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Comparison of the efficacy and safety of two formulations of diclofenac sodium 0.1% eyedrops in controlling postoperative inflammation after cataract surgery

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PURPOSE. *To compare the efficacy and safety of diclofenac sodium 0.1% eyedrops packaged in an Abak multidose container without preservative (Dicloabak) with the reference product, sodium merthiolate-preserved diclofenac sodium 0.1% eyedrops, in controlling postoperative inflammation after cataract surgery.*
METHODS. *The multicenter, controlled, randomized, single-masked study included 194 patients (Dicloabak 96, preserved diclofenac 98) scheduled to have cataract surgery by phacoemulsification with foldable intraocular lens. All were evaluated preoperatively and postoperatively after 1, 7, and 28 days. Postoperative inflammation was measured by the total score of anterior chamber cells and flare. Ocular plin, conjunctival hyperemia and ciliary flush were also assessed. Postoperative patient assessments also included visual acuity, objective tolerance by slit-lamp, fluorescein test, and subjective evaluation of local tolerance.*
RESULTS. *There was no statistically significant difference between the groups in the total score of flare and cells or the degree of conjunctival hyperemia and ciliary flush at any study visit. Dicloabak was demonstrated to be not inferior to preserved diclofenac at all assessment times. The overall assessment of local tolerance was similar for both study medications.*
CONCLUSIONS. *Preservative suppression did not alter diclofenac efficacy. Results support the good safety profile of both formulations when dosed three times daily for 4 weeks in absence of concomitant use of drugs potentially toxic for cornea. Preservative-free formulations like Dicloabak should be preferred to generic diclofenac formulations including other ingredients and may improve the safety profile of this topical nonsteroid anti-inflammatory drug. (Eur J Ophthalmol 2005; 15: 702-11)*

KEY WORDS. *ABAK system, Diclofenac, NSAID, Post-cataract inflammation, Preservative-free, Thiomersal*

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INTRODUCTION

Cataract surgery is one of the most frequently performed surgeries worldwide. Surgical trauma to the ocular structures can induce an inflammatory response including the release of prostaglandins and the recruitment of neutrophiles and macrophages. This process leads to clinically detectable perilimbal injection, flare, and cells in the anterior chamber (1).

In recent years refined surgical techniques as well as more biocompatible intraocular lenses (IOL) have contributed to a lower breakdown of the blood-aqueous barrier (1). However, intraocular inflammation has to be prevented in order to avoid complications such as relevant anterior segment inflammation exposing to intraocular pressure peaks, synechia occurrence with their possible mechanical consequences on the aqueous humor flow, and cystoid macular edema that could interfere with visual rehabilitation (1, 2). Topical corticosteroids have been initially used as a routine treatment postoperatively in order to reduce the inflammatory reaction. These drugs are, however, associated with various adverse effects such as raised intraocular pressure in corticosteroids responders, delayed wound healing, and increased risk of infection (3, 4). Nonsteroid anti-inflammatory drugs (NSAIDs) such as diclofenac have been initially found to be efficient in reducing blood-aqueous barrier breakdown and in preventing cystoid macular edema (5). Since then, topically applied NSAIDs are routinely employed as an alternative anti-inflammatory treatment to corticosteroids after cataract surgery (6).

Recently, it has been shown that the corneal safety profile of diclofenac eyedrops could be influenced by some excipients in generic diclofenac (7). Moreover, the ocular adverse effects of preservatives used in ophthalmology are well documented. Thiomersal is mainly at the origin of contact eczema and ocular allergies (8). Its toxicity is lower than that induced by other preservatives, but it has also been shown to be responsible for toxic impairments in experimental models (9, 10). Suppression of some excipients as preservatives from diclofenac ophthalmic solutions is a critical issue. They could make it possible to avoid numerous adverse effects of these products. Moreover, in the past, it was suggested that the removal of preservatives from the formulations of eyedrops could modify the clinical efficacy of active substances requiring penetration into the anterior chamber for exerting their activity. Diclofenac could be concerned when prescribed for the treatment of intraocular inflammation.

To address these issues and to improve the safety of diclofenac sodium 0.1% eyedrops it was decided to develop preservative-free diclofenac sodium 0.1% eyedrops in a multidose Abak container. Dicloabak eyedrops have an identical formulation to that of the brand diclofenac first marketed, except that they do not contain the preservative agent thiomersal.

