Treatment of mild to moderate Graves' ophthalmopathy with sodium diclofenac: a pilot study

Tratamento da oftalmopatia de Graves leve a moderada com diclofenato de sódio: um estudo piloto

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ABSTRACT

Objective: To report the use of sodium diclofenac, an antagonist of *PPAR*-gamma and cyclooxigenase-2 (COX-2) inhibitor in the treatment of mild to moderate Graves' ophthalmopathy. **Subjects and methods:** Thirteen patients with clinical activity score (CAS) 2 to 7 were treated during a period ranging from 3 to 12 months (mean 7.8 ± 3.4) with oral sodium diclofenac, 50 mg every 12 hours. **Results:** Extra-ocular muscle restriction and CAS improved significantly, p = 0.003 and = 0.004, respectively. Ocular pain and diplopia disappeared, except for one patient who reported improvement of these symptoms. No recurrence was found after interruption of treatment. **Conclusions:** Treatment of moderate Graves' ophthalmopathy with oral sodium diclofenac is a good, safe and less expensive therapeutic option. Like others new treatment trials, findings must be confirmed in a greater number of patients in a controlled study. Arq Bras Endocrinol Metab. 2011;55(9):692-5

Keywords

Moderate Graves' ophtalmopathy; treatment; sodium diclofenac; *PPAR*-gamma; cyclooxigenase-2

RESUMO

Objetivo: Relatar o uso do diclofenato de sódio, um antagonista do *PPAR*-gama e inibidor da ciclooxigenase-2 (COX-2) no tratamento da leve a moderada oftalmopatia de Graves. **Sujeitos e métodos:** Treze pacientes com CAS (*clinical activity score*) 2 a 7 foram tratados durante um período de 3 a 12 meses (média 7,6 ± 3,4) com diclofenaco de sódio por via oral na dose de 50 mg a cada 12 horas. **Resultados:** A restrição da musculatura extraocular e o índice CAS melhoraram de modo significativo, respectivamente p = 0,003 e p = 0,004. A dor ocular e a diplopia desapareceram, com exceção de um paciente que referiu melhora desses sintomas. Não houve recidiva após a interrupção do tratamento. **Conclusões:** O tratamento da oftalmopatia de Graves de média gravidade com diclofenaco de sódio por via oral é uma opção boa, segura e de baixo custo. Como outros novos tratamentos, ele deverá ser confirmado em um maior número de pacientes em estudos controlados. Arq Bras Endocrinol Metab. 2011;55(9):692-5

Descritores

Oftalmopatia de Graves moderada; tratamento; diclofenaco de sódio; *PPAR*-gama; ciclooxigenase-2

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INTRODUCTION

Graves' ophthalmopathy is an autoimmune condition in which intense orbital inflammation affects mainly the extra-ocular muscles and fibro-adipose tissue. The progression of the disease depends upon interactions between B and T lymphocytes and orbital fibroblasts (1). The increased knowledge on the pathogenesis of Graves' ophthalmopathy introduced new immunotherapeutic strategies directed to dampen one specific component of this immunological process. In general, these strategies are targeted to immunocompetent cells or cytokines involved in the orbital inflammation (1-3). One important player in this complex process is *PPAR*-gamma. In a previous study, we found a significant increase in the expression of *PPAR*-gamma in the orbital fibro-adipose tissue of patients with Graves' ophthal-

mopathy in the active stage, and a link with the peculiar increase of ocular adipose tissue (4). Otherwise, the gene of proinflammatory cyclooxigenase-2 (COX-2), another partner of the disease, was found overexpressed in severe and active phase of Graves' ophthalmopathy (5,6). According to these data, the use of a *PPAR*-gamma and COX-2 antagonist could theoretically be useful in the treatment of the orbital disease.

The aim of this prospective pilot study is to report the results of the use of sodium diclofenac, a nonsteroid anti-inflammatory drug (NSAID) that is a *PPAR*-gamma antagonist and COX-2 inhibitor, in the treatment of selected patients with Graves' ophthalmopathy (7,8).

