International Journal of Clinical Pharmacology and Therapeutics, Vol. 47 – No. 2/2009 (89-95)

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ISSN 0946-1965

Comparison of the efficacy and safety of a novel meloxicam ophthalmic formulation with a reference diclofenac solution in cataract surgery

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Key words
meloxicam – diclofenac – cataract surgery – inflammation – ophthalmic formulations

Abstract. A novel topical ophthalmic formulation of the preferential COX-2 inhibitor meloxicam has recently been developed. The purpose of the present study was to evaluate the efficacy and safety of this novel 0.03% meloxicam solution with regard to a reference 0.1% diclofenac formulation in a prospective, parallel, randomized, multicenter, double-blind study. Two groups of patients submitted to phacoemulsification with intraocular lens implantation were formed. Patients in one group were treated with meloxicam and those in the other group with diclofenac. Dosing was 1 drop t.i.d. for 30 days, beginning the first day after surgery, for both treatments. Inflammation was assessed by the presence of cells in the anterior chamber, anterior chamber flare, ciliary flush, photophobia and pain. Both treatments significantly reduced these indicators. Topical meloxicam and diclofenac produced a similar degree of burning sensation and conjunctival hyperemia. There was no significant difference between treatments in any of the measured parameters. It is concluded that the novel meloxicam solution is effective and safe. Meloxicam, however, did not offer any significant benefit over the diclofenac formulation in patients submitted to cataract surgery.

Received
October 24, 2007;
accepted
August 18, 2008

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Introduction

Cataract is a cloudiness or opacity of the eye lens which impedes the passage of light, leading to vision reduction and eventual blindness [Francis et al. 1999]. Surgery is the only option when cataract significantly affects the patient's daily life. The opaque lens is removed and replaced by an artificial intraocular lens. The procedure, however, results in significant inflammation in a large percentage of eyes if no medication is used. This occurs despite the availability refined surgical techniques, as well as more biocompatible intraocular lenses [Colin 2007, Francis et al. 1999]. Topical corticosteroids are commonly used in order to reduce the postoperative inflammatory reaction. Notwithstanding, steroids frequently produce adverse effects, including elevation of intraocular pressure, inhibition of wound healing and infection facilitation [Koay 1996]. As an alternative, topically applied nonsteroidal antiinflammatory drugs (NSAIDs) are used in the management of postoperative ocular inflammation, as well as for the prevention of intraoperative miosis during cataract surgery [Herbort et al. 2000]. NSAIDs are also employed in ophthalmology for the relief of symptoms associated to seasonal allergic conjunctivitis and for the reduction of ocular discomfort after refractive surgery [Colin 2007, O'Brien 2005, Sivaprasad et al. 2005].

NSAIDs produce analgesic and antiinflammatory effects by inhibiting prostaglandin synthesis by the cyclooxygenase (COX) enzyme. It is known that COX-1 is the constitutive enzyme isoform that produces prostaglandins under physiological stimuli. On the

other hand, the COX-2 isoform is induced by inflammation [Seibert et al. 1997, Smith and Dewitt 1996], although it is constitutive in certain tissues [Warner and Mitchell 2004]. This is also the case in ocular tissues; both COX-1 and COX-2 are expressed, but there is evidence that COX-2 is upregulated by inflammation [Amico et al. 2004, Ju and Neufeld 2002, Maihofner et al. 2001]. Hence the use of a preferential inhibitor of COX-2 after ocular injury appears to be justified.

Meloxicam is an NSAID derived from enolic acid that preferentially inhibits COX-2, while it exhibits potent analgesic and anti-inflammatory actions [Fleischmann et al. 2002, Pairet et al 1998, Simmons et al. 2004]. Moreover, it has been reported that meloxicam is endowed of additional mechanisms of analgesia, such as activation of the nitric oxide-cyclic GMP-K^+ channel pathway in peripheral tissue [Aguirre-Bañuelos and Granados-Soto 2000, Ortiz et al. 2005]. It has been demonstrated that meloxicam produces a significant analgesic effect after local administration to inflamed tissues [Ortiz et al. 2005], while it has been reported that its local ocular administration in laboratory animals is well-tolerated [Cruz et al. 2008, Stei et al. 1996]. It has also been documented that meloxicam is able to decrease leukocyte adhesion in the diabetic retina and reduces retinal tumor necrosis factor (TNF-α) [Hofbauer et al. 1999, Joussen et al. 2002]. Furthermore, recent animal studies suggest that topical meloxicam could be more effective in controlling ocular inflammation compared to nonselective NSAIDs [Cruz et al. 2008].

