European Journal of Ophthalmology / Vol. 17 no. 3, 2007 / pp. 341-349

Ocular symptoms and signs with preserved and preservative-free glaucoma medications

N. JAENEN[1], C. BAUDOUIN[2], P. POULIQUEN[3], G. MANNI[4], A. FIGUEIREDO[5], T. ZEYEN[1]

[1]U.Z. Sint Rafaël, Leuven - Belgium
[2]CNO des XV-XX, Paris
[3]Laboratoires Théa, Clermont-Ferrand - France
[4]Policlinico Tor Vergata, Roma - Italy
[5]Hospital Santa Maria, Lisbon - Portugal

PURPOSE. *To compare the prevalence of side effects between eyedrops with or without preservatives, in terms of subjective symptoms and objective signs in patients with open-angle glaucoma.*
METHODS. *In a multicenter cross-sectional epidemiologic survey in four European countries, ophthalmologists in private practice enrolled 9658 nonconsecutive patients using preservative (P) or preservative-free (PF) beta-blocking eyedrops between June 1997 and December 2003. Subjective symptoms, conjunctival and palpebral signs, and superficial punctate keratitis were explored before and after a change in therapy. For statistical analysis, a χ^2 test was used to calculate the differences in the prevalence of symptoms and signs with or without preservatives.*
RESULTS. *A total of 74% of the patients used P, 12% PF, 10% a P-PF combination, and in 4% the type of medication was unknown. Each recorded symptom and all the palpebral, conjunctival, and corneal signs were significantly more frequent ($p<0.0001$) in the P-group than in the PF-group, such as pain or discomfort during instillation (48 vs 19%), foreign body sensation (42 vs 15%), stinging or burning (48 vs 20%), and dry eye sensation (35 vs 16%). A total of 68% of the patients had a second visit performed, of whom 63% (6083) had been evaluated on treatment difference. A significant decrease ($p<0.0001$) of all ocular symptoms and signs was observed in patients in whom the preserved eyedrops were diminished in number or altered into preservative free drops.*
CONCLUSIONS. *Compared to preserved eyedrops, preservative free eyedrops are significantly less associated with ocular symptoms and signs of irritation. (Eur J Ophthalmol 2007; 17: 341-9)*

KEY WORDS. *Glaucoma, Preserved and preservative free eyedrops, Side effects*

Accepted: November 6, 2006

INTRODUCTION

Glaucoma is the second most relevant cause of blindness worldwide (1). Medical therapy constitutes the usual first line treatment for glaucomatous patients. Those patients will often need to use topical therapy for many years. Tolerance towards eyedrops plays a major role in compliance and adherence. Side effects of eyedrops could be due to the active component as well as to the preservatives (2). The most commonly used preservative is benzalkonium chloride, which exerts an antimicrobial effect by its powerful detergent action on bacterial walls and membranes (3). This detergent effect in combination with a partial destruction of mucous gland cells is responsible for the induced instability of the lachrymal film (4), involving a decrease of the tear break-up time and resulting in symptoms like irritation (5). An immunologic reaction with an increased presence of lymphocytes, macrophages, and Langerhans cells is reported following to chronic application of preservatives (6); sometimes this inflammation results in subconjunctival fibrosis (7). Moreover, preserved medications affect the result of filtering surgery; it was

 1120-6721/341-09$15.00/0

shown in studies on patients who underwent trabeculectomy that the longer the duration of the medical antiglaucoma treatment and the larger the number of drops administered before surgery, the lesser the chance of an adequate filtration bleb (8).

A great deal of research concerning toxicity of preservatives has already been done in vitro and in animals. In humans, a few interesting experimental studies performed under stress conditions have been carried out, showing deleterious effects of preservatives after the use of preserved eyedrops (5, 9, 10).

In 2002, Pisella et al published a study in which the prevalence of ocular symptoms and signs was compared between patients treated with eyedrops with or without preservatives in France (11). Our study is aimed to verify if these results are applicable in different European countries. Therefore, it compiles the results issued from the French survey and those obtained in similar surveys carried out in Italy, Belgium, and Portugal. In this article we endeavored to work out the difference in side effects between eyedrops either with or without preservatives, in terms of subjective symptoms and objective signs in glaucoma patients chronically treated with eyedrops either with or without preservatives.

