Eye (2007) 21, 58–64

www.nature.com/eye

CLINICAL STUDY

Dexamethasone–netilmicin: a new ophthalmic steroid–antibiotic combination. Efficacy and safety after cataract surgery

S Russo[1], V Papa[1], A Di Bella[1], A Favero[1], C Radulescu[1], O Gafencu[2], B Carstocea[2] and G Milazzo[1]

[1]Medical Department, SIFI S.p.A., Aci S.Antonio, Italy

[2]Department of Ophthalmology, Military Hospital, Bucharest, Romania

Correspondence: V Papa, SIFI SpA-Medical Department, Via Ercole Patti 36, 95020 Lavinaio (Catania), Italy
Tel: +39 095 7922375; Fax: +39 095 7893451.
E-mail: vincenzo_papa@sifi.it

Received: 16 May 2005
Accepted in revised form: 24 August 2005
Published online: 4 November 2005

A Favero is a private statistician (consultant of SIFI SpA)

The data included in this paper have been partially presented at ARVO 2003, Ft Lauderdale, FL, USA, 4–9 May 2003

The authors have no commercial or proprietary interest in the product described in this article. Simona Russo, Vincenzo Papa, Alessandro Di Bella, Constantin Radulescu and Giovanni Milazzo are employees of the manufacturer of the product described in this article (SIFI SpA, Italy)

Abstract

Purpose **The purpose of this study was to evaluate both efficacy and safety of a new ophthalmic steroid–antibiotic fixed combination containing dexamethasone and netilmicin in the postsurgical management of cataract surgery.**
Methods **In total, 223 patients were randomly treated with dexamethasone 1 mg/ml plus netilmicin 3 mg/ml ($n=148$), or dexamethasone 1 mg/ml plus tobramycin 3 mg/ml ($n=75$, TOBRADEX®) four times in a day for 7 ± 1 days starting immediately after surgery. Efficacy (anterior chamber (AC) inflammation, conjunctival hyperaemia, corneal and lid oedema, ocular infection, pain, photophobia and tearing) and safety (burning, stinging, blurred vision, intraocular pressure, and visual acuity) were analysed in the operated eye after 1 and 7 ± 1 days. A follow-up visit was performed at day 14 ± 2. The extent of AC inflammation, measured by slit-lamp according to a standard scoring system, was used as primary efficacy parameter.**
Results **At the primary end point (day 7) both fixed combinations were equally effective in reducing postoperative inflammation. The safety profile of the dexamethasone/netilmicin combination was excellent with no evidence of poor local tolerance or adverse reaction.**
Conclusions **A new fixed combination of dexamethasone and netilmicin was effective and safe in controlling ocular inflammation after cataract surgery.**
Eye (2007) **21,** 58–64. doi:10.1038/sj.eye.6702123; published online 4 November 2005

Keywords: cataract; fixed combination; netilmicin; dexamethasone

Introduction

Cataract surgery with intraocular lens (IOL) implantation is the most common ophthalmic surgical operation. This procedure is usually associated with varying degrees of postsurgical inflammation.[1] Although such inflammation is usually self-limited, the use of anti-inflammatory agents postoperatively can rapidly resolve this event. To date, topical corticosteroids still form the mainstay of the anti-inflammatory management of cataract extraction.[2,3]

Besides ocular inflammation, the major concern of ophthalmologists performing cataract surgery is the risk of ocular infection. Surgical wound infection and postoperative endophthalmitis are relatively rare but potentially devastating events, and therefore there is uniform agreement on the need for antibiotic prophylaxis in the cataract surgery.[1,3–5] Aminoglycosides and fluoroquinolones are the most prescribed ophthalmic antibiotics that can provide excellent coverage against most Gram-positive and Gram-negative organisms without significant clinical risk.

