European Journal of Ophthalmology / Vol. 9 no. 4, 1999 / pp. 269-275

Treatment of acute bacterial conjunctivitis with topical lomefloxacin 0.3% compared to topical ofloxacin 0.3%

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ABSTRACT: Purpose. *The main purpose of this prospective study was to compare the efficacy, local tolerance, and safety of topical lomefloxacin 0.3% and topical ofloxacin 0.3% in the treatment of acute bacterial conjunctivitis.*

Patients and Methods. *Forty patients with acute bacterial conjunctivitis were included in a randomized, prospective, parallel-group study. Twenty patients were assigned to the lomefloxacin group (Okacin®, CIBA Vision Ophthalmics) and 20 patients to ofloxacin (Oflox®, Allergan). Lomefloxacin 0.3% was given 1 drop every 2 hours during waking hours on the first day then twice daily for one week. Ofloxacin 0.3% eyedrops were given four times daily. All patients underwent eye examination and clinical findings were graded and recorded according to severity of lid hyperemia, lid edema, lid crusting, conjunctival edema and discharge, bulbar conjunctival hyperemia, palpebral conjunctival hyperemia, corneal edema, and ocular discomfort. The score for each clinical sign was recorded before and after treatment. The mean cumulative sum score (CSS) was obtained by adding the scores for signs and symptoms. All conjunctival swabs were cultured and tested for sensitivity. Patients with confirmed bacterial conjunctivitis were included.*

Results. *There were 10 male and 10 female patients in each group. The age range was from 1 to 78 years, and the mean age was 35 years in the lomefloxacin group. In the ofloxacin group the age range was from 1 to 70 years, and the mean age was 26 years. There was no significant difference between the two groups in relation to age or sex. The causative organisms were Staphylococcus epidermidis in 16 cases (36%), α-hemolytic Streptococci in 9 (20%), Haemophilus spp. 6 (13%), Staphylococcus aureus 5 (11%), Streptococcus pneumoniae 4 (9%), Pseudomonas aeruginosa 3 (7%), and other 2 (4%). The mean CSS for conjunctivitis was 12.1 before therapy in the lomefloxacin group and 12.7 in the ofloxacin group. On the 7th day of therapy, the mean CSS was 0.7 in the lomefloxacin group, and 1.6 for ofloxacin. All patients showed improvement, but a total of 18 out of 20 (88%) in the lomefloxacin group showed complete resolution compared to 15 (75%) in the ofloxacin group. The difference was not statistically significant (p = 0.08). Tolerance was excellent in both groups, and no side effects were reported. A burning sensation was noted by two patients, one in each group.*

Conclusions. *Lomefloxacin and ofloxacin were equally effective and safe in the treatment of acute bacterial conjunctivitis. (Eur J Ophthalmol 1999; 9: 269-75)*

KEY WORDS: Acute conjunctivitis, Bacterial conjunctivitis, Fluoroquinolones, Lomefloxacin, Ofloxacin, Quinolones

Accepted: April 19, 1999

 1120-6721/269-07$03.50/0

INTRODUCTION

Acute bacterial conjunctivitis causes mucopurulent discharge and conjunctival hyperemia. Other clinical signs and symptoms of less diagnostic value like chemosis, foreign body sensation, and watery eyes may occur. (1) Bacterial cultures are not routinely done because of cost factors, delay in obtaining the results, and in some patients the culture is negative (2-4). The reasons for the high percentage of low counts or negative cultures from patients with mucopurulent discharge may be related to the small number of organisms obtained and the way the swab is transferred to the laboratory and not placed on culture plates on site.

Topical treatment with a safe antibiotic is recommended to inhibit the causative agent and to prevent complications to adjacent ocular structures. The side effects of topical medications, lack of compliance, and potential emergence of bacterial resistance pose a challenge to the clinician, requiring the development of new antibiotics with a wide spectrum of activity and low frequency of dosing to assure compliance and good tolerance.

