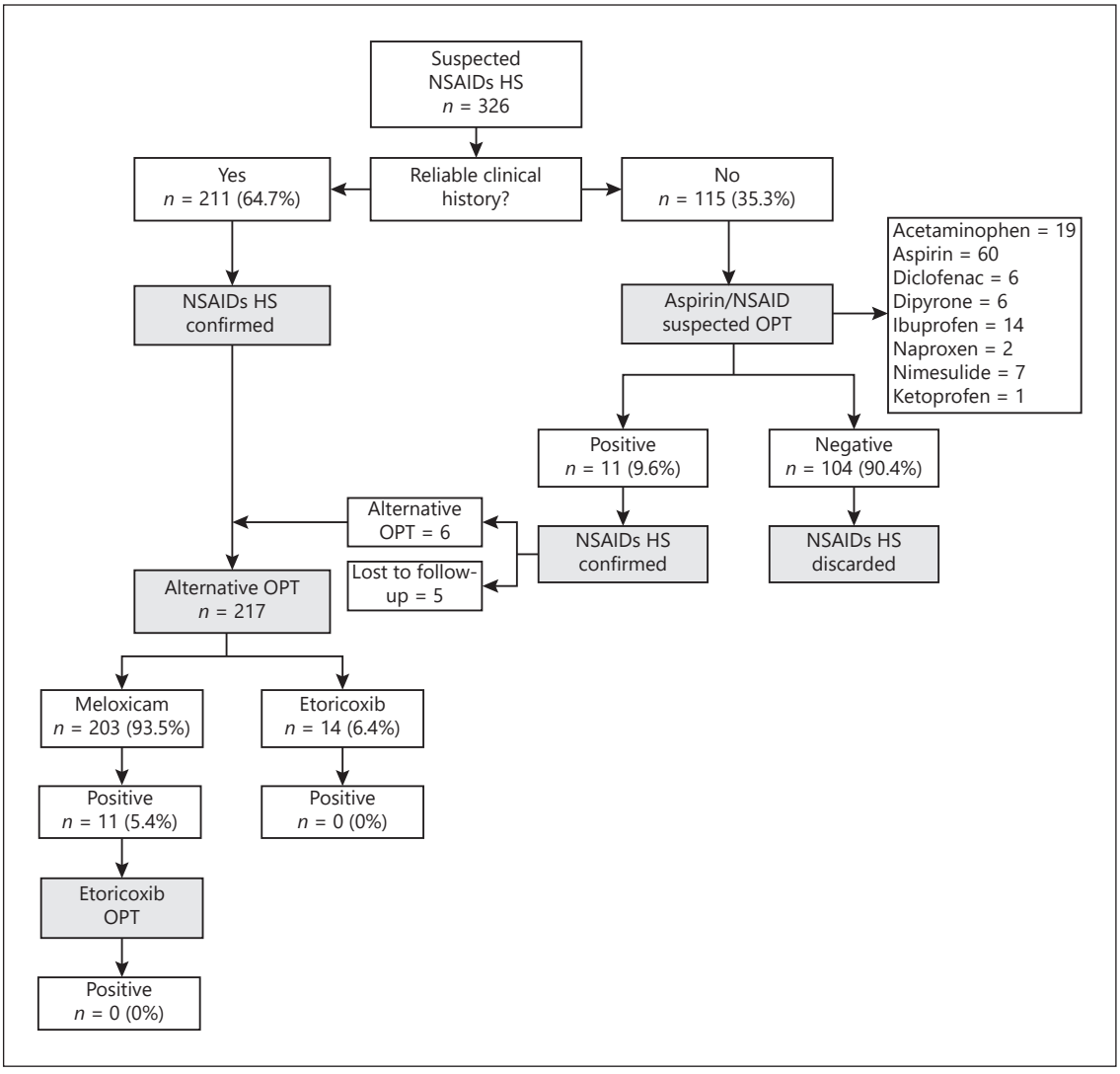

Fig. 1. Approach algorithm in patients with suspected NSAID hypersensitivity.*NSAIDs, nonsteroidal anti-inflammatory drugs; HS, hypersensitivity; OPT, oral provocation test.

underwent an OPT with aspirin or suspected drug. From the last group, it was possible to demonstrate NSAID tolerance in 104 patients. Of the 11 patients who reacted to the NSAID tested, 5 were lost to follow-up and 6 underwent OPT with alternative analgesics. In this last group, 4 patients underwent a meloxicam OPT, 2 of them being positive and, therefore, receiving etoricoxib in a second OPT with tolerance; the remaining 2 were challenged in the first instance with etoricoxib with tolerance too. In total, 203 patients underwent a meloxicam OPT, 11 of them being positive and, therefore, receiving etoricoxib in a second OPT. Fourteen patients were challenged in the first instance with etoricoxib. Altogether, 228 OPTs were carried out with alternative analgesics in 217 patients (203 with meloxicam and 25 with etoricoxib) (Fig. 1). The median age was 38 years, and 159 (73.2%) were women (Table 1). Information about latency period between the NSAID consumption and the beginning of reaction could be collected in 158 patients, occurring within the first hour in 66 patients (41.8%) and between 1 and 24 h in 61 patients (38.6%). The time between the reaction and medical consultation was an average of 4.08 years.