Thus, the postoperative pharmacology management of cataract extraction includes the use of a topical steroid with an antibiotic usually as a combination eye drop.[1,3,6] The concomitant administration of both agents in a single ophthalmic product overcomes the potential washout effect that may be seen when

separate medications are used. In addition, single administration of a combination product leads to better compliance and patient comfort.[7,8]

In the present study we evaluated both efficacy and safety of a new fixed combination of dexamethasone and netilmicin in patients undergoing cataract surgery. The efficacy of such product was compared to TOBRADEX®, a well accepted steroid/antibiotic combination that is currently marketed in several countries as a standard treatment to control postsurgical inflammation and prevent postsurgical infection.[9]

Dexamethasone is a potent fluorinated synthetic corticosteroid derived from hydrocortisone with structural changes that give to dexamethasone an anti-inflammatory activity about six times stronger than that of prednisone and prednisolone. Dexamethasone in various formulations (phosphate, alcohol) is the most widely used ophthalmic corticosteroid and has proven an effective treatment for ocular inflammation[10,11] even after cataract surgery.[1,3,12,13] *In vitro*, the alcohol form of 1 mg/ml dexamethasone is 15 times stronger than the corresponding phosphate.[14] However, dexamethasone phosphate is locally converted into its alcohol form by phosphatases present in the corneal epithelium.[15]

Netilmicin is a semisynthetic, third generation, aminoglycoside antibiotic with a wider spectrum of activity than other antibiotics of the same class, such as tobramycin and gentamicin.[16] In a recent study, the percentage of susceptibility of netilmicin was comparable to that of fluoroquinolones.[17] It is active against most of both Gram-negative and Gram-positive germs, including *S. aureus*, *S. epidermidis* and *S. coagulase negative*.[17,18] These organisms are the most common bacteria isolated in postoperative endophthalmitis and are usually recovered in the patient' external tissues, such as eyelids.[4,5] In addition, netilmicin is less susceptible to attack from many of the aminoglycoside-inactivating bacterial enzymes and therefore is active against strains resistant to gentamicin and tobramycin.[16]

Materials and methods

This prospective, randomised, double-blind, active controlled, parallel group study was conducted at the Department of Ophthalmology of the Military Hospital of Bucharest (Romania) between February and November 2002 in patients scheduled for phacoemulsification (corneal tunnel incision) and posterior chamber IOL implantation. The study protocol was reviewed and approved by the local ethics committee and conducted according to the Declaration of Helsinki and Good Clinical Practices. Written informed consent was obtained from all patients.

Patients and subsets

A total of 223 Caucasian patients were included in the study (Table 1). Patients were at least 40 years old and suffered from presenile or senile cataract. Exclusion criteria included: intraocular pressure (IOP) greater than 24 mmHg, any concomitant ocular pathology, herpes infection, proliferative diabetic retinopathy, ocular medications other than artificial tears, previous ocular surgery or laser treatment in the operated eye in the 6 months preceding surgery, known or suspected allergy to any of the ingredients in the study medications and use of topical or systemic steroids or nonsteroidal anti inflammatory drugs in the 15 days preceding surgery. All surgeries were performed by two surgeons with comparable surgical experience and technique.

Enrolled patients were randomly assigned to treatments groups by using a computer generated randomization list in a 2 : 1 ratio to receive an ophthalmic formulation containing dexamethasone 1 mg/ml plus netilmicin 3 mg/ml ($n = 148$, group 1) or dexamethasone 1 mg/ml plus tobramycin 3 mg/ml ($n = 75$, group 2). The latter combination is marketed world-wide since 1988 (TOBRADEX®) and it is considered as the 'golden standard' of steroid/antibiotic fixed combinations.[19,20] The use of placebo in the control group was not considered ethical.

Both products were packaged in an identical fashion to guarantee an appropriate masking for both patients and investigators. Benzalkonium chloride –(BAC) (at a concentration of 0.01% in TOBRADEX® and 0.005% in dexamethasone/netilmicin) was present in both formulations as preservative.