MATERIALS AND METHODS

This study was a multicenter cross-sectional epidemiologic survey examining patients' files who had consulted an ophthalmologist in private practice in four European countries, namely Italy, France, Belgium, and Portugal (the same sequence of the countries is consistently used throughout the article and the Tables). The results of the French study by Pisella et al have been incorporated in our study. Between June 1997 and December 2003, the ophthalmologists enrolled nonconsecutive patients using several types of beta-blocking eyedrops. Patients were allowed to use other non-glaucoma eyedrops, but the type and number of other eyedrops were recorded. Therefore, the patients received eyedrops in multidose vials containing a preservative, preservative-free eyedrops, monodose medication, or a combination of these. On most patients, two consecutive ophthalmic consultations in the form of standard check-ups were performed. Depending on the ophthalmologists' opinion, therapy was changed after the first examination.

At the first visit, demographic data and medical information were collected. The interviewees were questioned about the duration and type of treatment, the presence of preservatives, and the number of eyedrops administered. An assessment of treatments' tolerability occurred as well as an inquiry into the ocular symptoms during and after the instillation of the eyedrops: pain and discomfort during the instillation, foreign body sensation, stinging and burning, dry eye sensation, tearing, and eyelid itching. Conjunctival and palpebral signs were explored and special attention was paid to the presence of superficial punctate keratitis. At the end of the first visit the ophthalmologist could change the therapy. Reasons why ophthalmologists decided to change the treatment included intolerance, progression of the glaucoma, or therapeutic nonresponse. The ophthalmologists had to report changes in type or number of eyedrops. On the second visit the same anamnesis and clinical examination was repeated as in the first visit and the change in subjective symptoms and ocular signs was consistently noted.

Statistical analysis on data reported at the first visit was carried out by classifying patients into two main groups of medication: the preserved eyedrop group or P group (patients treated with at least one preserved eyedrop, possibly in combination with preservative free eyedrops or with monodose) and the preservative free eyedrop group or PF group (patients treated with preservative free eyedrops, monodose, or a combination of the two). For statistical analysis, a χ^2 test was used to calculate the differences in the prevalence of symptoms and signs with or without preservatives. After the second visit the change in ocular tolerance to eyedrops was compared in subgroups of patients according to the change in the therapeutic regimen.

RESULTS

A total of 9658 patients were enrolled by the ophthalmologists between June 1997 and December 2003 in four European countries (Italy, France, Belgium, and Portugal): 4,977 patients in Italy, 4,107 in France, 330 in Belgium, and 244 in Portugal (Tab. I). A total of 52.2% of patients were female. The average age was 65 years (range, 8 to 99 years). Of 9658 patients, 68% had a second visit performed (6532 patients), of whom 63% have been evaluated for treatment difference (Tab. I).

As shown in Table II, at the first visit, 74% of the patients were treated with preserved drops, 6% with preservative free eyedrops in multidose container, 6% with monodose

medication, and the remaining 10% with a combination of at least two sorts of treatments; no information about the kind of medication was available for 4% of the patients.
The first group (the group of patients receiving at least one preserved eyedrop or P group) covered a total of 8092 patients (83.8%). The preservative free eyedrop group or PF group covered 1138 patients (11.8%). Information about some prescribed medications was missing for 4.4% of the patients.

TABLE I - PATIENT DEMOGRAPHICS

	No. (%)
Patients enrolled	9658 (100)
Italy	4977 (51.5)
France	4107 (42.5)
Belgium	330 (3.4)
Portugal	244 (2.5)
Patients with two visits performed	6532 (67.6)
Patients evaluated for treatment difference	6083 (63.0)

TABLE II - EYEDROP MEDICATION AT FIRST VISIT

Treatment	Percentage
P	73.92
P + monodose	8.29
P + PF	1.57
PF	5.79
Monodose	5.79
PF + monodose	0.21
P+ PF + monodose	0.46
Not indicated	3.98