Fluoroquinolones are members of a class of antimicrobial drugs including ciprofloxacin, fleroxacin, lomefloxacin, norfloxacin, ofloxacin, pefloxacin and temafloxacin. These are all C-7 1-piperazinyl and C-7 fluoro-substituted quinolones. These drugs are modeled on nalidixic acid but are more potent than the parent compound. Nalidixic acid was introduced by Lesher et al (5) as a synthetic agent against gram-negative bacteria. Recently, several pyridone carboxylic acid antibacterial agents, derivatives of nalidixic acid, have been developed. Fluoroquinolones, derivatives of pyridone carboxylic acids with a fluorine atom added to the quinolone nucleus, provide a broad antibacterial spectrum against gram-positive and gram-negative bacteria (6, 7). The fluoroquinolones are thought to act by interfering with bacterial deoxyribonucleic acid (DNA) supercoiling through inhibition of DNA gyrase (8, 9). There is recent evidence that beside the gyrase (topoisomerase IV), bacterial topoisomerase II is also a target enzyme involved in the activity of fluoroquinolones (10, 11).

Lomefloxacin is a difluoroquinolone antibacterial agent developed in Japan. It carries two fluorine atoms attached to the quinolone nucleus (Fig. 1). The drug has a remarkably wide spectrum of antibacterial activity, including gram-positive and gram-negative organism (12-17). The drug has excellent ocular bioavailability and corneal penetration (18, 19). Ooishi et al (19) reported that topical application of 5 drops of lomefloxacin 0.3% gave rise to significantly higher tissue levels in the rabbit cornea and aqueous than systemic application of 20 mg/kg of lomefloxacin, in normal and inflamed eyes. With this regimen, the tissue concentration in the cornea was bactericidal for many pathogenic organisms for several hours.

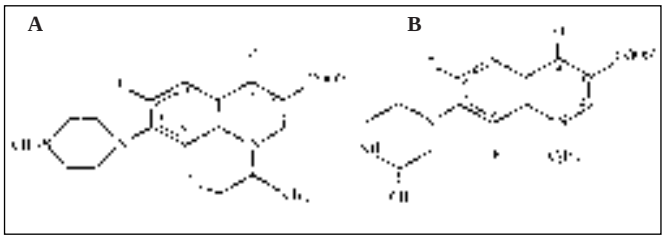

Fig. 1 - *Chemical structure of ofloxacin (A) and lomefloxacin (B).*

Ofloxacin is a fluoroquinolone carboxylic acid, structurally related to nalidixic acid and oxolinic acid. The drug has been found effective for the treatment of bacterial conjunctivitis (20).

This study compared the clinical efficacy, local tolerance, and safety of topical lomefloxacin 0.3% with topical ofloxacin 0.3% eyedrops in the treatment of acute bacterial conjunctivitis.

PATIENTS AND METHODS

Patients

A one-center, randomized, prospective, parallel-group study was carried out. A total of 45 consecutive patients suffering from acute bacterial conjunctivitis, with positve cultures, were entered. Forty patients completed the study and five were excluded. Patients with conjunctivitis of non-bacterial origin or other ocular diseases, patients on topical medications, with severe uncontrolled systemic disease, or known hypersensitivity to quinolones were excluded. Pregnant and lactating women were also excluded.

Topical medications

Patients with acute bacterial conjunctivitis were started at random either on topical lomefloxacin 0.3%

(Okacin®, CIBA Vision Ophthalmics) or topical ofloxacin 0.3% (Oflox®, Allergan) eyedrops. The initial loading dose of lomefloxacin was 1 drop every 2 hours during waking hours on the first treatment day followed by one drop twice daily for one week. Ofloxacin 0.3% was administered four times daily for one week.

Examination

Each patient was subjected to a complete ophthalmologic examination, and a conjunctival swab was taken for culture and sensitivity testing. Consent was obtained from each patient or his/her guardian. The study was approved by the Committee of Human Investigation of The Eye Center.

Patients were examined at presentation and on days 2 and 7 of treatment. Clinical evaluation included assessment of signs of conjunctivitis such as lid edema, lid crusting and lid hyperemia which were graded as 0 = absent, 1 = mild, 2 = moderate, 3 = severe. Discharge was graded as 0 = none, 1 = mild, 2 = moderate, 3 = severe. Conjunctival hyperemia (bulbar and palpebral) was graded as 0 = absent, 1 = bulbar conjunctiva pale reddish, 2 = bulbar conjunctiva bright red, 3 = definite chemosis of bulbar conjunctiva. Corneal edema was graded as 0 = absent, 1 = 25% involvement of the cornea, 2 = 26% to 50% of the cornea, 3 = more than 50% of the cornea. Ocular discomfort was graded as 0 = absent, 1 = present but not distressing, 2 = moderate (not interfering with daily life), 3 = severe and intolerable. The maximum total score of signs and symptoms was 24, and the minimum was zero. The outcome was evaluated on the basis of the cumulative sum score (CSS), as complete resolution, improvement, change from baseline, worse than baseline.

