Microbiological efficacy of lomefloxacin and other drugs regarding microorganisms isolated from the human conjunctiva

Atividade biocida da lomefloxacina em relação aos microorganismos isolados de conjuntiva humana

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ABSTRACT

Purpose: To evaluate and compare the *in vitro* susceptibility of human conjunctival bacterial isolates to various antimicrobial agents, including lomefloxacin, other fluoroquinolones (ciprofloxacin, norfloxacin, and ofloxacin), aminoglycosides (gentamicin, tobramycin, and amicacin), and cephalosporin (cephalothin). **Methods:** Antibiotic susceptibility tests conducted over a period of 27 months with 613 bacterial isolates from the conjunctiva were retrospectively analyzed. **Results:** In relation to the total number of positive isolates, the fluoroquinolones showed greater *in vitro* effectiveness than the other analyzed antibiotics. All bacterial isolates showed significantly higher susceptibility to ciprofloxacin than to lomefloxacin. **Conclusion:** The fluoroquinolones are not only equally effective against all conjunctival bacterial isolates, but they also show superior antimicrobial activity in comparison to aminoglycosides and cephalothin. These results suggest that fluoroquinolones, such as lomefloxacin, can be beneficially prescribed for conjunctival infections and also as prophylaxis in ocular surgery.

Keywords: Quinolones/therapeutic use; Fluoroquinolones/pharmacology; Conjunctival diseases/therapy; Conjunctival diseases/microbiology

INTRODUCTION

The most frequent infections of the conjunctiva which are submitted to laboratory evaluation are due to bacteria, and an initial treatment with broad-spectrum antibiotics is usually recommended after the clinical diagnosis and after scraping the site of infection[1-3]. Susceptibility tests for microorganisms isolated from ocular infections are recommended, since the results are useful not only in specific cases but also as epidemiological data[4-5].

The fluoroquinolones have been available in the United States of America since 1962. Lomefloxacin is a third-generation fluoroquinolone available in Brazil for systemic administration since 1993. Lomefloxacin is nearly completely absorbed when taken orally and is slowly eliminated, having a half-life of seven to eight hours[6]. Similar to other fluoroquinolones, lomefloxacin has a broad spectrum of action, including Gram-positive and -negative microorganisms. As a third-generation quinolone, it also has the advantage of being effective against some anaerobic bacteria[1-2, 7-10].

The antibacterial activity of fluoroquinolones, such as lomefloxacin, is mediated through inhibition of the bacterial enzyme DNA gyrase, resulting in failure to synthesize bacterial DNA. As a consequence, fluoroquinolones are bactericidal[1, 9, 11].

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Topical instillation of lomefloxacin, as compared to other quinolones, achieved better intraocular penetration, leading to higher concentrations in the aqueous humor[10, 12-13]. The manufacturer suggested twice a day topical use of lomefloxacin. Its liposolubility facilitates its storage in the goblet cells of the conjunctiva, providing bioavailability throughout the day[6]. Several studies have already demonstrated the efficacy of fluoroquinolones, used separately or in combination with other antibiotics, in the treatment of ocular infections of the conjunctiva or cornea[1-3, 11, 14-17].

The purpose of this study was to evaluate the *in vitro* susceptibility to lomefloxacin of microorganisms of the conjunctiva, isolated by the Ocular Microbiology Laboratory of the Federal University of São Paulo (UNIFESP-EPM), and also to compare lomefloxacin, in terms of effectiveness, with other fluoroquinolones (ciprofloxacin, norfloxacin, and ofloxacin), with aminoglycosides (amicacin, gentamicin, and tobramycin), and with a cephalosporin (cephalothin).

METHODS

The materials analyzed in this study were collected from patients treated at the São Paulo Hospital and also in the community. The samples for microbiological evaluation were obtained directly from the infected area in all cases of conjunctival infections. Sterile cotton swabs soaked in Brain-Heart-Infusion solution were used for collection of samples for cultures[18-19].

All the materials were inoculated onto sheep blood agar, chocolate agar, and Sabouraud dextrose agar[5, 20]. Microscopic evaluation of conjunctival smears by Gram stain and Giemsa stain was also included as part of the standard conjunctival scraping protocol, in order to assess the bacterial and cellular populations, respectively[21]. Cultures were considered positive when presenting a significant growth of at least two seeded samples in one or more plates.