P = Preserved eyedrops; PF = Preservative free eyedrops

Pain or discomfort during instillation (47.6%), stinging or burning (47.5%) were the most commonly reported symptoms in the P group followed by foreign body sensation (41.9%), dry eye sensations (34.9%), tearing (27.3%), and eyelid itching (23.8%) (Tab. III). The PF group included almost the same order of symptoms but with a significantly lower prevalence: stinging or burning in 19.6%, followed by pain or discomfort during instillation (18.5%), dry eye sensation (16.0%), foreign body sensation (14.8%), tearing (12.4%), and eyelid itching (9.4%) (Tab. III). Each recorded symptom was statistically more frequent in the P group than in the PF group.
Similarly, with respect to the palpebral, conjunctival, and corneal signs, there was a significant difference between the P and PF groups. In the P group, blepharitis, eczema, conjunctival hyperemia, follicles, fluorescein staining of the nasal bulbar conjunctiva, and superficial punctuate keratitis occurred mostly two to three times more often than in the PF group (Tab. IV). In the two groups, conjunctival hyperemia was the most widely reported sign (P group 53.0%, PF group 20.5%). Superficial punctate keratitis was present in 25.6% of the patients in the P group and in 8.9% of the patients in the PF group (Tab. IV).
Out of 9658 patients, 68% had a second visit performed (6532 patients), of whom 63% (6083) had been evaluated for treatment difference (Tab. I). The average interval between the visits was about 2 months (67 days), ranging from 1 to 750 days.
According to the changes of treatment after the first visit, patients having a second visit were classified and analyzed in five main groups (Tab. V). In 14.1% of the patients the preserved drops had not been changed at all (P-P group), whereas in the majority of patients having used preserved eyedrops, the eyedrops had been changed into preservative free eyedrops (51.8%) (P-PF group) or the number of preserved eyedrops had been diminished

TABLE III - VISIT 1: FREQUENCY OF OCULAR SYMPTOMS

Ocular symptoms (during or after instillation)	Preserved (P) eyedrops	Preservative free (PF) eyedrops	p value
Pain or discomfort during instillation	3826 (47.6)	202 (18.5)	<0.0001
Foreign body sensation	3369 (41.9)	163 (14.8)	<0.0001
Stinging or burning	3811 (47.5)	216 (19.6)	<0.0001
Dry eye sensation	2798 (34.9)	176 (16.0)	<0.0001
Tearing	2187 (27.3)	137 (12.4)	<0.0001
Eyelid itching	1911 (23.8)	103 (9.4)	<0.0001

Values are in N (%)

TABLE IV - VISIT 1: CLINICAL EXAMINATION

	Preserved (P) eyedrops	Preservative free (PF) eyedrops	p value (χ^2)
Palpebral signs			
Anterior blepharitis	1786 (22.2)	77 (6.8)	<0.0001
Posterior blepharitis	666 (8.3)	33 (2.9)	<0.0001
Eczema	730 (9.1)	20 (1.8)	<0.0001
Conjunctival signs			
Hyperemia	4278 (53.0)	231 (20.5)	<0.0001
Conjunctival follicles	17,040 (21.2)	78 (6.9)	<0.0001
Fluorescein staining in the nasal bulbar conjunctiva	1001 (12.5)	42 (3.8)	<0.0001
Corneal signs (superficial punctate keratitis)			
Absent	5631 (74.4)	916 (91.1)	
Mild	1809 (23.9)	80 (8.0)	<0.0001
Moderate/severe	132 (1.7)	9 (0.9)	

Values are n (%)

TABLE V - CHANGES OF MEDICATION

Visit 1–Visit 2	N (%)
P (preserved eyedrops) → P (preserved eyedrops)	857 (14.1)
P (preserved eyedrops) → PF (preservative free eyedrops)	3149 (51.8)
PF (preservative free eyedrops) → P (preserved eyedrops)	29 (4.8)
PF (preservative free eyedrops) → PF (preservative free eyedrops)	678 (11.1)
P (preserved eyedrops) → DP (decreased number of P eyedrops)	981 (16.1)

(16.1%) (P-DP group). A total of 4.8% of the patients were patients of the PF group who had changed to the preserved group (PF-P group), and 11.1% had continued using the preservative free eyedrops (PF-PF group). The statistical analysis within the abovementioned five groups showed the following results.