The originality and value of the studied medicinal product lie in its pharmaceutical presentation. Antimicrobial protection of the ophthalmic solution is ensured by a membrane of pore size 0.2 µm welded to the base of the dropper.

This study compared the safety and efficacy of diclofenac sodium 0.1% eyedrops without preservative (Dicloabak) with those of preserved diclofenac sodium 0.1% eyedrops to treat inflammation after routine phacoemulsification surgery.

METHODS

Study design

This was a multicenter, randomized, comparative study in patients scheduled to have cataract surgery. The study was approved by the Ethics Committee of the Bordeaux Hospital (France). Prior to their inclusion, all subjects received oral and written information about the study from the investigator and gave their signed consent to participate.

The design of this study was reference product controlled with a statistical analysis performed in non-inferiority hypothesis. This trial was carried out in a single-blind manner (investigator-masked). Indeed, due to the interference of the filter membrane with some preservatives, diclofenac sodium with preservative could not be packaged in an Abak vial. Therefore, it was not possible to ensure a double-masked design and procedures were used in order that the investigator could be masked to the delivered treatment. Indeed, the responsible participant for the perioperative instillations and the dispensation of the study product was another individual than the ophthalmologist.

Patient selection

The inclusion criteria were as follows: patients aged at least 50 years with senile or pre-senile uncomplicated cataract who were scheduled to undergo cataract surgery (phacoemulsification, foldable IOL [>8 and <30 diopters]).

The exclusion criteria included combined surgery; best-corrected visual acuity (VA) <1/10; pupillary dilatation <6 mm; intraocular pressure (IOP) >22 mmHg; inflammatory ocular disease; exfoliative syndrome; pigmentary dispersion syndrome; corneal disease; ocular trauma, infection, inflammation, surgery, and/or laser treatment in the last 3 months; surgical complication in the contralateral eye; dry eye syndrome and/or break-up time (BUT) <10 seconds; systemic corticoids, immunosuppressants, or NSAIDs before surgery and/or during the study; topical ocular treatments other than the study drugs; contact lenses; and peroperative intracamerular or subconjunctival injection.

Treatments

Patients were randomly allocated to receive either diclofenac sodium 0.1% eyedrops without preservative (Dicloabak, Laboratoires Théa) or diclofenac sodium 0.1% thiomersal-preserved eyedrops (Voltarène, Novartis Pharma, called preserved diclofenac in this article) according to the following dose regimen: one drop, two times (-1 h, -30 min) in the eye to be operated, during the hour preceding surgery; one drop at the end of surgery; one drop, two times during the 3 hours after surgery; and finally one drop, three times per day, in the operated eye, from day 1 to day 28 ± 3 days.

The patients received no preoperative or postoperative anti-inflammatory medication other than the study medication. All patients received gentamicin eyedrops (Gentalline, benzalkonium chloride preserved, Schering-Plough) in the following dose regimen as concomitant medication: one drop instilled in the operated eye at the end of surgery, 5 minutes after the study product instillation, followed by one drop instilled four times per day from day 0 to day 7. This antibiotic was chosen because it is one of the most commonly used antibiotics in patients undergoing cataract surgery. Moreover, it is the antibiotic used in fixed NSAID-antibiotic combinations for the topical anti-inflammatory treatment after cataract surgery.

Evaluation criteria

Patients were examined at day –14 ± 7 preoperatively and postoperatively at day 1, day 7 ± 1, and day 28 ± 3.

The primary efficacy variable was the total of the scores of flare and cells, both evaluated using five-point ordinal scales, as assessed in the operated eye on day 7 (scales presented in footnotes in Table I).

The secondary efficacy variables were anterior chamber cells score, flare score, objective ocular signs in slit lamp examination (conjunctival hyperemia and ciliary flush); subjective ocular signs (pain); overall assessment of anti-inflammatory response by the investigator; best-corrected VA; and failure rate.

Tolerance variables were subjective ocular symptoms (irritation, burning/stinging, eye dryness, and foreign body sensation; score: 0 = absent; 1 = mild; 2 = moderate; 3 = severe; 4 = intolerable); objective signs in slit lamp examination (palpebral edema, chemosis, conjunctival discharge, folliculo-papillary conjunctivitis, other ocular signs: 0 = none; 1 = mild; 2 = moderate; 3 = severe); intraocular pressure; global tolerance assessment by patient and investigator; and adverse events (AEs). Corneal punctuations stained by fluorescein were assessed by the following scoring: 0 = absent; 1 = ≤10% of corneal surface; 2 = >10% and ≤25%; 3 = >25% and ≤50%; 4 = >50%.