The treatment started immediately after surgery (day 0) and continued (one drop four times in a day) for 7 consecutive days. No other treatments were allowed

Table 1 Demographic characteristics (ITT subset)

	Test[a]	*Control*[b]	*Total*
Number of patients	148	75	223
Age (years)			
Mean (SD)	70.0 (11.0)	69.1 (10.9)	69.7 (10.9)
Range	41–91	40–90	40–91
Gender (number, %)			
Male	70 (47.3)	40 (53.3)	110 (49.3)
Female	78 (52.7)	35 (46.7)	113 (50.7)
Lens type (number, %)			
Foldable	44 (29.7)	21 (28.0)	65 (29.1)
Unfoldable	104 (70.3)	54 (72.0)	158 (70.9)

[a]Dexamethasone/netilmicin.
[b]TOBRADEX®.

until after the end of the trial except in case of absolute necessity.

Eight patients had intraoperative complications (capsule rupture followed by vitrectomy); these patients were considered not eligible and evaluated only for safety.

The assignment of patients to the different analysis set was decided before unblinding the database, as follows: (a) intent-to-treat (ITT) = all operated patients who received the treatment at least once ($n = 223$); (b) full-analysis (FA) = patients operated and treated for at least 5 days and that reached the end point examination (day 7 ± 1 after surgery) ($n = 208$, 135 in the group 1 and 73 in the group 2); (c) per-protocol (PP) = patients of the FA population without any relevant protocol deviation ($n = 203$, 132 in the group 1 and 71 in the group 2).

Evaluation

Patients were examined before surgery (day 0) and postoperatively at day 1 and day 7 ± 1 (end point evaluation). A follow-up visit was performed at day 14 ± 2. The examination at each visit included best-corrected visual acuity, slit-lamp examination, funduscopy, and applanation tonometry assessment of IOP. The primary variable chosen to assess drug efficacy was the anterior chamber (AC) inflammation. AC inflammation was evaluated by slit-lamp examination and scored from none to severe using a 0–3 point scale as already described.[21] Other criteria of efficacy included conjunctival hyperaemia, corneal and lid oedema, ocular infection, and ocular discomfort. The tolerance variables assessed were the degree of burning, stinging, and blurred vision. All these clinical variables were also graded from none to severe using a 0–3 point scale.[21] Safety variables that were monitored during the trial were visual acuity, IOP, and funduscopy. Only two physicians have been involved in all clinical evaluation.

Statistics

The assessment of the primary efficacy parameter (AC inflammation) was mainly based on the evaluation of the AC flare by comparing both the 'efficacy rate' (primary efficacy parameter) and the 'percentage of responders' (secondary efficacy parameter) at the study end point (day 7 ± 1, after surgery). The 'efficacy rate' was defined as the percentage of patients displaying absent (score = 0) or mild (score = 1) degree of AC flare.[22] The 'percentage of responders' was defined as the percentage of patients showing a decrease of AC flare score from baseline and those scoring 0 at baseline and also at the end point.[22]

The study was designed to show that dexamethasone/netilmicin was not inferior to TOBRADEX®. Analysis of efficacy was performed by means of one-sided 97.5%-confidence intervals test, with a delta of 15%, a power of 90% and a lower margin of −15.

For the other efficacy parameters and for the tolerance variables, intraindividual score differences were compared between treatments by the Wilcoxon test for independent samples. Moreover, in order to assess treatment efficacy independently from baseline levels, nonparametric analyses were also performed within each treatment group by comparing the score differences between baseline and each visit (Pratt–Wilcoxon test). IOP and visual acuity of the operated eye were evaluated by analysis of variance. The between-treatment differences were estimated together with one-sided 97.5%-confidence intervals.

Statistical analyses were performed on predefined subsets. Efficacy was tested on PP and FA subsets; results obtained in the two sets were comparable and therefore only data obtained in the FA subset will be showed and discussed in details. Safety analysis was performed on ITT subset. Possible side effects of the study medications and any adverse events were listed and compared by Fisher's exact test.

The replacement of missing values was adopted for the FA population according to the last value option carried forward (LOCF) technique only if it was present a valid measurement at day 7 (visit 3).