A significant reduction of some ocular symptoms turned up in all the groups with the exception of the PF-P group. The decrease of ocular symptoms was most obvious in the P-PF group where any form of pain or discomfort was reduced from 52.4% to 7.8% (Tab. VI). All the ocular symptoms diminished three to five times. In the P-DP group the perception of stinging and burning during instillation lowered from 64.3% to 16.3% and all the other ocular symptoms had declined approximately two to four times (Tab. VII) as well. In the group with continuation of the preserved eyedrops (P-P group), there was no significant decrease of the foreign body sensation, the eyelid itching, and the dry eye sensation. In case of continuation of the preservative free eyedrops treatment (PF-PF group), the tearing had not decreased significantly.

At the occasion of the second visit, the prevalence of all the described ocular signs significantly decreased in the groups where the preserved eyedrops were diminished in number (P-DP group), or altered into preservative free drops (P-PF group) with more than five times less fluorescein staining at the second visit (Tabs. VI and VII). No significant difference was observed in the group where the preservative free drops were switched into preservative eyedrops (PF-P group). Only the hyperemia was reduced in the P-P group, and in the PF-PF group the hyperemia, the blepharitis, and the fluorescein staining decreased significantly. Concerning the superficial punctate keratitis, a significant decrease was only shown in the P-DP group (from 40.4% to 11.5%) and the P-PF group (from 29% to 5.7%) (Tabs. VI and VII).

DISCUSSION

In glaucoma, progression can be prevented in many cases by a chronic medical therapy, but the prescribed eyedrops have to be instilled over 20 years or more. Ocular surface problems are mostly due to the preservative nature of the eyedrops, while subjective symptoms during

TABLE VI - OCULAR SYMPTOMS AND SIGNS AT VISIT 1 AND 2 IN THE P-PF GROUP

Ocular symptoms and signs	Visit 1	Visit 2	p value
Ocular symptoms			
Pain or discomfort during instillation	1647 (52.42)	246 (7.82)	<0.0001
Foreign body sensation	1552 (49.44)	263 (8.37)	<0.0001
Stinging or burning	1689 (53.77)	282 (8.97)	<0.0001
Dry eye sensation	1353 (43.16)	351 (11.18)	<0.0001
Tearing	975 (31.14)	318 (10.13)	<0.0001
Eyelid itching	845 (26.95)	170 (5.41)	<0.0001
Ocular signs			
Anterior blepharitis	829 (26.38)	27 (8.71)	<0.0001
Posterior blepharitis	286 (9.13)	88 (2.80)	<0.0001
Eczema	345 (11.00)	92 (2.93)	<0.0001
Hyperemia	2,024 (64.36)	503 (15.99)	<0.0001
Follicles	663 (21.13)	166 (5.28)	<0.0001
Fluorescein staining	428 (13.65)	78 (2.48)	<0.0001
Superficial punctate keratitis	841 (28.99)	162 (5.66)	<0.0001

Values are n (%)
P = Preserved eyedrops; PF = Preservative free eyedrops

TABLE VII - OCULAR SYMPTOMS AND SIGNS AT VISIT 1 AND 2 IN THE P-DP GROUP

Ocular symptoms and signs	Visit 1	Visit 2	p values
Ocular symptoms			
Pain or discomfort during instillation	587 (59.96)	167 (17.04)	<0.0001
Foreign body sensation	564 (57.61)	151 (15.39)	<0.0001
Stinging or burning	629 (64.25)	160 (16.31)	<0.0001
Dry eye sensation	475 (48.52)	210 (21.41)	<0.0001
Tearing	394 (40.25)	197 (20.08)	<0.0001
Eyelid itching	335 (34.22)	77 (7.85)	<0.0001
Ocular signs			
Anterior blepharitis	306 (31.26)	122 (12.45)	<0.0001
Posterior blepharitis	112 (11.44)	40 (4.08)	<0.0001
Eczema	170 (17.35)	36 (3.67)	<0.0001
Hyperemia	619 (63.16)	270 (27.55)	<0.0001
Follicles	256 (26.15)	92 (9.41)	<0.0001
Fluorescein staining	115 (11.75)	47 (4.81)	<0.0001
Superficial punctate keratitis	376 (40.43)	106 (11.54)	<0.0001

Values are n (%)
P = Preserved eyedrops; DP = Decreased number of P eyedrops

and after instillation affect compliance and tolerance of therapy, thereby determining the success of the medical treatment of glaucoma.