Of all the patients who underwent an OPT with alternative analgesics, 192 (88.4%) had atopic comorbidities and 26 (12%) had concomitant chronic urticaria. Three

Table 1. Demographic and clinical characteristics of the patients with an alternative-NSAID OPT

Characteristic	Meloxicam (n = 203)	Etoricoxib (n = 14)	Total (n = 217)
Age, years*			38 (23–53)
Sex (female)			159 (73.2)
Comorbidities			
Rhinitis	109 (53.6)	4 (28.6)	113 (52)
Asthma	56 (27.5)	3 (21.4)	59 (27.2)
Food allergy	9 (4.4)	1 (7.1)	10 (4.6)
Atopic dermatitis	10 (4.9)	0	10 (4.6)
Chronic urticaria	25 (12.3)	1 (7.1)	26 (12)
Hymenoptera allergy	4 (1.9)	0	4 (1.8)
Reactions to other drugs	3 (1.4)	0	3 (1.4)
Family history of allergy	30 (14.7)	1 (7.1)	31 (14.3)
Manifestations of initial reaction			
Cutaneous (urticaria and/or angioedema)	124 (61)	8 (57.1)	132 (60.8)
Respiratory (bronchial and/or nasal symptoms)†	9 (4.4)	1 (7.1)	10 (4.6)
Anaphylaxis	37 (18.2)	2 (14.3)	39 (18)
ND	33 (16.2)	3 (21.4)	36 (16.5)

The values are presented as n (%). NSAIDs, nonsteroidal anti-inflammatory drugs; OPT, oral provocation test; ND, no data. * Median (IQR). † Bronchial symptoms: dyspnea, wheezing, and cough; nasal symptoms: rhinorrhea and nasal congestion.

(1.3%) had a history of previous reaction to other drugs. One hundred and thirty-two patients (60.8%) had a history of skin manifestations induced by NSAIDs: urticaria in 27 cases (12.4%), angioedema in 79 (36.4%%), and urticaria + angioedema in 26 (12%). Ten patients (4.6%) had presented respiratory manifestations due to NSAIDs. Anaphylaxis due to NSAIDs was found in 39 cases (18%); 30 were induced by 2 or more NSAIDs, and 9 were induced by by a single NSAID. No patient underwent a skin test for NSAIDs. In patients with suspected severe IgE-mediated reactions, for example, single NSAID-induced anaphylaxis, an OPT was performed directly with COX-2-selective NSAIDs, looking for the safest alternative for the patient.

Meloxicam OPT

Two hundred and three OPTs were performed with meloxicam; of those, 199 (98%) were performed in 2 steps and only 4 (2%) in 3 steps. There were no provocations with greater number of steps. A cumulative dose of meloxicam of 15 mg was used in all of them, and 106 (52.2%) were performed with concentrations of 50% in each step.

Only 11 (5.4%) reacted to meloxicam provocation, and the drug was well tolerated by the remaining 192 patients (94.6%). Of the patients who reacted to meloxicam challenge, 3 (2.8%) had been performed in 2 steps with equal concentrations in each step and 8 (8.2%) in percentages of 34 and 66% of the therapeutic dose in each step. In a second instance, these patients underwent an etoricoxib OPT and was tolerated by all. The dose of meloxicam inducing reaction was the total cumulative dose in all patients. All reactions were easily controlled with oral antihistamines. All patients with a history of NSAID anaphylaxis were negative on the meloxicam OPT.