Statistical analysis

The number of patients (192 patients) was planned to achieve an 80% probability of showing that the tested product was not inferior to the reference product.

This was a noninferiority clinical trial.

The evaluation of the primary variable was based upon a two-sided 95% confidence interval (CI) on the mean difference in total score (Dicloabak-preserved diclofenac) in the per protocol population. Dicloabak was considered not inferior to preserved diclofenac if the upper limit of this interval was at most 0.5 points.

The two-sided 95% CI was planned to be calculated by an analysis of variance (ANOVA) or, in case of non-normality of the residuals, by a nonparametric method.

For the other secondary efficacy variables and the tolerance variables, t-test, Mann-Whitney test, and Fisher exact test were applied.

These tests were performed two-sided, at the 5% level of significance.

RESULTS

Description of the population: a total of 203 patients were enrolled for the study by 36 centers.

Of the 203 enrolled patients, 194 were randomized, received study medication, and underwent cataract surgery. Patient distributions and study discontinuations per group in intention-to-treat (ITT) and per protocol (PP) populations are presented in Table II.

In the PP population, the mean ± SD age of the patients was 74.6 ± 7.3 years, ranging from 51.3 to 90.5 years. There was a slightly higher proportion of women (92; 56.4%) than men (71; 43.6%). There were no significant differences between the two treatment groups with respect to age (p=0.42; Mann-Whitney test) or sex (p=0.84; chi-square test).

There were no notable differences between the two treatment groups for the medical history, in particular regarding diabetes mellitus and ocular conditions or diseases predisposing patients to an increase in postoperative inflammation.

There were no statistically significant differences between the two treatment groups for any of the ocular examination variables at baseline. All patients underwent cataract surgery by phacoemulsification with implantation of a foldable intraocular lens (IOL). Demographic characteristics of the ITT and PP populations were similar. The three patients per group who presented with peroperative complications were excluded from the PP population.

Efficacy

The results of the total score of anterior chamber cells and flare are shown in Table I.

The mean ± SD (median) total scores on day 7 in the PP population (primary efficacy variable) were 0.25 ± 0.54 (0.0) in the Dicloabak group and 0.39 ± 0.91 (0.0) in the preserved diclofenac group. Dicloabak was demonstrated to be not inferior to preserved diclofenac for the primary efficacy variable (the residuals were not normally distributed, thus two-sided 95% CI on the median difference was used: $[0; 0]_{95}$).

Furthermore, using the same nonparametric analysis for the total scores of cells and flare from the other assessment times (days 1, 3, and 28; Tab. I), Dicloabak was demonstrated to be not inferior to preserved diclofenac at all assessment times.

Severe anterior chamber inflammations were classified as treatment failure. They occurred in one patient in the Dicloabak group (this reaction was actually due to possible subacute endophthalmitis; another similar complication occurred on the same day in the same center) and in three patients in the preserved diclofenac eyedrops group. These anterior chamber inflammations caused premature discontinuation of the patients from the study. All cases were treated and fully recovered. Excluding these patients with a treatment failure, very few patients in both treatment groups presented with an anterior chamber inflammation at day 7 (Tab. III). Increases in the inci-

TABLE I - TOTAL SCORE OF ANTERIOR CHAMBER CELLS AND FLARE* (PP population)

Visit	Dicloabak (n=80)		Preserved diclofenac (n=83)		Two-sided 95% CI†		
	Mean ± SD	Median	Mean ± SD	Median	Parametric‡	Non-parametric	Non-inferiority
Inclusion	0.03±0.16	0.0	0.00±0.00	0.0	—	—	—
Day 1	1.39±1.06	1.0	1.48±1.04	1.0	[-0.36; 0.17]	[0; 0]	Accepted
Day 3§	0.65±0.77	0.5	0.75±0.87	1.0	[-0.31; 0.13]	[0; 0]	Accepted
Day 7	0.25±0.54	0.0	0.39±0.91	0.0	[-0.35; 0.08]	[0; 0]	Accepted
Day 28¶	0.08±0.36	0.0	0.05±0.22	0.0	[-0.07; 0.13]	[0; 0]	Accepted