Pisella et al demonstrated the lower prevalence of ocular symptoms and signs in preservative free eyedrops, in comparison with preserved eyedrops in glaucoma treatment (11).

In our study, we pooled the results of Pisella et al's patients in France with identical studies carried out in Italy, Belgium, and Portugal. One of the merits of this study is the fact that it was performed in four different countries, with a population of 9658 patients, examined by many in-

TABLE VIII - PREVALENCE OF SYMPTOMS AND OCULAR SIGNS AT VISIT 1 AND VISIT 2 FOR THE FOUR DIFFERENT COUNTRIES IN THE P-PF GROUP

Ocular symptoms and signs	Total Visit 1	Total Visit 2	France Visit 1	France Visit 2	Italy Visit 1	Italy Visit 2	Belgium Visit 1	Belgium Visit 2	Portugal Visit 1	Portugal Visit 2
Ocular symptoms										
Foreign body sensation	49	8 (–41)	43	13 (–31)	50	7 (–43)	57	15 (–42)	44	8 (–36)
Dry eye sensation	43	11 (–32)	33	12 (–21)	45	11 (–34)	35	15 (–20)	37	9 (–28)
Tearing	31	10 (–21)	32	10 (–22)	31	10 (–21)	32	7 (–25)	28	14 (–14)
Eyelid itching	27	5 (–22)	24	5 (–19)	27	5 (–22)	33	9 (–24)	33	2 (–29)
Ocular signs										
Hyperemia	64	16 (–48)	61	16 (–45)	65	16 (–49)	64	17 (–47)	55	13 (–22)
Follicles	21	5 (–16)	34	9 (–25)	18	4 (–14)	38	11 (–27)	17	7 (–10)
Superficial keratitis	29	6 (–23)	25	5 (20)	29	5 (–24)	44	22 (–22)	16	15 (–1)

Values are percentages. (% difference between Visit 1 and Visit 2).
P = Preserved eyedrops; PF = Preservative free eyedrops

TABLE IX - PREVALENCE OF OCULAR SYMPTOMS AND SIGNS AT VISIT 1 AND VISIT 2 FOR THE FOUR DIFFERENT COUNTRIES IN THE P-DP GROUP

Ocular symptoms and signs	Total Visit 1	Total Visit 2	France Visit 1	France Visit 2	Italy Visit 1	Italy Visit 2	Belgium Visit 1	Belgium Visit 2	Portugal Visit 1	Portugal Visit 2
Ocular symptoms										
Foreign body sensation	58	15 (–43)	35	19 (–36)	62	16 (–46)	62	21 (–41)	55	24 (–31)
Dry eye sensation	49	21 (–28)	36	12 (–24)	50	22 (–28)	35	15 (–20)	55	31 (–22)
Tearing	40	20 (–20)	36	26 (–10)	41	20 (–21)	24	12 (–12)	48	41 (–7)
Eyelid itching	34	8 (–26)	25	7 (–18)	36	10 (–26)	18	6 (–12)	38	14 (–24)
Ocular signs										
Hyperemia	63	28 (–35)	68	30 (–38)	65	27 (–38)	74	32 (–42)	72	55 (–17)
Follicles	26	9 (–17)	39	14 (–25)	28	8 (–20)	24	6 (–18)	34	28 (–6)
Superficial keratitis	40	12 (–28)	23	9 (–14)	43	11 (–32)	50	26 (–24)	57	41 (–16)

Values are percentages. (% difference between Visit 1 and Visit 2).
P = Preserved eyedrops; DP = Decreased number of P eyedrops

dividual ophthalmologists, generally prescribing both preserved and preservative free eyedrops.

Conspicuous in the European study is that the differences in symptoms between the preserved group and the preservative free group were even more explicit than in the French study (11).