Etoricoxib OPT

Fourteen patients in the first instance and 11 additional patients who had been positive on meloxicam challenge underwent an etoricoxib OPT. All etoricoxib OPTs were performed in 2 steps, 16 (64%) in equal concentrations each and 9 (36%) in concentrations of 25 and 75% each step, for a total dose of 120 mg. Etoricoxib was well tolerated in all the patients, including those who had presented NSAID anaphylaxis**.**

Discussion

Choosing an alternative drug in patients with a history of NSAID hypersensitivity represents a real problem in daily clinical practice. COX-2-preferential inhibitors

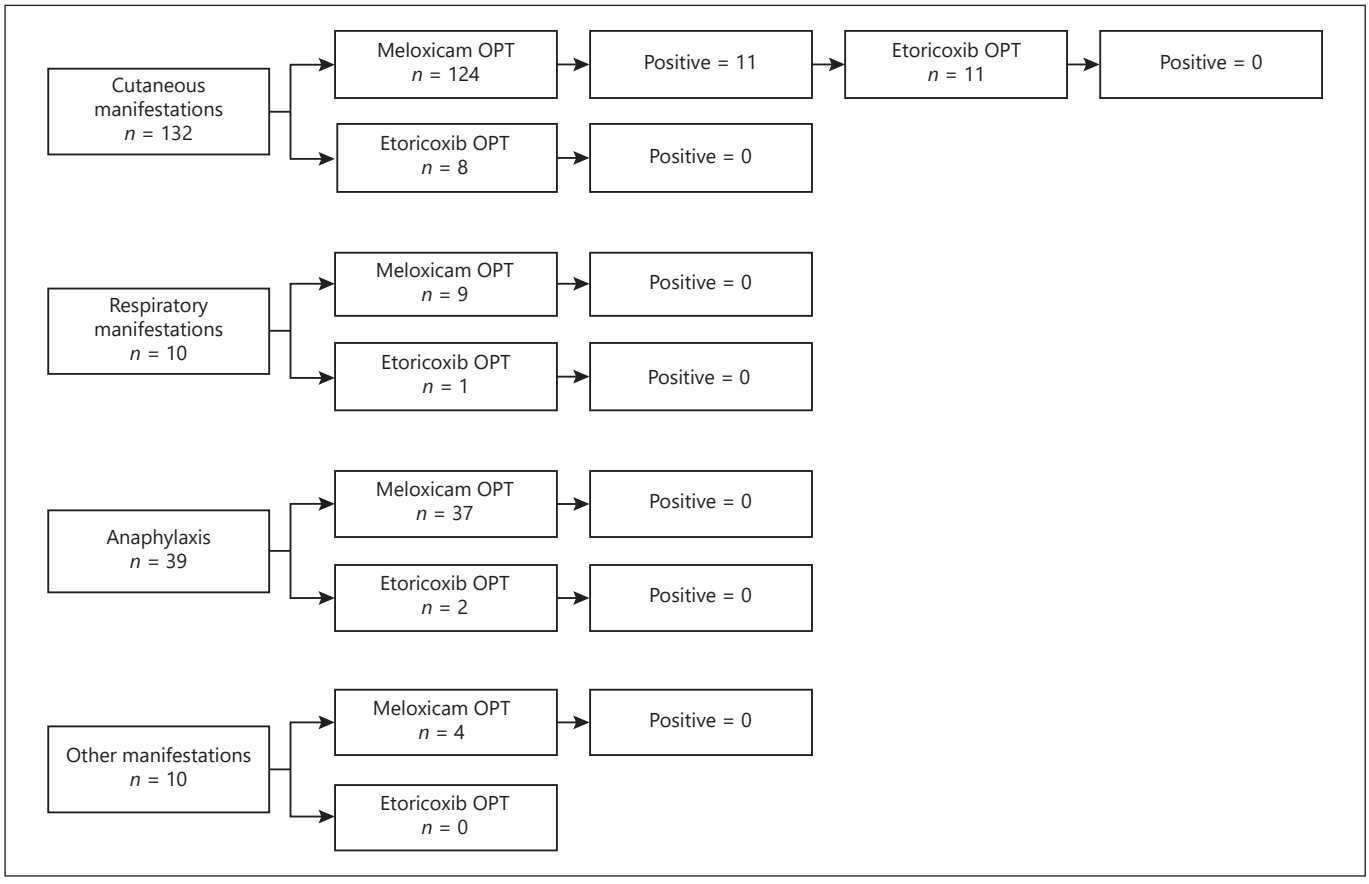

Fig. 2. Result of the OPT according to initial manifestation of NSAID hypersensitivity. NSAIDs, nonsteroidal anti-inflammatory drugs; OPT, oral provocation test.

(nimesulide and meloxicam) or COX-2-selective inhibitors have been used in these cases.