*The total score was the sum of the scores of cells and flare (maximum possible total score = 8). Cells: 0 = No cells; 1 = 1–5 cells; 2 = 6–15 cells; 3 = 16-30 cells; 4 = >30 cells. Flare: 0 = Absent; 1 = Trace barely detectable; 2 = Mild intensity (iris and lens details clear); 3 = Moderate intensity (iris and lens details not clear); 4 = Strong intensity (iris and lens details not visible and fibrin in the anterior chamber).
†Two-sided 95% confidence interval on mean difference (Dicloabak - preserved diclofenac)
‡These results are presented to ease the understanding of the results although the residuals were not normally distributed, even after appropriate transformation
§Two patients in the Dicloabak group had missing data on day 3
¶For seven preserved diclofenac eyedrops patients and six Dicloabak patients, D28 data were excluded due to protocol deviations

dence and severity of cells and flare were observed on day 1 followed by gradual decreases in the incidence and severity of both parameters on days 3 and 7, and a return to values near the preoperative levels by day 28. Conjunctival hyperemia and ciliary flush followed a similar evolution. The incidence and severity of ocular pain increased on day 1 in both treatment groups and then remained mild, and stable through days 3, 7, and 28. No statistically significant difference was observed between the treatment groups for any of the parameters.

The investigator assessed the anti-inflammatory response as "very satisfactory" or "satisfactory" for 98.7% of patients in the Dicloabak group and 95.1% of patients in the preserved diclofenac group. There was no statistically significant difference between the treatment groups.

All the efficacy results were also confirmed by statistical analysis in ITT population.

Local tolerance and safety

Safety parameters are presented in the ITT population.

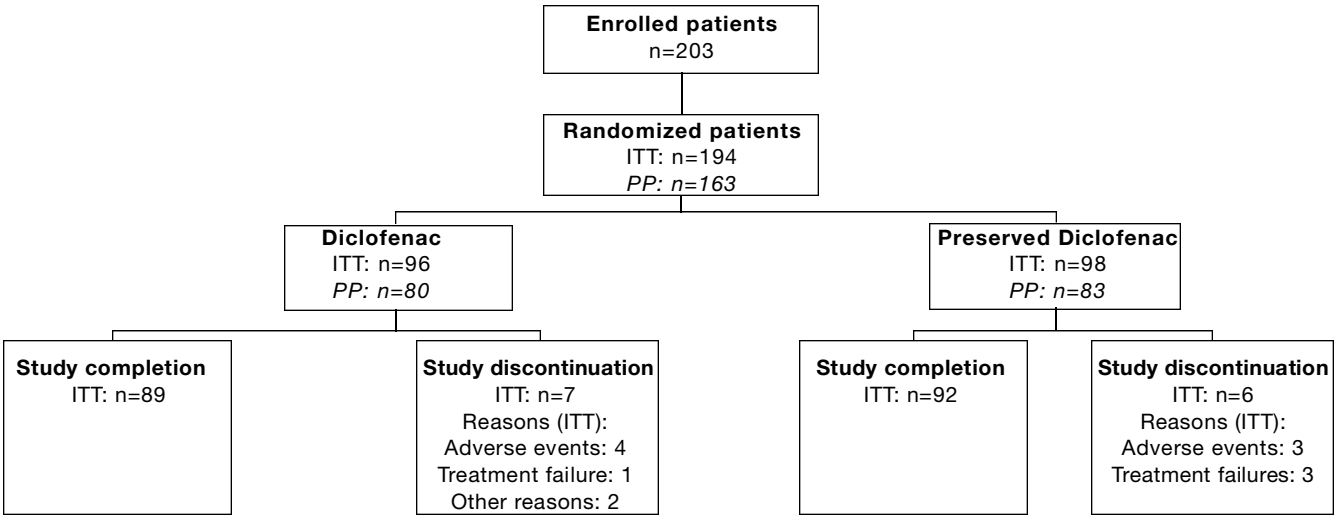
There were slight increases in the incidence of mild irritation, burning/stinging, eye dryness, and foreign body sensation on day 1 in both groups, which then remained stable through days 3, 7, and 28 (Tab. IV). However, fewer than 5% of patients in each treatment group had clinically relevant (i.e., > grade 1) subjective ocular symptoms at any visit with the exception of foreign body sensation, which occurred in <6.5% of patients in the preserved diclofenac eyedrops group on day 28. No clinically relevant differences could be highlighted between treatment groups.