At the first visit, the same symptoms were investigated, but in the P group, foreign body sensation (50% vs 31%) and dry eye sensation (43% vs 23%) were more frequent in the Italian, Portuguese, and Belgian group combined compared to the French group. With respect to the ocular signs, the greater difference between the P group and the

PF group was obvious for the mild superficial punctate keratitis (27 to 7% vs 17 to 9% for the combined and French groups, respectively). This difference is mainly explained by the higher prevalence of signs and symptoms in the Italian group (the largest cohort with 52% of the patients). Not surprisingly, the difference in signs and symptoms was also comparable with Pisella et al's study when changing the preserved drops to preservative free, or diminishing the amount of daily instilled drops. Analyzing the results per country, we can draw some interesting conclusions (Tabs. VIII and IX).

In Italy, with 4129 patients, some subjective symptoms, namely dryness (44%), tears (32%), and itching (28%), and signs, namely hyperemia (62%) and follicles (20%), were more frequent in patients having taken eyedrops with preservatives than in the other countries. The decrease in subjective symptoms has been marked and statistically significant in all the cases with the switch to preservative free eyedrops between the first and the second visit. Surprisingly, a statistically nonsignificant decrease in symptoms was also observed in patients in the PF-PF and P-P groups. Yet the results of the objective signs were comparable to the results of the four countries pooled together.

In Belgium the difference in subjective symptoms using preserved eyedrops versus those using preservative free drops was greater than in other countries. At the same time all ocular signs were more pronounced in patients using preserved eyedrops compared to the total group of the four countries.

In the Portuguese study group, an identical tendency was being shown as in the European study group, but with slightly less symptoms and signs, except for the eyelid itching.

An advantage of this study was the fact that not only the patients who had to change or stop the preservative eyedrops were included, as was the case in some other studies (van Beek et al [12]). The share of reported symptoms in the entire ophthalmologic population who instilled some kind of eyedrops was much higher in that way, because the patients continuing their eyedrops were also included in our study.

Bron et al (13) published comparable results in a prospective clinical trial evaluating the efficacy and safety of a single daily instillation of preservative free timolol in 435 patients with open-angle glaucoma and ocular hypertension previously treated with a twice-daily regimen of preserved timolol. The improvement of the tolerance was associated with the maintenance of IOP control. In Bron et al's study, all the subjective symptoms and ocular signs showed a lower prevalence in patients when treated with preserved timolol twice daily than in our patients who used preserved eyedrops, probably because the number of preserved eyedrops used daily by the patients in our study was much higher. Moreover, this study was prospective and most likely toxic reactions require longer durations of treatment to develop and may be missed or underestimated in prospective randomized clinical trials.

The slight decrease in symptoms as well as in some objective signs in the groups without any change of therapy (PF-PF and P-P group) can be interpreted on the basis of regression to the mean and the Hawthorne effect. Regression to the mean is a principle stating that of related measurements, the second is expected to be closer to the mean than the first. On the other hand, it is a statistical phenomenon causing outcomes to be more likely to fall toward the center of a statistical distribution. The Hawthorne effect is a significant positive effect due to the higher motivation of patients participating in a study (14).

In vitro studies have shown that preservatives are toxic for the ocular surface cells, namely the conjunctival epithelium and keratocytes (15-17), corneal endothelium (17), and the deeper ocular tissues (fibroblast of the Tenon's capsule [18], cells of the trabecular meshwork [17, 19], and lens epithelium [20]). The adhesion, proliferation, metabolism, and membrane integrity of conjunctival cells is diminished with lower concentrations (5) and in higher concentrations the preservatives are cytotoxic, inducing apoptosis (21-23). The toxic effect depends on the dose, concentration, and duration of exposure time (22).

In patients with primary open angle glaucoma, Pisella et al (24) demonstrated that medical treatment of more than 1 year induced a greater expression of the inflammation markers HLA-DR and ICAM-1 in conjunctival tissue when preserved beta-blocking eyedrops were instilled in comparison to preservative free eyedrops. An increase of the expression of inflammation marker IL1 beta has been shown in ocular hypertensive patients treated with preservative beta blockers in comparison with preservative-free eyedrops in a crossover study by Manni et al (25).