PATIENTS AND METHODS

Thirteen patients without ocular treatment at least 3 months before the study were selected by showing clinical activity score (CAS) 2 to 7. Five patients with CAS 2 who sought treatment were included because of a complaint of distressing ocular pain, diplopia or severe conjunctival hyperemia. They were evaluated monthly on the first 3 months, and afterwards, every 2 months. Patients with optic neuropathy or renal disease were excluded. The duration of Graves' ophthalmopathy ranged from 4 to 60 months (mean 32.1 ± 16.9 months), age ranged from 24 to 66 years old (mean 42.7 ± 14.8 years), and 7 patients were females. Seven patients were hyperthyroid, under treatment with methimazole; and three of them were hypothyroid, receiving L-thyroxine. Three of them were euthyroid. Antibodies to the TSH receptor were positive in 10 patients. All patients had variable degrees of spindle shaped extra-ocular muscle thickness, as shown by orbital computed tomography scan. The same examiner evaluated the restriction of extra-ocular muscle by means of scores 0 to 4, where zero represented absence of restriction, and 4, inability to drive the eye to the points shown in figure 1. Proptosis was measured by Hertel exophthalmometer, and diplopia was also investigated. Figure 1 shows one of the patients of the study and the representation of his extra-ocular muscle evaluation. Oral sodium diclofenac was administered every 12 hours in a maximum period of 12 months, or interrupted after signs or symptoms disappeared. The administration period ranged from 3 to 12 months (mean 7.8 ± 3.4 months). Local eye adjuvant therapy to all patients consisted of ointments and lubricating drops. Oral omeprazole was also prescribed in the case of gastric pain.

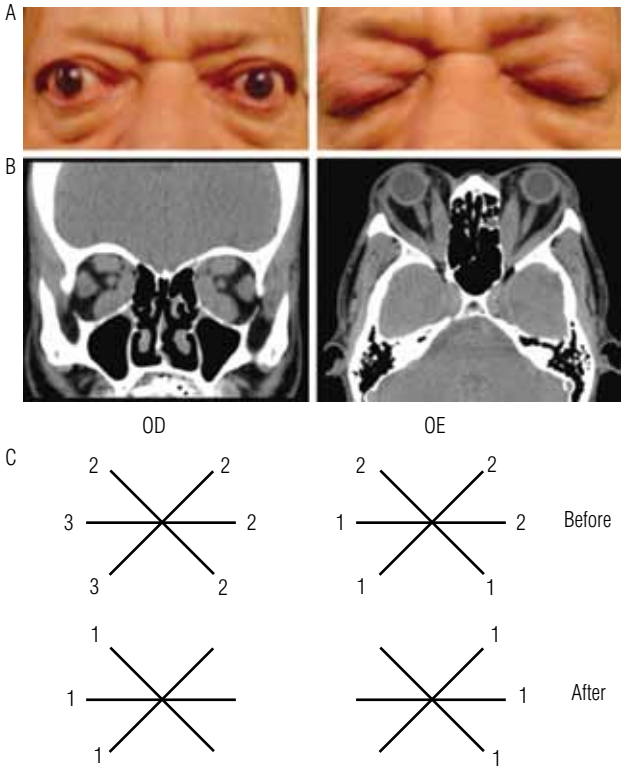

Figure 1. (A) Characteristic Graves' ophtalmopathy; (B) Computed tomography scans of the orbits; (C) Schematic representation of extra-ocular muscle restriction.

Blood counts and renal and liver function were assessed during the treatment.

Paired t test was used in the statistical comparison of proptosis and the sum of extra-ocular muscle restriction scores of the right and left eye of each patient, before and after the treatment. Wilcoxon non-parametric test was used to compare the changes in CAS index.

Informed consent was obtained from all patients.