The incidence of ocular signs in the slit lamp examination was low in the operated eyes in this study. Palpebral edema, chemosis, and folliculo-papillary conjunctivitis occurred in fewer than 5% of patients in each treatment group at each study visit. Conjunctival discharge was reported in 10 to 12% of patients on day 1 but the incidence gradually decreased through days 3 to 28. All the objective signs observed during this study were mild or moderate in severity.

The incidence and severity of fluorescein-stained punctuations increased in both treatment groups on days 1 and 3, reaching a maximum on day 7. After 1 month of treatment, incidence and severity decreased: approximately 83% of patients had no punctuations stained by fluorescein. One patient per treatment group has a clinically relevant superficial punctate keratitis.

The treatment-related ocular AEs reported during the study are summarized in Table V. Nonserious AEs causing premature discontinuation of the patient from the study occurred in four patients in the Dicloabak group (moderate burning sensation for two patients, severe superficial punctate keratitis for one patient, and moderate keratitis for one patient) and three patients in the

TABLE II - PATIENT DISTRIBUTION



preserved diclofenac eyedrops group (severe keratitis for one patient, irritation/burning/stinging sensation and foreign body sensation for one patient, and death of one patient due to cardiac arrest unrelated to study drug). There were no notable differences between the two treatment groups with respect to the type, frequency, or severity of the treatment-related AEs.

The global tolerance assessment by the investigator was "satisfactory" or "very satisfactory" for 96.8% of patients in the Dicloabak group and 95.8% of patients in the preserved diclofenac group. Approximately 95% of patients in each treatment group reported that the treatment was well tolerated.

DISCUSSION

In this clinical trial involving a large number of patients, we evaluated intraocular inflammation using the slit lamp to grade the amount of anterior chamber cells and flare using five-point ordinal scales. Although this method of evaluation is semiquantitative, unlike laser

TABLE III - FREQUENCY DISTRIBUTION OF ANTERIOR CHAMBER CELLS AND FLARE, NUMBER OF PATIENTS (%) (PP Population)

	Dicloabak (n=80)*†					**Preserved diclofenac (n=83)†**				
	Frequency distribution of anterior chamber cells per severity grade, n (%)									
	0	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
Inclusion	80 (100)	0	0	0	0	83 (100)	0	0	0	0
Day 1	29 (36.2)	39 (48.7)	11 (13.8)	1 (1.3)	0	25 (30.1)	46 (55.4)	9 (10.9)	3 (3.6)	0
Day 3*	50 (64.1)	26 (33.3)	2 (2.6)	0	0	48 (57.8)	34 (41.0)	0	1 (1.2)	0
Day 7	68 (85.0)	11 (13.7)	1 (1.3)	0	0	68 (81.9)	14 (16.9)	0	0	1 (1.2)
Day 28†	70 (94.6)	4 (5.4)	0	0	0	72 (94.7)	4 (5.3)	0	0	0
	Frequency distribution of anterior chamber flare per severity grade, n (%)									
	0	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
Inclusion	78 (97.5)	2 (2.5)	0	0	0	83 (100)	0	0	0	0
Day 1	39 (48.8)	35 (43.7)	6 (7.5)	0	0	37 (44.6)	42 (50.6	4 (4.8)	0	0
Day 3*	59 (75.6)	17 (21.8)	2 (2.6)	0	0	60 (72.3)	21 (25.3)	2 (2.4)	0	0
Day 7	73 (91.2)	7 (8.8)	0	0	0	72 (86.7)	8 (9.6)	3 (3.7)	0	0
Day 28†	72 (97.3)	2 (2.7)	0	0	0	76 (100.0)	0	0	0	0

*Twopatients in the Dicloabak group had missing data on day 3
†For seven preserved diclofenac eyedrops patients and six Dicloabak patients, D28 data were excluded due to protocol deviations

flare-photometry which provides quantitative results, slit-lamp evaluation continues to be a valid, accurate, reproducible, and widely used method to evaluate anterior chamber inflammation (11-14). The advantage of this method is that it is quick and easy to perform, and does not require any special equipment. This was an important factor in the design of our study as it was performed not only in excellence centers, but also in private practice centers.

In our study a low inflammatory reaction was induced by the cataract surgery, as shown in the level of anterior chamber cells and flare values on the day after surgery (day 1). This could be linked to the improvement of the current phacoemulsification technique with small incision (1, 15). On the other hand, the cataract grade was not highly severe in our study and may allow a short time surgery inducing a low local inflammatory reaction.