A topical ophthalmic formulation of meloxicam (Coxylan Ofteno) has recently been introduced in therapeutics [COFEPRIS 2005]. Therefore, the purpose of the present study was to comparatively evaluate the efficacy and safety of this novel meloxicam formulation in patients submitted to cataract surgery with regard to a reference ophthalmic formulation containing the nonselective NSAID diclofenac.

Material and methods

Medication

The medications used in this study were two commercially available topical ophthalmic formulations: 0.1% diclofenac sodium solution (3-A Ofteno), Laboratorios Sophia, SA de CV, Mexico), and 0.03% meloxicam solution (Coxylan Ofteno) Laboratorios Sophia, SA de CV, Mexico). Both formulations were provided by the manufacturer. Formulations were transferred to undistinguishable appropriate vials, in accordance with a double-blind design.

Patients

This was a parallel, comparative, multicenter, prospective, randomized, double-blind clinical study carried out according to the recommendations of the Declaration of Helsinki with its subsequent amendments. The protocol was approved by the Ethics Committee of the Instituto Médico de la Visión (Universidad de Montemorelos, Nuevo León, Mexico), and all enrolled patients gave written informed consent for participation.

Patients submitted to phacoemulsification with implantation of an intraocular lens (IOL), were recruited from five centers in Mexico and randomly divided into two groups. In Group 1 70 patients, 30 males (42%) and 40 females (57.1%), were included, having (mean ± SD) 61.2 ± 15.5 years of age. Group 2 consisted of 76 patients, 31 males (40.8%) and 45 females (59.2%), having 62.7 ± 13.6 years of age. There were no statistically significant differences between groups in age, male/female proportion and number of eyes operated. Exclusion criteria were intraoperative complication, any concomitant topical ophthalmic medication, any concomitant systemic medication that could alter the results of the study, history of hypersensitivity to any of the components of both formulations, fertile women without any acceptable contraceptive method, patients who participated in other clinical studies in the past 90 days, incapability to understand the protocol and any past or present additional ocular disease that could affect treatment response or evaluation.

Study protocol

The study was performed including two parallel groups of patients submitted to cataract surgery. Surgery (phacoemulsification

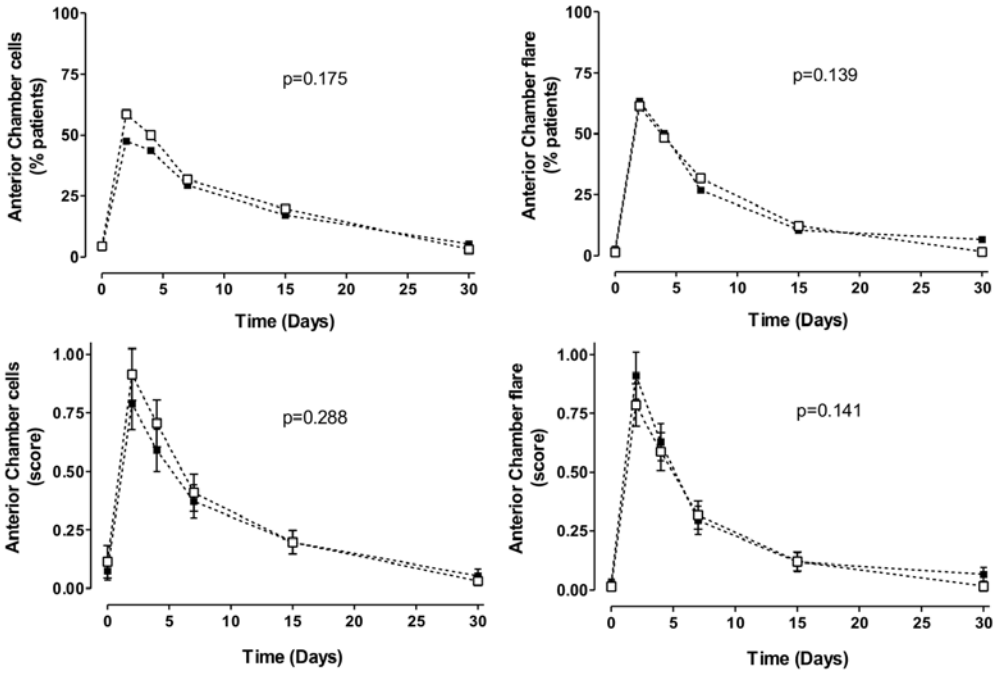

Figure 1. Top panels: Percentage of patients submitted to cataract surgery treated with topical ophthalmic solutions containing meloxicam (white symbols) or diclofenac (black symbols) exhibiting anterior chamber cells and anterior chamber flare. Bottom panels: severity (mean ± SD) of these symptoms in those patients who presented them evaluated by a 0 – 3 Likert scale. There were no significant differences between treatments, p values are indicated in the corresponding panels. See text for details on the statistical analysis.