On the other hand, there was a reduction in the expression of M1/MUC5AC, markers of goblet cells, suggesting that these cells were diminished in number after a long-term treatment with preserved eyedrops in comparison with preservative free eyedrops. The degree of inflammation of the conjunctiva is therefore lower in patients treat-

ed with preservative free eyedrops. In addition, the integrity of the eye surface and the goblet cells is conserved better (4, 26).
Furthermore, a greater corneal toxicity of preservative eyedrops has been demonstrated in several studies (27-29). The preservatives induce the loss of microvilli of the corneal epithelium (29), folding of the cell membranes (29), and micro-erosions staining with fluorescein (27, 28).
Ramselaar et al (9) compared the instillation of anesthetics with and without preservatives in healthy persons and showed a higher corneal permeability when preservatives were used, appearing to be more toxic.
The detergent effects of the preservatives provoke a dissolution of lipid layer tear film resulting in a decrease in tear break-up time (8). In a double blind clinical survey Baudouin and de Lunardo (30) compared tolerance of carteolol 2% with or without benzalkonium chloride in healthy volunteers, and noted a significantly higher degree of hyperemia and a lower tear break-up time in the group using the preservative eyedrops.

CONCLUSIONS

The results of this European study showed that preservative free eyedrops are significantly less associated with ocular symptoms and signs of irritation than preserved eyedrops. The use of preservative free eyedrops may therefore improve compliance and adherence in the medical treatment of glaucoma.

ACKNOWLEDGEMENTS

This clinical trial was funded by Laboratoires Théa, Clermont-Ferrand, France.

No author has any proprietary interest, except Pascale Pouliquen, who is employed by the Laboratoires Théa, the sponsor of the study.

Reprint requests to:
Thierry Zeyen, PhD
UZ Leuven
Capucijnenvoer 33
B 3000 Leuven, Belgium
thierry.zeyen@uz.kuleuven.ac.be

REFERENCES

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2001; 90: 262-67.
2. Wilson LA. To preserve or not to preserve, is that the question? Br J Ophthalmol 1996; 80: 583-4.
3. Dantas PE, Uesugui E, Nishiwaki-Dantas MC, Mimica LJ. Antibacterial activity of anesthetic solutions and preservatives: an in vitro comparative study. Cornea 2000; 19: 353-4.
4. Yalvac IS, Gedikoglu G, Karagoz Y, et al. Effects of antiglaucoma drugs on ocular surface. Acta Ophthalmol Scand 1995; 73: 246-8.
5. Wilson WS, Duncan AJ, Jay JL. Effect of benzalkonium chloride on the stability of the precorneal tear film in rabbit and man. Br J Ophthalmol 1975; 59: 667-9.
6. Broadway DC, Grierson I, O'Brien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. I. The conjunctival cell profile. Arch Ophthalmol 1994; 112: 1437-45.
7. Schwab IR, Linberg JV, Gioia VM, Benson WH, Chao GM. Foreshortening of the inferior conjunctival fornix associated with chronic glaucoma medications. Ophthalmology 1992; 99: 197-202.
8. Broadway DC, Grierson I, O'Brien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. II. The outcome of filtration surgery. Arch Ophthalmol 1994; 112: 1446-54.
9. Ramselaar JA, Boot JP, van Haeringen NJ, van Best JA, Oosterhuis JA. Corneal epithelial permeability after instillation of ophthalmic solutions containing local anaesthetics and preservatives. Curr Eye Res 1988; 7: 947-50.
10. Nguyen TP, Nishimoto JH, Nakamura CY, De Land PN. Comparison of carboxymethylcellulose vs. hydroxypropyl methylcellulose as a gonioscopic fluid. Optom Vis Sci 1996; 73: 466-72.
11. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. Br J Ophthalmol 2002; 86: 418-23.
12. van Beek LM, de Keizer RJ, Polak BC, Elzenaar PR, van Haeringen NJ, Kijlstra A. Incidence of ocular side effects of topical beta blockers in the Netherlands. Br J Ophthalmol 2000; 84: 856-9.
13. Bron A, Chiambaretta F, Pouliquen P, Rigal D, Rouland JF. Efficacy and safety of substituting a twice-daily regimen of timolol with a single daily instillation of non-preserved beta-blocker in patients with chronic glaucoma or ocular hypertension. J Fr Ophtalmol 2003; 26: 668-74.