A flow chart was kept for each patient including days 0, 2 and 7. Day 14 was optional.

RESULTS

Forty-five patients entered the study; 23 received lomefloxacin 0.3%, and 22 received ofloxacin 0.3%. Five patients were dropped either because of negative culture or other causes such as lack of compliance. The lomefloxacin group comprised 20 patients (10 men and 10 women) aged from 1 to 78 years (mean 35 years). The ofloxacin group comprised 20 patients (10 men and 10 women), aged from 1 to 70 years (mean 26 years). There was no difference in age in the two groups.

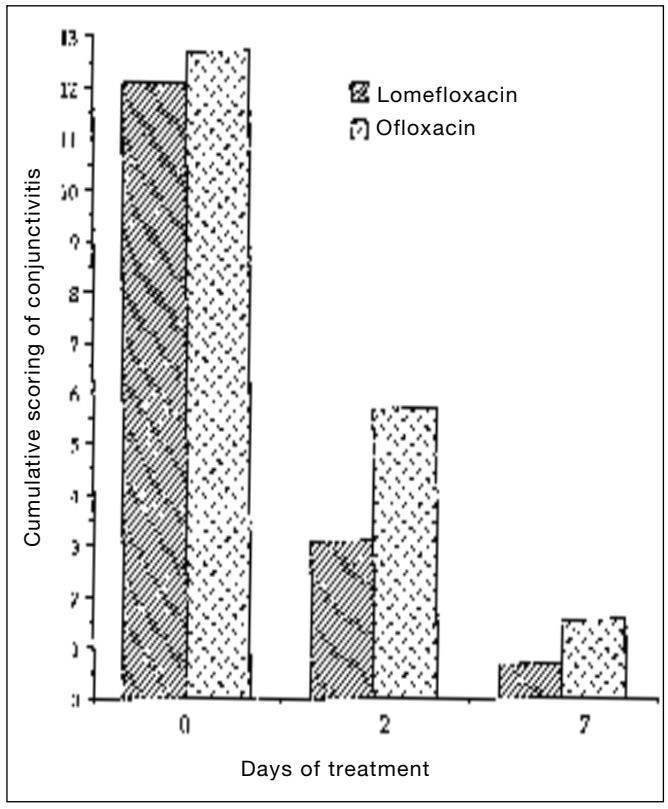

Fig. 2 - *Clinical response to topical lomefloxacin and ofloxacin in 40 patients with acute bacterial conjunctivitis.*

Forty-five isolates comprising eight organisms were obtained. Table I shows the distribution of causative organisms in the two treatment groups. The average CSS for conjunctivitis according to the grading system at the time of the diagnosis (day 0) was 12.1 in the lomefloxacin group and 12.7 in the ofloxacin group; On day 2, it had decreased to 3.1 respectively and 5.8, and to 0.7 and 1.6 by day 7 (Tab. II). The clinical responses to the two drugs, with the CSS, are shown in Figure 2. Eighteen (88%) out of 20 patients in the lomefloxacin group had complete resolution, and 15 (75%) out of 20 patients in the ofloxacin group, but all patients in both groups showed improvement. The difference was not statistically significant ($p = 0.08$). One patient in the lomefloxacin group and one patient in the ofloxacin group complained of a burning sensation after instilling the drop.