Results

Efficacy

Efficacy data are displayed in Tables 2 and 3**.** Both treatments were effective in decreasing overtime ocular inflammation, as demonstrated by the within-group analysis of efficacy (Table 2). In addition, the 'efficacy rate' and the 'percentage of responders' in each treatment group were comparable (Table 3) as indicated by the lower limit of the 97.5% one-sided confidence intervals (greater than −0.15) at both day 7 and day 14 after surgery. No differences were observed in the evaluation of all other efficacy parameters (Table 2, between group analysis). All these data demonstrate therefore that the new fixed combination containing dexamethasone/netilmicin is effective and not inferior than TOBRADEX®.

Safety

Three patients of the dexamethasone/netilmicin group did not complete the study due to adverse events (hepatic coma, bacterial conjunctivitis, lower limb ischemia), but they were all judged not related with treatment. The tolerance variables assessed were the

Table 2 Efficacy parameters: within and between treatment analyses (FA subset)

Parameter	*Day after surgery*	*Within-treatment analysis*				*Between-treatment analysis*[a]
		Test[b]		*Control*[c]		
		Z[d]	P-*value*[e]	Z[d]	P-*value*[e]	P-*value*[e]
AC flare	7	10.29	<0.0001	7.46	<0.0001	0.923
	14	11.14	<0.0001	7.94	<0.0001	0.144
AC cells	7	10.33	<0.0001	7.44	<0.0001	0.645
	14	11.19	<0.0001	7.91	<0.0001	0.040
Conjunctival hyperaemia	7	9.00	<0.0001	7.25	<0.0001	0.120
	14	10.17	<0.0001	7.61	<0.0001	0.214
Corneal oedema	7	10.03	<0.0001	6.79	<0.0001	0.105
	14	10.31	<0.0001	7.59	<0.0001	0.129
Lid oedema	7	Not applicable	Not applicable		0.141	
	14				0.468	
Pain	7	3.23	0.0012	3.10	0.0020	0.207
	14	3.38	0.0007	3.87	0.0001	0.033
Photophobia	7	3.07	0.0021	2.15	0.0315	0.996
	14	3.04	0.0024	2.82	0.0048	0.536
Tearing	7	3.80	0.0001	2.55	0.0108	0.676
	14	4.12	<0.0001	2.81	0.0049	0.776

[a]Wilcoxon rank-sum test.
[b]Dexamethasone/netilmicin.
[c]TOBRADEX®.
[d]Pratt–Wilcoxon test.
[e]Two sided *P*-value.

Table 3 Efficacy rates and rates of responders (FA subset)

Parameter	*Test*[a]		*Control*[b]		*Lower limit of the 97.5% CI*[c]
No. of patients	*135*		*73*		
	n	%	n	%	
Efficacy rates					
Day 7	133	98.52	73	100	−0.035
Day 14	135	100	73	100	—
Responders					
Day 7	110	81.48	59	80.82	−0.105
Day 14	133	98.52	72	98.63	−0.035

[a]Dexamethasone/netilmicin.
[b]TOBRADEX®.
[c]Computed using normal approximation method for the rate difference (Test−Control). According to Blackwelder WC. 'Proving the null hypothesis' in clinical trials. *Controlled Clinical Trials* 1982; **3**: 345–353.

Table 4 Safety parameters: within and between treatment analyses (FA subset)

Parameter	*Day after surgery*	*Within-treatment analysis*				*Between-treatment analysis*[a]
		Test[b]		*Control*[c]		
		Z[d]	P-*value*[e]	Z[d]	P-*value*[e]	P-*value*[e]
Burning	7	4.29	<0.0001	3.31	0.0009	0.839
	14	4.69	<0.0001	3.31	0.0009	1.000
Stinging	7	3.22	0.0013	3.10	0.0019	0.522
	14	4.46	<0.0001	3.25	0.0011	0.963
Blurred	7	3.67	0.0002	2.81	0.0049	0.945
vision	14	4.37	<0.0001	4.42	<0.0001	0.194