with implantation of an IOL) was performed in a standardized way, occurring without any complication in all patients included. There were no statistically significant differences between groups regarding operation time and phacoemulsification time or energy. After surgery, patients in Group 1 were treated with 1 drop of the 0.1% diclofenac solution 3 times per day, whereas patients in Group 2 were treated with 1 drop of a 0.03% meloxicam solution, also 3 times per day. Follow-up visits were scheduled on Days 2, 4, 7, 15 and 30, after surgery and initiation of treatment. The presence of inflammatory symptoms was determined as described previously [Italian Diclofenac Study Group 1997]. The presence of cells in the anterior chamber, anterior chamber flare, ciliary flush, photophobia and pain were assessed. The number of patients exhibiting these symptoms was recorded and the severity of the symptom was evaluated using a 0 – 3 Likert scale, 0 being the absence and 3 being the maximal manifestation of the symptom. Safety was evaluated by the presence and severity of burning sensation after NSAID instillation and of conjunctival hyperemia, determined as previously described [González et al. 2007]. Follow-up examinations also included best-corrected visual acuity, applanation tonometry, and slit-lamp examination.

Statistical analysis

The purpose of the study was to compare the novel meloxicam formulation with the reference diclofenac formulation. In a first approach, the percentages (proportions) of patients exhibiting anterior chamber cells, anterior chamber flare, ciliary flush, photophobia and pain with each treatment were determined. Treatments were compared using the χ^2-test. In a second approach, the severity of the above-mentioned symptoms in those patients exhibiting them was estimated using a Likert scale. In this case, comparisons between meloxicam and diclofenac were performed by the Mann-Whitney U-test. Statistical analysis was carried out using the SPSS 11.0 version software (SPSS Inc., Chicago, IL, USA). Differences were considered to achieve statistical significance when $p < 0.05$.

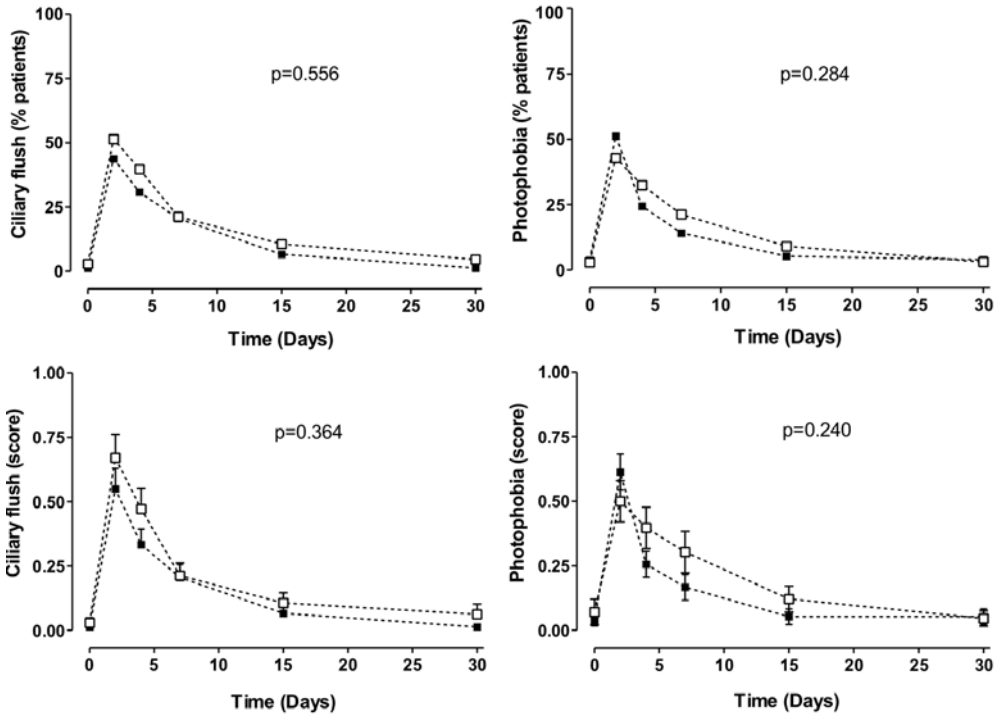

Figure 2. Top panels: Percentage of patients submitted to cataract surgery treated with topical ophthalmic solutions containing meloxicam (white symbols) or diclofenac (black symbols) exhibiting ciliary flush and photophobia. Bottom panels: Severity (mean ± SD) of these symptoms in those patients who presented them evaluated by a 0 – 3 Likert scale. There were no significant differences between treatments, p values are indicated in the corresponding panels. See text for details on the statistical analysis.