TABLE I - CAUSATIVE ORGANISMS IN 45 CASES OF BACTERIAL CONJUNCTIVITIS TREATED WITH EITHER OFLOXACIN OR LOMEFLOXACIN

Organisms	**Ofloxacin**		**Lomefloxacin**			
	No.	**(%)**	**No.**	**(%)**	**Total**	**(%)**
Staphylococcus epidermidis	3	(13)	13	(59)	16	(36)
Streptococcus viridans	4	(17)	5	(23)	9	(20)
Haemophilus spp.	5	(22)	1	(4.5)	6	(13)
Staphylococcus aureus	3	(13)	2	(9)	5	(11)
Pneumoniae	4	(17)	0	(0)	4	(9)
Pseudomonas aeruginosa	2	(9)	1	(4.5)	3	(7)
Others	2	(9)	0	(0)	2	(4)
Total	23	(100)	22	(100)	45	(100)

TABLE II - CLINICAL RESPONSE TO TOPICAL LOMEFLOXACIN 0.3% OR OFLOXACIN 0.3%

	Day 0		**Day 2**		**Day 7**	
	Lomefloxacin	**Ofloxacin**	**Lomefloxacin**	**Ofloxacin**	**Lomefloxacin**	**Ofloxacin**
Lid hyperemia	0-3 (1.4) 19/20 (95%)	0-3 (1.3) 18/20 (90%)	0-3 (0.4) 8/20 (40%)	0-2 (0.5) 8/20 (40%)	0-2 (0.1) 3/20 (15%)	0-1 (0.15) 3/20 (15%)
Lid edema	0-3 (1.5) 18/20 (90%)	0-3 (1.4) 18/20 (90%)	0-3 (0.3) 5/20 (25%)	0-2 (0.5) 8/20 (40%)	0-1 (0.04) 1/20 (5%)	0-1 (0.1) 2/20 (10%)
Lid crusting	0-3 (2) 20/20 (100%)	0-3 (1.5) 20/20 (100%)	0-3 (0.2) 3/20 (15%)	0-1 (0.4) 8/20 (40%)	0 (0) 0	0-1 (0.2) 3/20 (15%)
Conjunctival edema and discharge	0-3 (2) 20/20 (100%)	0-3 (2.2) 20/20 (100%)	0-3 (0.5) 9/20 (45%)	0-2 (1.05) 13/20 (65%)	0-1 (0.2) 2/20 (10%)	0-2 (0.4) 5/20 (25%)
Bulbar conjunctival hyperemia	0-3 (2) 20/20 (100%)	0-3 (2.5) 20/20 (100%)	0-3 (0.8) 14/20 (70%)	0-3 (1.2) 16/20 (80%)	0-1 (0.2) 3/20 (15%)	0-2 (0.4) 7/20 (35%)
Palpebral conjunctival hyperemia	0-3 (2) 20/20 (100%)	0-3 (2.7) 20/20 (100%)	0-1 (0.6) 12/20 (60%)	0-3 (1.05) 16/20 (80%)	0-10 (0.1) 2/20 (10%)	0-1 (0.2) 4/20 (20%)
Corneal edema	0-3 (0.4) 3/20 (15%)	0 0.20 0	0-2 (0.2) 2/20 (10%)	0-2 (0.1) 1/20 (10%)	0 (0) 0	0-2 (0.1) 1/20 (10%)
Ocular discomfort	0-3 (0.8) 8/20 (40%)	0-3 (0.9) 9/20 (45%)	0-2 (0.1) 2/20 (10%)	0-2 (0.1) 1/20 (10%)	0-1 (0.04) 1/20 (5%)	0
	12.1	12.7	3.1	5.8	0.7	1.6

p = 0.08

DISCUSSION

The new quinolones, which comprise a number of nalidixic acid derivatives, have aroused interest as potent, broad-spectrum bactericidal agents (21, 22). Their effect on host defense mechanisms has been investigated, with conflicting findings. Ciprofloxacin was found to enhance humoral immune responses in the mouse (23). Other investigators reported that ciprofloxacin did not affect *in vitro* antibody production by human lymphocytes. Ciprofloxacin, perfloxacin, and ofloxacin all inhibited the human lymphocyte proliferative response to phytohemagglutinin stimulation (24). This effect was subsequently not confirmed although (25). When the quinolones' effects on phagocytic leukocytes were examined, perfloxacin inhibited polymorphonuclear (PMN) leukocyte chemotaxis (26) but it also enhanced the PMN leukocyte phagocytic capabilities (2, 27). The quinolones appear to defense mechanisms enhance the antimicrobial activity of the body. Lomefloxacin enhanced cell-mediated immune responses even at a sub minimal inhibitory concentration (MIC), primarily due to accumulation within macrophages and PMN enhancing and accelerating their bacterial killing. As the accumulation in such immune cells is greater with lomefloxacin than other fluoroquinolones, this might influence its overall *in vivo* activity (28-30).