[a]Wilcoxon rank-sum test.
[b]Dexamethasone/netilmicin.
[c]TOBRADEX®.
[d]Pratt–Wilcoxon test.
[e]Two-sided *P*-value.

degree of burning, stinging, and blurred vision. Their intensity was generally rated as none or mild at all study visits without any statistically significant difference between treatment groups (Table 4). Moreover, within treatment comparisons showed that such symptoms significantly improved over time in both group of treatment (data not shown). Safety variables that were monitored during the trial were visual acuity and IOP. Regarding the IOP, there was a mean decrease of 1–2 mmHg in both treatment groups at all postoperative visits over measurements at the screening visit (Figure 1). No difference between treatment groups in mean change from screening was detected at any visit. Three patients (all in the dexamethasone/netilmicin group) could be classified as intermediate corticosteroid responders (ie delta IOP over baseline within 6 and 16 mmHg), and no patients had a clinically significant IOP increases (10 mmHg or greater).[23]

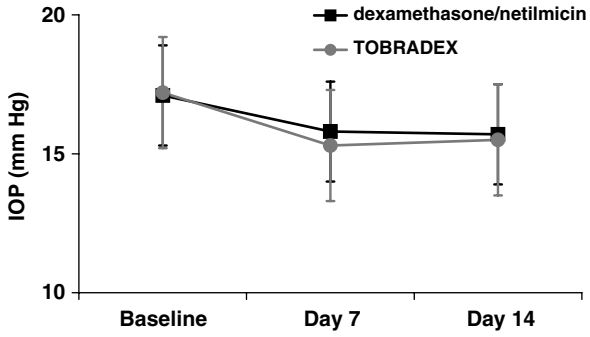

Figure 1 Intraocular pressure data. Baseline values are referred to the screening visit.

Discussion

Cataract surgery is one of the most frequently performed surgeries in the world.[24] The techniques of cataract extractions have evolved significantly during the past decade, resulting in decreased intraocular inflammation following this procedure.[1] Some patients can have surgery even with no inflammation, but it is not possible to date to predict such outcome and therefore anti-inflammatory agents are routinely used in nearly all patients. Even if both steroidal and nonsteroidal anti-inflammatory drugs have been successful utilised in the control of postoperative inflammation,[2,20,25–27] corticosteroids offer the widest range of activity by ameliorating the effect of the preformed mediators of inflammation as well as attenuating the release of newly formed mediators.[28] Therefore, they still form the mainstay of the anti-inflammatory management of cataract extraction.[2,28,29]

Beyond ocular inflammation, the other concern of ophthalmologists performing cataract surgery is the risk of ocular infection. The use of antibiotics in cataract surgery includes a variety of practices, such as preoperative topical antibiotics, intraoperative antibiotics in the irrigating solution, subconjunctival antibiotics, and postoperative topical antibiotics.[4,5] Although many of these practices are largely empirical, the evidence that most of the postsurgical infections result from the intraocular introduction of bacterial flora from the eye and adjacent skin during surgery has led to the increasing importance of the use of perioperative antibiotics.[1,3–5] Accordingly, also the Center for Disease Control and Prevention (CDC) included in 1999 for the first time ophthalmology in the 'Recommendations for Prevention of Surgical Site Infection'.[30]

Antibiotics and corticosteroids are usually given after surgery to patients either separated from or in combination.[6] The use of the latter option is usually preferred since it improves patients compliance and reduce cost.[7,8] In addition, such therapy reduces the chance of an imprecise dosing or the potential washout effect that may be seen when separate medications are used. The reduced number of administrations provided by the combination product may be of particular benefit for elderly patients, who make up the majority of cataract surgeries.

The currently approved fixed combinations of steroids and antibiotics contain dexamethasone, hydrocortisone, predisolone, fluorometholone or loteprednol etabonate combined with sulphonamides or aminoglycosides (neomicin, gentamicin or tobramycin). The efficacy and safety of a new steroid/antibiotic fixed combination containing dexamethasone/netilmicin has been investigated in the present study.