Results

All patients included showed a favorable evolution after cataract surgery. However, despite the absence of complications, a significant number of patients exhibited inflammation and pain. As it can be appreciated in Figures 1 and 2, about half of the patients exhibited presence of anterior chamber cells, anterior chamber flare, ciliary flush and photophobia during the first follow-up visit. The number of patients exhibiting these symptoms, however, as well as the severity of the measured indicators, was reduced by either diclofenac or meloxicam. Nonetheless, no significant difference between treatments was detected. As it can be seen in Figure 3, the number by patients experiencing pain was lower than for patients exhibiting presence of anterior chamber cells, anterior chamber flare, ciliary flush and photophobia. Both, diclofenac and meloxicam topic ophthalmic solutions were effective in reducing the number of patients experiencing pain, as well as pain scores, although no significant difference was detected between the analgesic effect of both treatments.

Figure 4 shows the safety outcomes determined in this study. About half of the patients reported burning sensation after NSAID instillation, whereas a greater proportion exhibited conjunctival hyperemia. The number of patients exhibiting these symptoms, as well as their severity, however, decayed with time. As it was the case with pain and inflammation indicators, no significant difference between diclofenac and meloxicam ophthalmic solutions was detected at any of the studied times. No other side effects were reported in follow-up visits. No patient treated with either meloxicam or diclofenac was withdrawn from the study due to side effects.

Discussion

It has been shown that there are two isoforms of the COX enzyme, COX-1 and COX-2 [Seibert et al. 1997, Vane and Botting 1995]. It has been demonstrated that both isoforms are expressed in the eye [Ju and Neufeld 2002]. However, an injury to structures of the eye results in the upregulation of

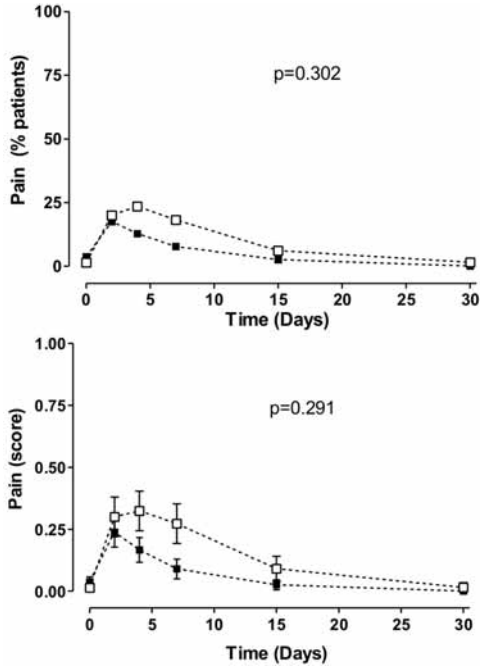

Figure 3. Top panel: Percentage of patients submitted to cataract surgery treated with topical ophthalmic solutions containing meloxicam (white symbols) or diclofenac (black symbols) exhibiting pain. Bottom panel: Severity (mean ± SD) of pain evaluated by a 0 – 3 Likert scale. There were no significant differences between treatments, p values are indicated in the corresponding panels. See text for details on the statistical analysis.

COX-2 in ocular tissues, with subsequent increase of prostaglandins [Amico et al. 2004]. Prostaglandins cause miosis, increase vascular permeability of the blood-ocular barriers, and produce hyperalgesia by sensitizing nociceptors to other algesic mediators [Amico et al. 2004, Ju and Neufeld 2002, Maihofner et al. 2001]. Cataract surgery is typically a situation of traumatic inflammation and, thus, results in an increase in prostaglandin synthesis by COX-2. It has been reported that NSAIDs are at least as efficacious as corticosteroid drops for controlling the inflammatory process after cataract surgery [Koay 1996]. Recent animal studies suggest that meloxicam, a preferential COX-2 inhibitor, could be more effective than diclofenac, a nonselective NSAID, in controlling ocular inflammation [Cruz et al. 2008]. Notwithstanding, information on the efficacy and safety of meloxicam ophthalmic formulations is scarce. Therefore, the present study was undertaken to compare the clinical efficacy and safety of two topical ophthalmic formulations, one containing meloxicam and the other the reference nonselective NSAID diclofenac, in patients submitted to cataract surgery.