Ofloxacin has a basic quinolone structure that inhibits DNA gyrase. The 4-pyridone-3-carboxylic acid moiety, which is the center of antibacterial activity, and the fluorine atom in the 6-position, improves binding to DNA gyrase and contribute to penetration of the cell membrane (4).

Lomefloxacin is a potent difluorinated quinolone antibiotic with broad-spectrum action against gram-positive and gram-negative bacteria (31). It has fast bactericidal effect at or double its MIC; Lomefloxacin facilitates the antimicrobial activity of the cellular immune response already at sub-MIC levels (32, 33), and its post-antibiotic effect further enhances its potent activity (33, 34). Two major structural features of lomefloxacin are the fluorine atoms in the 6- and 8-postions. The second fluorine atom in 8-position provides better penetration of the cell, giving better bioavailability in various tissues, with a longer biological half-life (5).

Lomefloxacin has now been developed as a 0.3% ophthalmic solution. Long-lasting high tear levels have been observed with two topical instillations. Excellent corneal penetration has been demonstrated with five instillations of the eye drops in albino rabbits (19, 35), and has been confirmed in humans (36, 37). Malminiemi et al (4) reported that treatment with hourly loading doses on day 1 followed by a twice-daily regimen of lomefloxacin significantly relieved clinical signs and symptoms and eradicated or reduced conjunctival bacteria. A short course of topical lomefloxacin was well tolerated and effective in curing bacterial conjunctivitis (4).

Acute bacterial conjunctivitis is a common clinical problem in ophthalmology. The disease is usually self-limiting but in certain severe cases it may lead to ocular complications. Many types of conjunctival infections can be cured by topical antimicrobial agents but the tenacity of bacteria and the emergence of resistant strains makes the continuous search for safe and effective antibiotics highly desirable.

In this study, we found that topical lomefloxacin and ofloxacin were well tolerated and highly effective in a management of bacterial conjunctivitis. Lomefloxacin was given one drop every two hours on the first day followed by twice daily for one week whereas ofloxacin was given four times daily for one week. This therapeutic approach with lomefloxacin assures compliance because of the twice-a-day dosage and yet assures high ocular tissue bioavailability. The loading dose of lomefloxacin may have rapid initial killing effects on the causative agents. Topical lomefloxacin 0.3% eyedrops were safe and effective in e treatment of acute bacterial conjunctivitis, significantly reducing clinical signs and symptoms within 48 hours. There was no statistically significant difference between lomefloxacin given every 2 hours for one day then twice daily, and topical ofloxacin 0.3% given four times daily.

In this clinical trial conjunctival swabs were obtained and placed on culture media immediately and all cases had positive cultures. There was no delay in processing the swabs, which explains the high yield of positive cultures, corroborating the clinical findings.

The data presented demonstrate that a short course of lomefloxacin is safe and well tolerated inducing a cure patients suffering from acute bacterial conjunctivitis. The high levels of lomefloxacin in the aqueous after topical therapy (19) make this broad-spectrum antibiotic suitable for prophylaxis before and

after intraocular surgery such as cataract extraction and penetrating keratoplasty. With only two groups of 20 patients it is not surprising to see no significant difference as the standard deviation of signs and symptoms usually seen in this indication may mask any superiority in medium-size studies, meaning the statistical power may be too low. Interestingly, the CSS were respectively about 46% and 56% smaller on days 2 and 7 in the lomefloxacin group, which seems to be a clinically relevant difference. On day 2 the difference in CSS seems significant. This is presumably partly due to the loading dose on the first day.

In conclusion, this study found that both lomefloxacin and ofloxacin are safe, effective, and well tolerated in the treatment of acute bacterial conjunctivitis. Although the clinical response was stability better in the lomefloxacin group, the difference was not significant.

ACKNOWLEDGEMENTS

The Authors would like to acknowledge the help and support of the Administrator of The Eye Center, Mrs. Najwa Tabbara, the assistance of Khaleel urRahman, microbiologist, and secretarial assistance from Vangie Ontoria.
This study was supported in part by The Eye Center and The Eye Foundation for Research in Ophthalmology, Riyadh, Saudi Arabia, and by CIBA Vision (A Novartis Company), Buläch, Switzerland.

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