The main objective of this study was to demonstrate the noninferiority of a combination of dexamethasone plus netilmicin compared to a standard effective combination of steroid plus antibiotic (TOBRADEX®)[9] in controlling postoperative inflammation and preventing postoperative ocular infections. The design of the study was consistent with the standard postoperative care of patients undergoing cataract extraction.[1,3] However, due to the excellent wound closure obtained with modern cataract surgery, it was decided to reduce the duration of treatment to 7 days. This restriction of the duration of therapy should ensure at the same time an effective control of postoperative inflammation and a lower incidence of both antibiotic resistance[4,5] and corticosteroid-related side effects.[31] As a potential limitation of the study, AC inflammation was measured, for practical reasons, by slit-lamp examination rather than by a laser flare and cell meter. Even if the scoring system used to measure flare and cells by slit-lamp examination is subjective and semiquantitative, yet it corresponds to the actual daily routine of practice. Moreover, close agreement between biomicroscopy and LCFM measurements has been described.[32]

The present findings indicate that new fixed combination of dexamethasone plus netilmicin was as effective as TOBRADEX® in reducing ocular inflammation after cataract surgery. There was a significant decrease in the amount of aqueous flare and cells, as well as of all other parameters of inflammations after 1 week of treatment. All parameters studied were comparable in the control and test group with no statistical significant differences. There was no evidence of rebound of signs after cessation of therapy. With respect to safety, dexamethasone/netilmicin combination had a favorable safety profile, including ocular tolerance.

A common safety concern with topical corticosteroids is the potential to cause an increase in IOP in susceptible individuals.[31] There was no issue with elevation in IOP in this study. A decrease of IOP is a common feature in

the follow-up of cataract surgery[33] and, as expected, a significant decrease of IOP mean levels from baseline through study visits was observed in the present clinical trial. None of the patients had a clinically significant IOP elevation (ie delta > 10 mmHg over the baseline value) according to the Stewart's criteria.[23] In addition, only three out of the 148 patients (2%) treated with the new steroid/antibiotic combination could be classified as intermediate steroid responders (ie delta IOP over baseline within 6 and 16 mmHg).[34] Such a low incidence of steroid responders was not unexpected since the duration of treatment in this study (7 days) is shorter than the traditional period (>15 days) for corticosteroid induced elevation in IOP.

Dexamethasone/netilmicin fixed combination has several advantages over TOBRADEX®. *First*, netilmicin is a the third generation aminoglycoside with a spectrum of activity comparable to that of fluoroquinolones.[17] It has an excellent clinical profile and (as opposed to tobramycin) a very low prevalence of resistance against the most common microorganisms involved in ocular infections.[17,18,35] Furthermore, netilmicin, in contrast to quinolones, has no toxicity for conjunctival and corneal cells.[36] *Second*, the new combination contains the water-soluble dexamethasone phosphate and therefore is formulated (unlike most of the commercially available steroid/antibiotic combinations) as a ready-to-use eye drops solution rather than suspension. The solution does not contain particles that may cause discomfort (as opposed to the lipid soluble preparation of TOBRADEX®, which is suspended but not dissolved in the vehicle). In addition, the drug concentration in a solution is more constant than it is in a suspension, providing more equal doses with each application. *Third*, the factor most commonly implicated in toxicity of topical medication to the ocular surface is the concentration of BAC,[37] whose concentration in the dexamethasone/netilmicin combination is half of that contained in TOBRADEX® (0.005 *vs* 0.01%, respectively). Interestingly, a recent paper demonstrated that drugs containing 0.005% BAC cause only minimal damage to the ocular surface even when dosed chronically.[38] Furthermore, the new product will also be the first steroid/antibiotic combination available in a preservative-free formulation; efficacy and safety of the latter is comparable to that of the preserved formulation reported herein (Russo S *et al*, unpublished data).