Antibiotic susceptibility was determined for all positive cultures using the Kirby-Bauer disc diffusion method[4, 21-22], with the antibiotic concentration in the disc individually determined for each antibiotic (Table 1)[4]. The reading was performed by measuring the diameter of the growth inhibiting zone around the disk[4], in agreement with the National Committee for Clinical Laboratory Standards (NCCLS) criteria for all antibiotics, with one of three resulting grades: resistant, intermediately sensitive, or susceptible (Table 1)[4-5, 23].

Laboratory test results of cases referred to the Ocular Microbiology Laboratory of the UNIFESP-EPM between November 1997 and February 2000 were retrospectively analyzed. Of the 2030 cases examined by the laboratory during the 27 months, a total of 1642 were diagnosed as conjunctivitis. Cultures were carried out and considered positive if showing growth of one or more microorganisms. This study was based on 613 positive bacterial isolates that were submitted to antibiotic susceptibility tests.

Table 1. Grading of antibiotic susceptibility by the disk diffusion method, according to the NCCLS criteria for different antibiotics (2000 - São Paulo, Brazil)

Antibiotic	Disk content (µg)	Diameter of the inhibiting zone around the disk (mm)		
		Resistant	Intermediate	Susceptible
Gentamicin	10	≤12	13 - 14	≥15
Amicacin	30	≤14	15 - 16	≥17
Tobramycin	10	≤12	13 - 14	≥15
Cephalothin	30	≤14	15 - 17	≥18
Lomefloxacin	10	≤18	19 - 21	≥22
Ciprofloxacin	5	≤15	16 - 20	≥21
Norfloxacin	10	≤12	13 - 16	≥17
Ofloxacin	5	≤12	13 - 15	≥16

In order to simplify analysis of the results of this study, strains were grouped as follows: coagulase-negative *Staphylococcus* (CNS); *Staphylococcus aureus* (S. aureus); *Haemophilus* sp (Haem); other Gram-positive cocci (CGP) such as *Streptococcus pneumoniae*, non-hemolytic *Streptococcus*, *Streptococcus* sp, and *Streptococcus viridians*; Gram-negative microorganisms (Gram Neg) such as *Proteus mirabilis*, *Proteus penneri*, *Serratia* sp, and *Neisseria* sp; other Gram-positive microorganisms (Gram Pos) such as *C. xerosis*; *Moraxella* sp (Morax); and *Pseudomonas* sp (Pseudo)[19].

Statistical analysis using the chi-square test was applied to one sample, assuming that the collection site did not bias the measured frequencies[24-25]. In order to verify the differences between the proportions of microorganisms susceptible to lomefloxacin and ciprofloxacin, a test for two proportions, whose populations were not independent, was used as proposed by McNemar. The statistical result calculated was defined as U_o^2[18]. The level of significance was 0.05 (5%).

RESULTS

A total of 613 bacterial isolates was examined in this study. Gram-positive cocci accounted for 539 (87.9%) of all bacterial isolates, being further classified as CNS in 390 (63.6%) of the cases and as S. aureus in 116 (18.9%) of the positive isolates. As for Gram-negative microorganisms, *Haemophilus* sp was the most frequently isolated (6.5% of total bacterial isolates) (Table 2).

Susceptibility to lomefloxacin was shown 98.5% of all bacterial isolates, including 99.5% of CNS and 99.1% of S. aureus. Almost all Gram-negative microorganisms were susceptible to lomefloxacin at a level of 93.3-100%, except for *Pseudomonas* sp, which was susceptible in only two out of four isolates (Table 2).

Of the 613 microbial isolates, 587 (95.8%) were susceptible to cephalothin. Among the aminoglycosides, amicacin was associated with the highest level of susceptibility (95.6%), but this antibiotic is not commercially available. The two drugs available for topical use, gentamicin and tobramycin, were associated with susceptibilities of around 91% (Table 2).

Table 2. Antibiotic susceptibility of conjunctival bacterial isolates to lomefloxacin, aminoglycosides and cephalothin (2000 - São Paulo, Brazil)

Bacteria	N	Antibiotics									
		Lomefloxacin		Amicacin		Gentamicin		Tobramycin		Cephalothin	
		N	%	N	%	N	%	N	%	N	%
CNS	390	388	99.5	390	100	356	91.3	364	93.3	387	99.2
S. aureus	116	115	99.1	116	100	111	95.7	110	94.8	110	94.8
Haem	40	40	100	35	87.5	36	90.0	38	95.0	39	97.5
CGP	33	30	90.9	13	39.4	22	66.7	17	51.5	32	97.0
Gram Neg	15	14	93.3	15	100	15	100	15	100	10	66.7
Morax	10	10	100	8	80.0	10	100	10	100	4	40.0
Gram Pos	5	5	100	5	100	5	100	5	100	5	100
Pseudo	4	2	50.0	4	100	4	100	4	100	0	0
TOTAL	613	604	98.5	586	95.6	559	91.2	563	91.8	587	98.5