Our efficacy results allow the conclusion that suppression of the preservative has no impact on anti-inflammatory effect of diclofenac as Dicloabak unpreserved formulation has a similar efficacy to that of preserved diclofenac at each follow-up visit. These results are supported by a high level of satisfaction of investigators concerning the anti-inflammatory response in each group. It should be highlighted that,

TABLE IV - PERCENTAGES OF PATIENTS IN DICLOABAK AND TREATMENT GROUPS WITH CLINICALLY RELEVANT SUBJECTIVE OCULAR SYMPTOMS (I.E., scored > grade 1) AT EACH STUDY VISIT

Subjective ocular symptoms	**Dicloabak**					**Preserved diclofenac**				
	Patients with clinically relevant symptoms, n (%)									
Visit	I n=95	D1 n=95	D3 n=93	D7 n=93	D28 n=92	I n=98	D1 n=97	D3 n=96	D7 n=96	D28 n=96
Irritation	0 (0.00)	0 (0.00)	0 (0.00)	4 (4.30)	1 (1.09)	0 (0.00)	1 (1.03)	2 (2.08)	1 (1.04)	4 (4.16)
Burning/ stinging	0 (0.00)	2 (2.11)	1 (1.08)	2 (2.15)	4 (4.35)	0 (0.00)	0 (0.00)	3 (3.12)	4 (4.17)	5 (5.20)
Eye dryness	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.09)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.04)
Foreign body sensation	0 (0.00)	1 (1.05)	1 (1.08)	2 (2.15)	4 (4.35)	0 (0.00)	1 (1.03)	2 (2.08)	5 (5.21)	6 (6.24)

I = Inclusion

TABLE V - NUMBER OF PATIENTS WITH TREATMENT-RELATED ADVERSE EVENTS (AE)

Treatment-related AE*	**N (%) (ITT population)**			
	Dicloabak (n=96)		**Preserved diclofenac (n=98)**	
Superficial punctate keratitis	3	(3.1)	3	(3.1)
Eye pain†	2	(2.1)	3	(3.1)
Conjunctivitis	1	(1.0)	2	(2.0)
Dry eye	1	(1.0)	1	(1.0)
Tearing	1	(1.0)	0	(0)
Delay of the epithelial healing of traumatic peroperative ulceration	1	(1.0)	0	(0)

*Severe anterior chamber inflammations were described as treatment failures in the efficacy results
†Eye pain: this term includes burning sensation, drop intolerance, itching, stinging/pruritus, and/or foreign body sensation

in our study, patients received no additional corticotherapy, even immediately after surgery, supporting that diclofenac monotherapy is sufficient to control postoperative inflammation. The results of this study extend the currently published literature by demonstrating that diclofenac sodium 0.1% is one of the most potent anti-inflammatory drugs in controlling the signs and symptoms of ocular inflammation after cataract surgery. Numerous clinical trials were carried out and the results are unequivocal: diclofenac is as effective as (2, 11, 16-18), or in a few cases more effective than (19, 20), topically applied steroids in the management of postoperative inflammation. Comparisons of diclofenac sodium with other topically applied NSAIDs like indomethacin, flurbiprofen, ketorolac, or naproxen show that diclofenac 0.1% is also as effective as other NSAIDs (16, 21-24), or even more effective (25, 26) for attenuating postoperative inflammation in patients undergoing cataract surgery.

Regarding to the tolerance and safety results of our clinical study, the collection and analysis of the safety criteria were properly controlled by directed questioning and eye examination, at all the visits. This approach is optimal for detecting all adverse events, whatever their actual impact on the patients.

As expected, there were slight increases in the incidence of mild irritation, burning/stinging, eye dryness, and foreign body sensation on day 1 after cataract surgery, which then remained stable through days 3, 7, and 28. The frequency of occurrence of ocular symptoms had little clinical impact; they were always mild or moderate, and had no effects on how the patients rated global tolerance of diclofenac sodium 0.1%. The incidence of objective ocular signs in the slit lamp examination and the occurrence of AEs were low in the operated eyes in the study. In both treatment groups, an increase in fluorescein-stained punctuations on day 7 was observed and may have been due to the combination of sodium diclofenac and gentamicin which was given for the first 7 days after surgery, as suggested by literature data (12, 27). The number of fluorescein-stained punctuations dramatically decreased on day 28 after a 3-week monotherapy with diclofenac 0.1% eyedrops. Corneal punctuations demonstrated by fluorescein are a well-known adverse effect of diclofenac (1, 7, 28). However, neither corneal erosion nor ulcers were observed in this study. In conclusion, this clinical trial allows the conclusion that the corneal safety of diclofenac sodium 0.1% monotherapy is satisfactory when no combinations with other eyedrops potentially toxic for cornea are prescribed.