In conclusion, the fixed combination of dexamethasone and netilmicin resulted to be safe, well tolerated, and effective in controlling ocular inflammation after routine cataract surgery. This formulation can be considered for use in a wide spectrum of postsurgical prophylaxis regimens and to achieve better patient compliance with medication.

References

1 Rowen S. Preoperative and postoperative medications used for cataract surgery. *Curr Opin Ophthalmol* 1999; **10**: 29–35.
2 Simone JN, Whitacre MM. Effects of anti-inflammatory drugs following cataract extraction. *Curr Opin Ophthalmol* 2001; **12**: 63–67.
3 Abel Jr R, Abel AD. Perioperative antibiotic, steroid, and nonsteroidal anti-inflammatory agents in cataract intraocular lens surgery. *Curr Opin Ophthalmol* 1997; **8**: 29–32.
4 Liesegang TJ. Use of antimicrobials to prevent postoperative infection in patients with cataracts. *Curr Opin Ophthalmol* 2001; **12**: 68–74.
5 Soriano ES, Nishi M. Endophthalmitis: incidence and prevention. *Curr Opin Ophthalmol* 2005; **16**: 65–70.
6 Stewart RH, Kimbrough RL, Smith JP, deFaller JM. Use of steroid/antibiotic prophylaxis in intraocular lens implantation: a double-masked study v placebo. *Ann Ophthalmol* 1983; **15**: 24–28.
7 Barber BL, Strahlman ER, Laibovitz R, Guess HA, Reines SA. Validation of a questionnaire for comparing the tolerability of ophthalmic medications. *Ophthalmology* 1997; **104**: 334–342.
8 Hugues FC, Le Jeunne C. Systemic and local tolerability of ophthalmic drug formulations. An update. *Drug Saf* 1993; **8**: 365–380.
9 Notivol R, Bertin D, Amin D, Whitling A, Kennedy M, Cockrum PC. Comparison of topical tobramycin-dexamethasone with dexamethasone–neomycin–polymyxin and neomycin–polymyxin–gramicidin for control of inflammation after cataract surgery: results of a multicenter, prospective, three-arm, randomized, double-masked, controlled, parallel-group study. *Clin Ther* 2004; **26**: 1274–1285.
10 Nielsen RH. The use of dexamethasone in ophthalmologic steroid therapy: a preliminary report. *Arch Ophthalmol* 1959; **62**: 438–444.
11 Gordon DM. Use of dexamethasone in eye disease. *JAMA* 1960; **172**: 311–312.
12 Drews RC. Management of postoperative inflammation: dexamethasone *vs* flurbiprofen, a quantitative study using the new Flare Cell Meter. *Ophthalmic Surg* 1990; **21**: 560–562.
13 Othenin-Girard P, Tritten JJ, Pittet N, Herbort CP. Dexamethasone *vs* diclofenac sodium eyedrops to treat inflammation after cataract surgery. *J Cataract Refract Surg* 1994; **20**: 9–12.
14 Leibowitz HM, Kupferman A, Stewart RH, Kimbrough RL. Evaluation of dexamethasone acetate as a topical ophthalmic formulation. *Am J Ophthalmol* 1978; **86**: 418–423.
15 Weijtens O, Schoemaker RC, Romijn FP, Cohen AF, Lentjes EG, van Meurs JC. Intraocular penetration and systemic absorption after topical application of dexamethasone disodium phosphate. *Ophthalmology* 2002; **109**: 1887–1891.
16 Campoli-Richards DM, Chaplin S, Sayce RH, Goa KL. Netilmicin. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1989; **38**: 703–756.
17 Papa V, Aragona P, Scuderi AC, Blanco AR, Zola P, Di Bella A *et al.* Treatment of acute bacterial conjunctivitis with topical netilmicin. *Cornea* 2002; **21**: 43–47.
18 Bonfiglio G, Scuderi AC, Russo G. Netilmicin: *in vitro* activity, time-kill evaluation and postantibiotic effect on microorganisms isolated from ocular infections. *Chemotherapy* 2001; **47**: 117–122.