14. James EL, Talbot L. Conducting research in general practice: lessons learnt from experience. Health Promot J Austr 2005; 16: 41-6.
15. Lapalus P, Ettaiche M, Fredj-Reygrobellet D, Jambou D, Elena PP. Cytotoxicity studies in ophthalmology. Lens Eye Toxic Res 1990; 7: 231-42.
16. Parnigotto PP, Bassani V, Montesi F, Conconi MT. Bovine corneal stroma and epithelium reconstructed in vitro: characterisation and response to surfactants. Eye 1998; 12: 304-10.
17. Samples JR, Binder PS, Nayak S. The effect of epinephrine and benzalkonium chloride on cultured corneal endothelial and trabecular meshwork cells. Exp Eye Res 1989; 49: 1-12.
18. Williams DE, Nguyen KD, Shapourifar-Tehrani S, Kitada S, Lee DA. Effects of timolol, betaxolol, and levobunolol on human Tenon's fibroblasts in tissue culture. Invest Ophthalmol Vis Sci 1992; 33: 2233-41.
19. Hamard P, Blondin C, Debbasch C, Warnet JM, Baudouin C, Brignole F. In vitro effects of preserved and unpreserved antiglaucoma drugs on apoptotic marker expression by human trabecular cells. Graefes Arch Clin Exp Ophthalmol 2003; 241: 1037-43.
20. Goto Y, Ibaraki N, Miyake K. Human lens epithelial cell damage and stimulation of their secretion of chemical mediators by benzalkonium chloride rather than latanoprost and timolol. Arch Ophthalmol 2003; 121: 835-9.
21. De Saint Jean M, Brignole F, Bringuier AF, Bauchet A, Feldmann G, Baudouin C. Effects of benzalkonium chloride on growth and survival of Chang conjunctival cells. Invest Ophthalmol Vis Sci 1999; 40: 619-30.
22. De Saint Jean M, Debbasch C, Brignole F, Rat P, Warnet JM, Baudouin C. Toxicity of preserved and unpreserved antiglaucoma topical drugs in an in vitro model of conjunctival cells. Curr Eye Res 2000; 20: 85-94.
23. Takahashi N, Mukai Y. Cytotoxicity of benzalkonium chloride in cell culture. In: Blodi R, Brancato R, Cristini G, et al. Proceedings of the XXVth International Congress of Ophthalmology. Rome. May 4–10, 1986; Acta XXV Conc. Ophtalmol. Amsterdam: Ed. Kugler & Ghedini, 1987; 1: 564-9.
24. Pisella PJ, Lala E, Parier V, Brignole F, Baudouin C. Effect of preservatives on the conjunctiva: a comparative study of beta-blocker eyedrops with and without preservatives in glaucoma patients. J Fr Ophtalmol 2003; 26: 675-9.
25. Manni G, Centofanti M, Oddone F, Parravano M, Bucci M. Interleukin-1 tear concentration in glaucomatous and ocular hypertensive patients treated with preservative-free nonselective beta-blockers. Am J Ophthalmol 2005; 139: 72-7.
26. Mietz H, Niesen U, Krieglstein GK. The effect of preservatives and antiglaucomatous medication on the histopathology of the conjunctiva. Graefes Arch Clin Exp Ophthalmol 1994; 232: 561-5.
27. Furrer P, Mayer JM, Plazonnet B, Gurny R. Ocular tolerance of preservatives on the murine cornea. Eur J Pharm Biopharm 1999; 47: 105-12.
28. Furrer P, Berger J, Mayer JM, Gurny R. A comparative study of the ocular tolerance of 3 timolol-based preparations: the influence of preservatives on ocular tolerance. J Fr Ophtalmol 2001; 24: 13-9.
29. Noecker RJ, Herrygers LA, Anwaruddin R. Corneal and conjunctival changes caused by commonly used glaucoma medications. Cornea 2004; 23: 490-6.
30. Baudouin C, de Lunardo C. Short-term comparative study of topical 2% carteolol with and without benzalkonium chloride in healthy volunteers. Br J Ophthalmol 1998; 82: 39-42.