Original Article

Meloxicam Tolerance in Hypersensitivity to Nonsteroidal Anti-Inflammatory Drugs

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Abstract. *Background:* Patients with aspirin-sensitive respiratory and skin diseases experience cross reactions to all nonsteroidal anti-inflammatory drugs (NSAIDs) which inhibit cyclooxigenase (COX) enzymes. The need to identify an alternative drug that is safe and reliable is a common problem in clinical practice.
Objective: The aim of this study was to test the tolerability of meloxicam in NSAID-sensitive patients.
Methods: Between January 2005 and February 2006 we performed single-blind oral challenge tests with meloxicam in NSAID-intolerant patients, exposing them first to placebo and then, after 30 minutes, to the first dose of meloxicam (7.5 mg). After 30 minutes, if no response appeared, the last dose of meloxicam (15 mg) was given, for a total accumulated dose of 22.5 mg. The test was considered positive if urticaria, erythema, and/or angioedema appeared.
Results: We tested 114 patients: 36% men and 64% women whose mean age was 45.81 years. Meloxicam was well tolerated in 109 of the 114 patients (95.62%) and only 5 (4.38%) developed an adverse reaction (urticaria in all cases).
Conclusion: This study shows that meloxicam can be a good option for NSAID-intolerant patients: it was safe for over 95% of the patients and is easier to obtain than celecoxib or etoricoxib. However, we think that a patient should be tested in an allergy unit before it is prescribed.

Key Words: Angioedema. Meloxicam. Nonsteroidal anti-inflammatory drugs. Tolerance. Urticaria. Drug allergy.

Resumen. *Antecedentes:* Los pacientes con hipersensibilidad cutánea o respiratoria a la aspirina presentan reacciones cruzadas con todos los antiinflamatorios no esteroideos (AINEs) que inhiben la ciclooxigenasa (COX). La necesidad de identificar una medicación alternativa que sea segura y fácil de conseguir es un problema en la práctica clínica.
Objetivo: El objetivo de este estudio fue probar la tolerancia del meloxicam en pacientes con intolerancia a los AINEs.
Métodos: Desde enero de 2005 a Febrero de 2006 hicimos pruebas de exposición oral controlada simple ciego con meloxicam a pacientes con intolerancia a los AINEs. Después de obtener el consentimiento informado, los pacientes se expusieron a dosis crecientes de meloxicam. Durante el día de la exposición recibían una primera dosis de placebo y pasados 30 minutos, la primera dosis de meloxicam (7.5 mg) y después de otros 30 minutos, si no presentaban ninguna reacción, la última dosis de meloxicam (15 mg) (dosis total acumulada: 22.5 mg). La prueba se consideraba positiva si aparecía urticaria, eritema y/o angioedema.
Resultados: Se incluyeron 108 pacientes: 36% de hombres y 64% de mujeres, con una edad media de 45.81 años. Meloxicam se toleró en 103/108 de los pacientes (95.37%) y tan sólo 5/108 (4.62%) presentó una reacción adversa (urticaria en todos los casos).
Conclusión: Este estudio muestra que meloxicam puede ser una buena opción para los pacientes con intolerancia a los AINEs : es seguro y es más fácil de obtener que el celecoxib o etoricoxib, pero creemos que se debe probar primero en una Unidad de Alergia antes de su prescripción.

Palabras Clave: Angioedema. Meloxicam. Antiinflamatorios no esteroideos. AINEs. Tolerancia. Urticaria. Alergia a medicamentos.

Introduction

Patients with aspirin-sensitive respiratory and cutaneous diseases experience cross reactions to all nonsteroidal anti-inflammatory drugs (NSAIDs) which inhibit cyclooxygenase (COX) enzymes. As drugs which selectively inhibit COX-2 are now available, questions are raised as to whether cross-reactivity occurs between aspirin and these COX-2 inhibitors [1]. The need to identify an alternative drug that is safe and reliable is a common problem in clinical practice.

Some studies have shown that rofecoxib is safe in these patients [2], but after its withdrawal from the market, we observed problems with its substitutes (celecoxib, etoricoxib) because general practitioners and pharmacists prefer not to prescribe them and pharmacists prefer not to recommend them due to the supposed risk of cardiovascular events. We therefore decided to test another alternative drug for these patients. Nettis et al [3] confirmed that meloxicam is a tolerated NSAID, as Quanrantino et al [4] and Kosnic et al [5] had previously demonstrated. Meloxicam exerts an inhibitory effect on prostaglandin H synthases (PGHS) or COX enzymes that catalyze the conversion of arachidonic acid to prostaglandin endoperoxides with a high preference for the second isoform [3]. The small number of positive oral challenges may be partly explained, according to Nettis and colleagues, by the selectivity of action on the PGHS-2 isoform.

