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Montelukast in 2 Atopic Patients With Intolerance to Nonsteroidal Anti-Inflammatory Drugs and Paracetamol: 5-Year Follow-Up

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Key words: Meloxicam. Montelukast. Nonsteroidal anti-inflammatory drug hypersensitivity. Paracetamol. Tolerance.

Palabras clave: Meloxicam. Montelukast. Hipersensibilidad a antiinflamatorios no esteroides. Paracetamol. Tolerancia.

Hypersensitivity to acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) is a relatively common condition in patients with chronic urticaria and in adults with asthma [1], with a self-reported prevalence of less than 2% in the general population [2]. Increased production of cysteinyl leukotrienes due to the interference of NSAIDs with cyclooxygenase (COX) metabolism is a possible physiopathological pathway underlying the clinical manifestations [3]. In recent years, COX-2 selective inhibitors have been proposed as valid alternatives for patients with hypersensitivity to ASA or NSAIDs [4]. However, in a small percentage of very sensitive patients who may also react to paracetamol, which is a very weak COX inhibitor, even these new drugs are not tolerated and this problem is a challenge in clinical practice [5,6].

The authors report the clinical data from a period of 5 years for 2 asthmatic patients with sensitivity to multiple NSAIDs (including COX-2 selective inhibitors and paracetamol). We present the outcome of administration of montelukast, a leukotriene receptor antagonist, which was also indicated for the control of their mild respiratory atopic disease.

Both patients were females, aged 30 and 41 years. They were referred for a 10-year history of severe generalized urticaria and angioedema occurring less than 1 hour after the intake of 500 mg of ASA or paracetamol. At the time of referral, due to the progressive severity of the reactions, they did not have any suitable medication to control fever or pain. Both patients had also had persistent rhinitis and mild persistent asthma since childhood. Symptoms were under control with low doses of inhaled steroids. They had normal lung function and were both atopic, both sensitized to mite and 1 to grass and *Parietaria judaica*.

Over a period of approximately 1 month, we performed single-blind placebo controlled challenges with the more selective COX-2 inhibitors available in our market at that time (meloxicam, 7.5 mg, and nimesulide, 100 mg) and also with paracetamol (500 mg); responses were positive (generalized urticaria and angioedema) and were controlled with symptomatic treatment. Subsequently they were started on montelukast 10 mg per day as a single treatment, to treat their mild asthma and rhinitis. After 4 and 6 weeks of treatment, respectively, we performed new single-blind placebo controlled challenges with meloxicam (7.5 mg) and paracetamol (1000 mg), obtaining negative results. Both patients continued montelukast as their single asthma-control therapy, rarely needing to use short-acting bronchodilators for relief. They were also able to take the allowed anti-inflammatory and antipyretic drugs on an as-needed basis with full tolerance.

In both these patients with ASA/NSAID and paracetamol sensitivity, the use of montelukast allowed the as-needed intake of these drugs over a period of 5 years. We have tried the same approach in 3 nonatopic patients with intolerance to paracetamol and NSAIDs, but none of them achieved tolerance to these drugs while using montelukast 10 mg daily for 2 weeks before challenges (data available on request).

Consistent with our results, Pérez et al [7] demonstrated that leukotriene antagonists can inhibit skin reactions at least partially in 60% of patients with reactions related to NSAID use. This has also been shown by other authors [8]. Also in line with our data, more recently Serrano et al [9] reported the efficacy of montelukast in preventing adverse reactions

to NSAIDs, COX-2 selective inhibitors, and paracetamol in a 52-year-old patient. Nevertheless, montelukast could not prevent severe allergic reaction to diclofenac in another case [10].

In conclusion, we report the usefulness of montelukast in providing clinically significant tolerance to paracetamol and meloxicam used on an as-needed basis by atopic asthma patients with hypersensitivity to these drugs. Although not observed in placebo-controlled conditions, these findings were confirmed over a follow-up of 5 years. However, based on our experience this approach does not seem to be effective in nonatopic patients, using a 10-mg dose of montelukast. In patients with NSAID hypersensitivity who have a clinical indication to take these drugs on a regular basis, a tolerance induction protocol could be an alternative.

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Anaphylactic Shock Caused by Tick (*Rhipicephalus sanguineous*)

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Palabras clave: Anafilaxia. Reactividad cruzada. Garrapatas. *Rhipicephalus sanguineous.*

Ticks frequently cause human disease by transmitting infectious agents (protozoa, rickettsia, bacteria, and viruses) [1]. Toxic local reactions are common, but systemic immunoglobulin (Ig) E-mediated reactions after tick bites are very seldom reported. Allergy to *Argas reflexus* [2], *Ixodes ricinus* [3], *Ixodes holocyclus* [4] and *Ixodes pacificus* [5] is well documented, but there is only 1 case of allergy to *Rhipicephalus* species in the literature [6]. We now report a case of anaphylaxis due to *Rhipicephalus sanguineous*.

A 58-year-old goatherd was referred to our service for evaluation after he experienced heavy sweating, sickness, chest tightness, dyspnea, and loss of consciousness after a tick bite. On arrival at the hospital during that episode, his systolic blood pressure was 80 mm Hg and oxygen saturation was 88%. He was vomiting and had generalized urticaria. Two ticks were found on his skin. He responded to epinephrine, antihistamines and corticosteroids. Afterwards, he reported to us that he had had a similar reaction after a tick bite 5 years ago and that he had a history of severe, recurrent reactions after tick bites. He had no history of previous allergies or family allergies.

Proteins from the whole body of ticks were extracted with phosphate buffered saline by stirring for 1 hour at 4ºC. The soluble fraction was separated by centrifugation at 22 000g for 20 minutes at 4ºC. The tick extract was then dialyzed against distilled water, filtered, and lyophilized. The protein concentration of the extract (24% wt/wt) was determined (Biorad, Hercules, California, USA).

Specific IgE against tick extract was measured by an enzyme allergosorbent test according to the manufacturer's instructions (Hytec-Specific IgE EIA, Hycor Biomedical Inc, Garden Grove, California, USA).

Protein extract of tick was separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE). Separated protein bands were electrophoretically transferred to polyvinylene difluoride membranes. The binding of IgE antibody to allergens was analyzed by Western blot using serum from the allergic patient and antihuman immunoglobulin (Ig) E peroxidase conjugate (Dako, Carpinteria, California, USA). Chemiluminescence detection reagents (Western Lightning Chemiluminescence Reagent Plus, Perkin Elmer, Boston, Massachusetts, USA) was added following the manufacturer's instructions.

The skin prick test did not indicate sensitization to common inhalants, foods, *Anisakis simplex*, latex, amoxicillin,