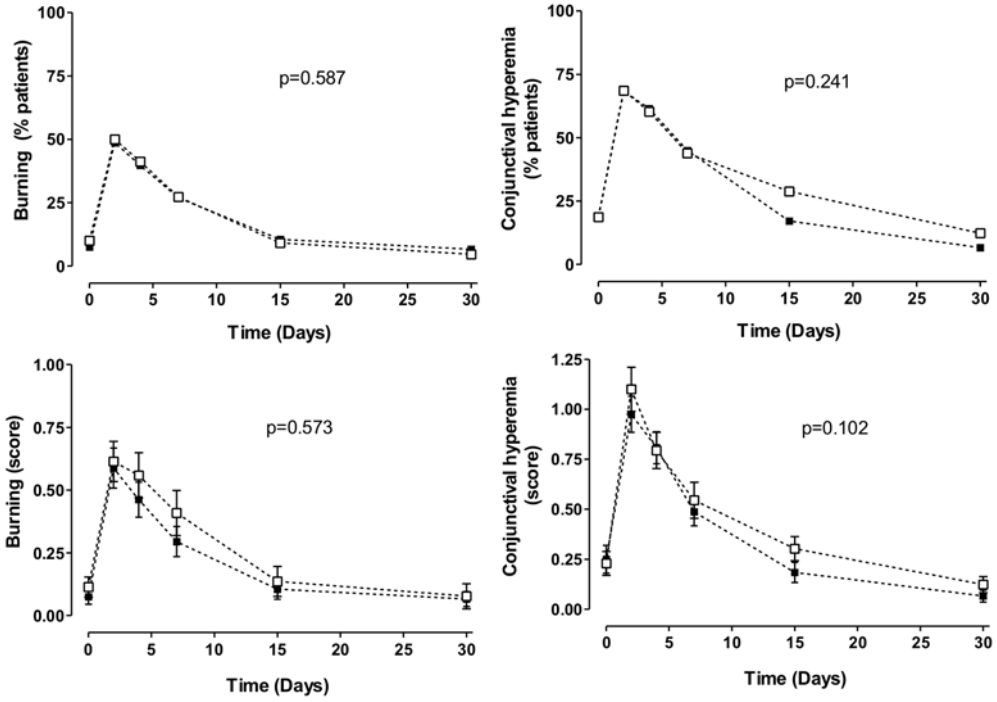

Figure 4. Top panels: Percentage of patients submitted to cataract surgery treated with topical ophthalmic solutions containing meloxicam (white symbols) or diclofenac (black symbols) exhibiting burning sensation and conjunctival hyperemia. Bottom panels: Severity (mean ± SD) of these symptoms in those patients who presented them evaluated by a 0 – 3 Likert scale. There were no significant differences between treatments, p values are indicated in the corresponding panels. See text for details on the statistical analysis.

As reported by other authors [Colin 2007, Francis et al. 1999], we found inflammation and pain in a significant number of patients following cataract surgery despite the absence of transoperative complications. Both treatments studied showed a similar efficacy in reducing pain and inflammation. These results indicate that meloxicam, when adequately formulated, is capable of crossing the cornea and penetrate into the eye when administrated as a topical ophthalmic solution. Furthermore, our results provide evidence that the studied meloxicam ophthalmic formulation exhibits a reasonable efficacy and safety. This meloxicam formulation, thus, represents a new option for the treatment of ocular inflammation. Further clinical studies are required to examine if meloxicam provides additional benefits, compared to non-selective COX inhibitors, in other ocular pathologies involving inflammation, as suggested by recent animal studies [Cruz et al. 2008]. It should be noted, however, that in the present parallel group study, meloxicam did not offer any significant benefit over the diclofenac formulation.

In conclusion, the present study shows that 0.03% meloxicam and 0.1% diclofenac ophthalmic solutions yield similar results in the control of postoperative inflammation after uncomplicated cataract surgery performed by phacoemulsification followed by the implantation of an intraocular lens.

Acknowledgment

This study was supported by Laboratorios Sophia S.A. de C.V. Guadalajara, Jalisco, Mexico.

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