RESULTS

Table 1 summarizes the evolution of the symptoms and signs of the disease before and after the treatment.

Ocular pain and diplopia disappeared, except in one patient who still showed some discomfort. The improvements in extra-ocular muscle function and CAS were statistically significant, $p = 0.003$ and $p = 0.004$, respectively. Proptosis was unaltered.

No renal or liver injury was found. Two patients complained of gastric pain, which was relieved by oral omeprazole.

No recurrence was found after treatment was interrupted.

Table 1. Result of treatment of mild to moderate Graves' ophthalmopathy with 50 mg of oral sodium diclofenac every 12 hours

	Ocular pain (n = 6)	Diplopia (n = 5)	Muscle restriction[a] (scores 0-4) (n = 11)	Proptosis[b] (mm) Right n = 13	Proptosis[b] (mm) Left n = 13	CAS[c] n = 13
Before treatment	6	5	5.23 ± 4.34	26.04 ± 4.20	23.38 ± 3.57	3.61 ± 1.44
After treatment	1	1	3.38 ± 4.53	25.08 ± 3.60	23.00 ± 3.67	2.30 ± 1.03
p			= 0.003	ns	ns	= 0.004

a) Mean of the sum of muscle restriction scores of right and left eye (see text); b) Mean; c) Mean of clinical activity score (CAS).

DISCUSSION

Conventional management of severe Graves' opthalmopathy is usually based on nonspecific immunosuppression with high doses of corticosteroids or orbital decompression (9). The novel strategies of treatment comprises B lymphocyte depletion (10,11) or anticytokines (12,13). In general, they are expensive, administered parenterally and, sometimes, not deprived of adverse effects (14). *PPAR*-gamma is a substantial component of the orbital inflammatory process, as observed earlier. Another evidence of the *PPAR*-gamma contribution in the pathogenicity of Graves' ophalmopathy was obtained after the report on adverse effects of insulin-sensitizing *PPAR*-gamma agonists, the thiazoledinediones, on the natural course of the ocular disease (15,16). These findings strengthen the previous suggestion that take into account *PPAR*-gamma as one inducer of the characteristic orbital adipose tissue accumulation of the thyroid eye disease. (4). According to these data, therapeutic efforts to antagonize *PPAR*--gamma should theoretically be useful in the management of ophthalmopathy. Sodium diclofenac, besides antagonizing *PPAR*-gamma, has a potent inhibiting action upon COX-2, another player of the autoimmune orbital process. This enzyme converts arachidonic acid to prostaglandin, a relevant factor on inflammation and adipogenesis, and a natural ligand of *PPAR*-gamma (17). Graves' ophthamopathy of mild to moderate intensity but with troublesome symptoms, is usually managed with orbital radiotherapy or corticosteroids in variables doses. This type of treatment is usually associated with many and, sometimes undesirable, side effects. The favorable results achieved with sodium diclofenac on the distressing diplopia and ocular pain were noteworthy in this preliminary survey. In addition, impaired extra-ocular muscle function and clinical activity score of the disease improved significantly. It is relevant that gastric pain was the only side effect reported by two patients. Treatment of Graves' ophthalmopathy has a long story, with many different drugs and strategies tested. Few of them resisted the test of daily clinical practice. Treatment with indomethacin, another nonsteroidal anti-inflammatory drug, which is a non-selective inhibitor of Cox 1 and 2, is an example. It was used many years ago as a rectal suppository in a non-controlled therapeutic trial in seven patients with modest results, but it was further disregarded (18).

In conclusion, oral sodium diclofenac in the treatment of mild to moderate Graves' ophthalmopathy resulted in almost complete relief of diplopia and pain, and significant improvement of the extra-ocular muscle restriction and CAS.

The results of this pilot study, if confirmed in a controlled trial with a greater number of patients, could be a good option in the treatment of selected patients with ocular complications caused by Graves' disease, because of the feasibility, low cost and almost absence of side effects of this treatment.

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