These results confirm the good efficacy/safety ratio for diclofenac when some prescription rules are followed such as no prolonged treatment at high dosage, careful follow-up in case of ocular surface disease, no uncontrolled concurrent use of antibiotics or steroids susceptible to increase the corneal risk, and choice of diclofenac formulations excluding excipients that have been hypothesized to alter diclofenac safety profile (Polyquad polyquaternium, tocophersolan, and mannitol) (7). Indeed, like other nonsteroidal anti-inflammatory agents, corneal infiltrates and epithelial defects have been published after use of diclofenac. Such events occur at a low rate and usually in the presence of high doses of medication and/or ocular comorbidities, in particular abnormalities of the ocular surface such as preexisting superficial keratitis (7). Risk factors in patients with such corneal problems included rheumatoid arthritis, dry eye, rosacea, corneal epithelial defects or keratopathy, neurotrophic ulcer, topical steroids, and diabetes (1, 28, 29). Many reported cases occur in patients with dry eyes who are concurrently using corticosteroids (1, 30). Antibiotics such as gentamicin may lead to an increased corneal toxicity of diclofenac sodium eyedrops (27). This toxicity of gentamicin can be increased by the fact that gentamicin eyedrops are preserved by benzalkonium chloride. Moreover, some ingredients contained in other formulations of diclofenac were judged to be responsible for an increase of the occurrence and the severity of the corneal complications as perforations (7, 30, 31). In particular, severe AEs might have been more likely to occur at lower doses and in routine postoperative settings with generic diclofenac containing Polyquad polyquaternium, tocophersolan, and mannitol (7).

This clinical study design in patients was not able to detect any statistically significant difference between the two diclofenac formulations. The duration of postoperative treatment was 4 weeks. A longer treatment period could have been able to detect a difference in particular in susceptible patients. It should be remembered that many ophthalmologists suggest a 2-month therapy with diclofenac sodium 0.1% eyedrops three times per day. In contrast, a previous safe-

ty clinical trial performed in healthy volunteers by Chiambaretta et al (32) compared both diclofenac formulations in 40 healthy volunteers for 1 month and showed a between-group difference. After 1 week of 5 times daily instillations, the frequency of irritation/burning/stinging and the mean subjective ocular symptoms total score were statistically significantly lower in the Dicloabak-treated eyes than in the preserved diclofenac eyedrops treated eyes. The biomicroscopy examination confirmed that there was a better tolerance without thiomersal after 1 month of treatment: there was a significantly better lissamine green score in the Dicloabak group (p=0.001; Wilcoxon's test).

The discrepancy between our study (phase III) and this clinical trial in healthy volunteers (phase I) could be explained by a more adapted methodology of the latter for detecting slight differences: the dosage was higher in the phase 1 study than in our study and more susceptible to reveal the potential toxicity of each treatment, our design was group-parallel and that of the phase I study was intraindividual (randomized eye versus contralateral eye), and ocular surface examination by lissamine green was also performed in the phase I study, in contrast to our study. Two hypotheses could be raised concerning the potentially deleterious role of thiomersal. First, although mercurial derivatives are known to be less toxic than other preservatives, the slight potential toxic effect of sodium merthiolate on cornea (9, 10) could be sufficient to induce increased staining by lissamine green in healthy volunteers at high dosages. Secondly, thiomersal could act as other excipients such as those contained in generic diclofenac (7) and increase diclofenac toxicity.

CONCLUSIONS

The findings of our study agree with the current literature that document that diclofenac sodium 0.1% eyedrops are an effective and safe treatment for controlling postoperative inflammation in patients having routine cataract surgery.

The study results support the good safety profile of both formulations when dosed three times daily for 4 weeks in absence of concomitant use of drugs potentially toxic for cornea.

These formulations should be preferred to generic diclofenac formulations including other ingredients. In addition, based on the results of a previous clinical trial (32), Dicloabak, without preservative, may improve the safety profile of this NSAID ophthalmic preparation.

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