19 Kraff MC, Martin RG, Neumann AC, Weinstein AJ. Efficacy of diclofenac sodium ophthalmic solution *vs* placebo in reducing inflammation following cataract extraction and posterior chamber lens implantation. *J Cataract Refract Surg* 1994; **20**: 138–144.
20 Laurell CG, Zetterstrom C. Effects of dexamethasone, diclofenac, or placebo on the inflammatory response after cataract surgery. *Br J Ophthalmol* 2002; **86**: 1380–1384.
21 Papa V, Milazzo G, Santocono M, Servolle V, Sourdille P, Santiago PY *et al*. Naproxen ophthalmic solution to manage inflammation after phacoemulsification. *J Cataract Refract Surg* 2002; **28**: 321–327.
22 Missotten L, Richard C, Trinquand C. Topical 0.1% indomethacin solution *vs* topical 0.1% dexamethasone solution in the prevention of inflammation after cataract surgery. The Study Group. *Ophthalmologica* 2001; **215**: 43–50.
23 Stewart RH, Smith JP, Rosenthal AL. Ocular pressure response to fluorometholone acetate and dexamethasone sodium phosphate. *Curr Eye Res* 1984; **3**: 835–839.
24 El-Harazi SM, Feldman RM. Control of intra-ocular inflammation associated with cataract surgery. *Curr Opin Ophthalmol* 2001; **12**: 4–8.
25 Flach AJ. Cyclo-oxygenase inhibitors in ophthalmology. *Surv Ophthalmol* 1992; **36**: 259–284.
26 Flach AJ. Topical nonsteroidal antiinflammatory drugs in ophthalmology. *Int Ophthalmol Clin* 2002; **42**: 1–11.
27 Sanders DR, Kraff M. Steroidal and nonsteroidal anti-inflammatory agents. Effect on postsurgical inflammation and blood-aqueous humor barrier breakdown. *Arch Ophthalmol* 1984; **102**: 1453–1456.
28 Sherif Z, Pleyer U. Corticosteroids in ophthalmology: past-present-future. *Ophthalmologica* 2002; **216**: 305–315.
29 Bezan DJ. Postoperative care of the cataract patient. In: Bartlett JD JS (ed). *Clinical Ocular Pharmacology*. Butterworth-Heinemann: Boston, MA, 1995, pp 793–808.
30 Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1999; **20**: 250–278; quiz 279–280.
31 Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. *Curr Opin Ophthalmol* 2000; **11**: 478–483.
32 Roberts CW, Brennan KM. A comparison of topical diclofenac with prednisolone for postcataract inflammation. *Arch Ophthalmol* 1995; **113**: 725–727.
33 Sacca S, Marletta A, Pascotto A, Barabino S, Rolando M, Giannetti R *et al*. Daily tonometric curves after cataract surgery. *Br J Ophthalmol* 2001; **85**: 24–29.
34 Armaly MF. Statistical attributes of the steroid hypertensive response in the clinically normal eye. I. The demonstration of three levels of response. *Invest Ophthalmol* 1965; **26**: 187–197.
35 Milazzo G, Papa V, Carstocea B, Chercota G, Rodica P, Gafencu O *et al*. Topical netilmicin compared with tobramycin in the treatment of external ocular infection. *Int J Clin Pharmacol Ther* 1999; **37**: 243–248.
36 Papa V, Leonardi A, Getuli C, Pacelli V, Russo P, Milazzo G. Effect of ofloxacin and netilmicin on human corneal and conjunctival cells *in vitro*. *J Ocular Pharm Ther* 2003; **19**: 535–545.
37 Noecker R. Effects of common ophthalmic preservatives on ocular health. *Adv Ther* 2001; **18**: 205–215.
38 Noecker RJ, Herrygers LA, Anwaruddin R. Corneal and conjunctival changes caused by commonly used glaucoma medications. *Cornea* 2004; **23**: 490–496.