In the present study, we found that most patients with NSAID hypersensitivity tolerate an alternative option: meloxicam in 94.5% and etoricoxib in 100% of cases, evaluated by an OPT performed in just 2 steps (98.2%), at 30-min intervals, and with concentrations of 50%/50% of total therapeutic dose in more than a half of patients. When we evaluated the OPT result in relation to the hypersensitivity phenotype, a tolerability of 100% was found in patients with respiratory manifestations and anaphylaxis induced by NSAIDs for both meloxicam and etoricoxib. Only 8.3% of patients with cutaneous manifestations developed a reaction on meloxicam challenge, but subsequently tolerating etoricoxib (Fig. 2). In agreement with published data, and although no studies have been published including this type of "simplified" approach, it seems reasonable to think that it is safe, practical, and feasible. In this sense, Prieto et al. [14] reported a meloxicam tolerability in 96.1% of patients evaluated, being 95.6% (22/23) in the asthma/NSAID intolerance group and 96.4% (27/28) in the group of NSAID intolerance with cutaneous manifestations. Similarly, Bavbek et al. [12] reported the safety of this drug in patients with aspirin-exacerbated respiratory disease (AERD), since only one of 21 patients reacted during the challenge, although the total therapeutic dose used by them was 7.5 mg, which is lower than the one used in our study, suggesting that meloxicam does not lose its COX-2-preferential inhibition when increasing the dose. Goksel et al. [11] demonstrated that 91.4% of patients with NSAID-induced urticaria/angioedema tolerated 7.5 mg of meloxicam. These studies reinforced the findings of Quaratino et al. [15], who showed a tolerability of 98.9% (175/177) at the same doses and phenotype. However, the protocols used in all these studies are much longer, even carried out over several days and, in many cases, in hospitalized patients, being more expensive, with greater consumption of time and resources.

With respect to etoricoxib, it was well tolerated by 100% of patients in the OPT. All etoricoxib challenges were carried out in 2 steps and 64% with equal concentrations in each step (50%/50%), for a total cumulative dose of 120 mg. Viola et al. [16] reported the safety of etoricoxib in 31 patients with NSAID hypersensitivity after an OPT with the same dose; however, the protocol design was different, beginning with placebo 1 week before, and challenged with 2 progressive steps of 10 and 90%, or 3 steps, starting with 1/100 of total dose in the case of anaphylaxis history.

More recently, Llanora et al. [17] reported a 95% tolerance to 120 mg of etoricoxib in 74 Asian patients with NSAID intolerance. Previous studies showed similar data, such as the study by Sánchez-Borges et al. [18] who administered the same dose of etoricoxib to 56 patients with NSAID hypersensitivity, finding a tolerability of 92.9%. Lower doses have also been evaluated by Nettis et al. [19] who administered etoricoxib 90 mg to 141 patients, and only 2 patients (1.4%) reacted during the OPT.

An important aspect to discuss is the definition of NSAID hypersensitivity that was used. Dona et al. [2] proposed that the history of 3 or more episodes of reaction to 2 different NSAIDs was predictive for the cross-reactive type of hypersensitivity. However, in the present study, the history of a single reaction (cutaneous, respiratory, or anaphylactic) to 2 or more NSAIDs of different chemical groups was used to define cross hypersensitivity, while in those with no conclusive medical history, an OPT with aspirin or with the suspected culprit drug was carried out first, taking those who were positive as NSAID hypersensitive. Also, patients with single NSAID-induced anaphylaxis were directly challenged with COX-2-selective NSAIDs, looking for the safest alternative for the patient. It is possible that some of the latter patients were not true cross-reactors and have been considered as such without making a more precise diagnosis, which could be a weakness of the study. Finally, long-term use and tolerance to COX-2 inhibitors have been reported in most of the patients with NSAID sensitivity (including those with anaphylactoid reaction), with previous negativity on a single-masked, placebo-controlled OPT [20].

In conclusion, an open OPT with selective (meloxicam) or specific (etoricoxib) COX-2 inhibitors performed in 2 steps, even in equal concentrations (50–50%), seems to be safe in patients with a history of NSAID hypersensitivity, including anaphylaxis. The total number of patients, as well as the number of those challenged with meloxicam, represents an important strength. However, the authors recognize the small sample size in those challenged with etoricoxib as a limitation of the study, but it reinforces findings from previous studies where its safety has been described [17–19]. Subsequent studies are required to validate and reproduce these data and probably to evaluate the use of an open single total dose challenge as a true alternative to assess the tolerability of COX-2-selective drugs in patients with NSAID sensitivity, as long as the necessary resources are available to treat potential serious reactions.

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Statement of Ethics

This study was approved by the Ethics Committee in biomedical research IRB/EC of Fundación Valle del Lili, Approval Number 170–2019. The participants or parents/guardians signed informed consent.

Conflict of Interest Statement

All authors disclose no conflicts of interest.

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Author Contributions

Dolly Vanessa Rojas Mejía (D.V.R.M.) and Carlos Daniel Serrano Reyes had the idea and wrote the manuscript. D.V.R.M. also built the database with Diana Lucía Silva Espinosa. The latter and Luis Fernando Ramírez included patients, made writing suggestions, and provided references. Diana Marcela Martínez analyzed the database and planned the methodology.

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