CNS - coagulase-negative *Staphylococcus*; **S. aureus** - *Staphylococcus aureus*; **Haem** - *Haemophilus* sp; **CGP** - other Gram positive cocci (*Streptococcus pneumoniae,* non-hemolytic *Streptococcus, Streptococcus* sp and *Streptococcus viridans*); **Gram Neg** - Gram negative microorganisms (*Proteus mirabilis, Proteus penneri, Serratia* sp and *Neisseria* sp); **Morax** - Moraxella sp; **Gram Pos** - Gram positive microorganisms (*C. xerosis*); **Pseudo -** *Pseudomonas* sp

The overall susceptibility of the bacterial isolates to the quinolones, including lomefloxacin, the newer quinolone, is at a level greater than 98.5%. Ciprofloxacin had the broadest activity, with 610 isolates (99.5%) being sensitive (Table 3). Ciprofloxacin was associated with significantly more instances of susceptibility than was lomefloxacin (Table 4).

CONCLUSIONS

Many ophthalmologists start treatment of external ocular infections before the causative microorganisms have been identified or submitted to antibiotic susceptibility tests. Consequently, broad-spectrum antibiotics are routinely used in the treatment of ocular infections[4, 23, 26].

Although the majority of cases of bacterial conjunctivitis are presumably self-limited, without the need for medical intervention, studies have demonstrated that antibiotic therapy hastens the eradication of bacteria, prevents the dissemination of the infection to other structures, decreases the risk of systemic disease, and shortens the symptomatic period, allowing the patient to return more quickly to his/her normal activities[1, 3-4, 23, 26].

As in previous studies, many of our cultures showed no microbial growth. There are several possible explanations for this finding, including insufficient material, the use of topical antibiotics before cultures could be inoculated, viral etiology, or the presence of microorganisms that do not grow in regular media, such as anaerobic bacteria or Mycobacteria[19-20, 31].

Some antimicrobial drugs are subject to restricted use. For instance, cephalothin is highly effective against Gram-positive cocci, but can be obtained only in specially formulated prescriptions and in cases of demonstrated need. Its circumscribed use is intended to prevent the development of resistant strains.

According to several studies, the development of resistance of ocular bacteria to many aminoglycosides has limited

Table 3. Antibiotic susceptibility of conjunctival bacterial isolates to fluoroquinolones (2000 - São Paulo, Brazil)

Bacteria	N	Antibiotics							
		Lomefloxacin		Ciprofloxacin		Norfloxacin		Ofloxacin	
		N	%	N	%	N	%	N	%
CNS	390	388	99.5	388	99.5	388	99.5	388	99.5
S. aureus	116	115	99.1	115	99.1	115	99.1	115	99.1
Haem	40	40	100	40	100	40	100	40	100
CGP	33	30	90.9	33	100	33	100	32	97.0
Gram Neg	15	14	93.3	15	100	14	93.3	14	93.3
Morax	10	10	100	10	100	10	100	10	100
Gram Pos	5	5	100	5	100	5	100	5	100
Pseudo	4	2	50.0	4	100	4	100	2	50.0
TOTAL	613	604	98.5	610	99.5	609	99.3	606	98.9

CNS - coagulase-negative *Staphylococcus*; **S. aureus -** *Staphylococcus aureus*; **Haem -** *Haemophilus* sp; **CGP -** other Gram positive cocci (*Streptococcus pneumoniae*, non-hemolytic *Streptococcus*, *Streptococcus* sp and *Streptococcus viridans*); **Gram Neg** - Gram negative microorganisms (*Proteus mirabilis, Proteus penneri, Serratia* sp and *Neisseria* sp); **Morax -** *Moraxella* sp; **Gram Pos -** Gram positive microorganisms (*C. xerosis*); **Pseudo -** *Pseudomonas* sp

Table 4. Comparison of antibiotic susceptibilities of conjunctival bacterial isolates to lomefloxacin and ciprofloxacin (2000 - São Paulo, Brazil)