The aim of this study was to test the tolerability of meloxicam in NSAID-sensitive patients.

Material and Methods

Patients who had reported problems with at least 2 NSAIDs or who had had a positive oral challenge with acetylsalicylic acid were enrolled between January 2005 and February 2006. The inclusion and exclusion criteria are listed in the table. All patients signed an informed consent form before the challenge test.

Inclusion and Exclusion Criteria

Inclusion Criteria
– Adults
– Documented reactions with at least two different NSAIDs or positive oral challenge to acetylsalicylic acid
– Informed consent signed
Exclusion Criteria
– Informed consent not signed
– Contraindication to discontinuing the use of histamine 1 receptor antagonists 5 days before the oral challenge
– Contraindication to discontinuing the use of drugs like B-blockers 2 days before the oral challenge
– Patients with gastrointestinal symptoms
– Pregnancy or breast feeding
– Contraindication to eventual use of epinephrine
– Subjects with psychosomatic disorders

To evaluate meloxicam tolerance all subjects underwent a single-blind placebo-controlled oral challenge. On the challenge day they received first a placebo capsule (lactose) and, after 30 minutes, the first dose of meloxicam (7.5 mg) and after 30 minutes, if no response appeared, the last dose of meloxicam (15 mg). The total accumulated dose was 22.5 mg. All substances were given in opaque capsules prepared by the hospital's pharmacy. During the challenge forced expiratory volume in 1 second (FEV_1) was monitored. After the last dose patients were kept under observation for 3 hours and they could return to or telephone the hospital if they developed delayed reactions. The test was considered positive if urticaria, erythema, angioedema, and/or respiratory symptoms developed.

Results

We enrolled 108 patients: 36% men and 64% women whose mean age was 45.81 years. We distributed subjects in 2 groups: patients who had problems with at least 2 different NSAIDs (clinical diagnosis, 90.35%) and patients with a positive oral challenge test to aspirin (tested diagnosis, 9.65%). All subjects had a demonstrated clinical history of adverse reaction after taking various NSAIDs: 35.18% of them had experienced urticaria alone, 41.66% angioedema and 23.14% urticaria plus angioedema. The latency period between the drug intake and the reaction occurred in less than an hour in 39.47% of patients, between 2 and 6 hours later in 50% of patients, and more than 6 hours later in 10.53% of patients.

Meloxicam was well tolerated by 103 out of 108 patients (95.37%) and only 5 of the 108 patients (4.62%) presented an adverse reaction, which was a slight urticaria in all the cases. All subjects had a FEV_1 of greater than 80% of the predicted value.

Discussion

Intolerance to acetylsalicylic acid and other NSAIDs is a serious problem in clinical practice. Our results are consistent with findings that this analgesic intolerance is more common in middle aged females [6] and that there are certain accompanying conditions, such as asthma, rhinitis, or chronic urticaria [7-9]. Mastalerz et al [10] demonstrated that both patients with chronic idiopathic urticaria and with asthma induced by aspirin exhibit high levels of eicosanoids. They concluded that increased levels of leukotriene 4, total cysteinyl leukotriene and prostaglandin D2 found after ingestion of aspirin in both groups of patients were due to inhibition of COX-1 rather than COX-2. Moreover, clinical symptoms were caused by COX-1 as well as COX-2 inhibition. A more recent paper from the same authors showed that the genes that code for leukotriene C4 synthase display polymorphism; thus,

eicosanoid elevation in patients with chronic idiopathic urticaria and aspirin-induced asthma could be a hereditary behavior [11].

At the moment, there are no NSAIDs whose use is absolutely free of adverse reactions so, it is important to suggest alternative analgesics to these patients because most of them are frightened after suffering a reaction. The best-tolerated drugs on the market at this time are paracetamol and celecoxib [12]. Recent studies have indicated possible adverse effects of coxibs on the cardiovascular system [13-15]. Focusing on this side effect many physicians do not want to prescribe COX-2 inhibitors and pharmacists do not recommend them, so our patients are without alternative analgesics except paracetamol. We therefore decided to test meloxicam as an alternative because it is easy to obtain and because findings from small trials have shown good tolerance [3, 6].

Our study shows that meloxicam can be a good option for NSAID-intolerant patients: it was safe for these patients and is easier to purchase than celecoxib or etoricoxib. However, we think it should first be tested in an allergy unit before it is prescribed for an individual.

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