Bacteria	N	Antibiotics				Statistical analysis
		Lomefloxacin		Ciprofloxacin		U_0^2
		N	%	N	%	$X_{CRIT}^2 > 3.84$
CNS	390	388	99.5	388	99.5	T.E
S. aureus	116	115	99.1	115	99.1	T.E
Haem	40	40	100	40	100	T.E
CGP	33	30	90.9	33	100	2.999 N.S.
Gram Neg	15	14	93.3	15	100	1.000 N.S.
Morax	10	10	100	10	100	T.E
Gram Pos	5	5	100	5	100	T.E
Pseudo	4	2	50.0	4	100	2.000 N.S.
TOTAL	613	604	98.5	610	99.5	6.008 (*)

U_0^2: Statistical Test; T.E: Test exemption; N.S.: Not significant; (*): Significant

CNS - coagulase-negative *Staphylococcus*; **S. aureus -** *Staphylococcus aureus*; **Haem -** *Haemophilus* sp; **CGP -** other Gram positive cocci (*Streptococcus pneumoniae*, non-hemolytic *Streptococcus*, *Streptococcus* sp and *Streptococcus viridans*); **Gram Neg -** Gram negative microorganisms (*Proteus mirabilis*, *Proteus penneri*, *Serratia* sp and *Neisseria* sp); **Morax** - *Moraxella* sp; **Gram Pos -** Gram positive microorganisms (*C. xerosis*); **Pseudo -** *Pseudomonas* sp

their usefulness. The mechanism of action of the fluoroquinolones helps to account for the low incidence of resistant microorganisms[1, 3]. The fluoroquinolones have a broad spectrum of action[1-3, 21], and are stable drugs as marketed in the form of eye drops at a concentration of 3 mg/ml[1]. It is known that the susceptibility of anaerobic bacteria is greater to third-generation quinolones, such as lomefloxacin. As anaerobic bacteria were not assessed in this study, we could not verify these findings[9].

While other studies have demonstrated the susceptibility of Gram-positive and Gram-negative bacteria to quinolones[1-3, 14, 26, 32], stocks of CNS and S. aureus resistant to quinolones were described by the same laboratory that discovered an increasing number of strains of Gram-positive cocci resistant to prescribed topical antibiotics[21, 33-34].

The use of an antibiotic as a prophylactic drug prior to ocular surgery has the objective of eliminating most, if not all, microorganisms present in the conjunctiva. In this way, the risk of infection during surgery and in the immediate postoperative period, when the surgical wound is not yet closed, can be minimized. It is of particular concern that the prophylactic topical antibiotic used should be able to reach its minimal inhibitory concentration in the anterior chamber or vitreous.

Basic research on lomefloxacin, to evaluate its *in vitro* effectiveness, its speed of action, its concentration at the site of infection, and its half-life, is being performed to guarantee satisfaction of the minimum requirements for drugs intended for ophthalmic use[7, 9-10, 12]. *In vitro* susceptibilities of isolated ocular microorganisms do not always translate into *in vivo* efficacy of particular drugs, but they are nonetheless strong epidemiological and therapeutic indicators[4, 27 -28]. In conclusion, we recommend prescribing lomefloxacin and other quinolones[1-3, 14, 26-27, 32, 34] for the treatment of conjunctival infections and for prophylaxis in ocular surgery.

RESUMO

Objetivo: Avaliar e comparar a atividade biocida in vitro de bactérias isoladas da conjuntiva humana à lomefloxacina, a outras fluorquinolonas (ciprofloxacina, norfloxacina e ofloxacina), aos aminoglicosídeos (gentamicina, tobramicina e amicacina) e à cefalosporina (cefalotina). **Métodos:** Foram analisados retrospectivamente os resultados dos antibiogramas realizados no período de 27 meses com 613 bactérias isoladas da conjuntiva. **Resultados:** A eficácia *in vitro* das quinolonas de acordo com o total dos isolamentos positivos foi superior em relação aos outros antibióticos avaliados. A suscetibilidade do total de bactérias à ciprofloxacina foi significantemente mais alta quando comparada à lomefloxacina. **Conclusão:** Os resultados praticamente equivalentes da suscetibilidade de bactérias isoladas da conjuntiva a fluorquinolonas, associado à maior eficácia deste grupo de antimicrobianos em relação aos aminoglicosídeos e à cefalotina, representam uma possibilidade de prescrição de quinolonas, como lomefloxacina, no tratamento de infecções conjuntivais, além do possível uso profilático em cirurgias oculares.

Descritores: Quinolonas/uso terapêutico; Fluoroquinolona/farmacologia; Doenças da conjuntiva/terapia; Doenças da conjuntiva/microbiologia

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