Polskie Towarzystwo Okulistyczne
www.pto.com.pl

KLINIKA OCZNA 2021, 123, 3: 122–128
Received: 7.04.2021 Accepted: 6.05.2021

ARTYKUŁ POGLĄDOWY

Access this article online

Website:
www.klinikaoczna.pl

DOI:
https://doi.org/10.5114/ko.2021.107313

Levofloxacin in everyday ophthalmic practice: current state of knowledge

Michał Post, Anna Okruszko, Jacek P. Szaflik

Department of Ophthalmology, Independent Public Clinical Ophthalmology Hospital in Warsaw, Medical University of Warsaw, Poland

ABSTRACT

Fluoroquinolones are among the most widely used antibiotics in ophthalmology. Based on the example of levofloxacin, the authors review the literature on the applications of fluoroquinolones in everyday ophthalmic practice. The analysis focuses on evaluating the role of levofloxacin in the treatment of the most common infections and perioperative prophylaxis, antibiotic resistance to fluoroquinolones, and safety of this group of drugs.

KEY WORDS: levofloxacin, fluoroquinolones, conjunctivitis, keratitis, endophthalmitis, perioperative prophylaxis.

INTRODUCTION

Fluoroquinolones are synthetic antibiotics with a broad spectrum of activity. They inhibit DNA gyrase (topoisomerase II) and topoisomerase IV, which are key enzymes involved in DNA replication and transcription. Inhibition of these enzymes leads to the death of bacterial cells; topoisomerase IV (encoded by the parC and parE genes) is the main target for most Gram (+) bacteria, while DNA gyrase (encoded by the gyrA and gyrB genes) – for Gram (–) bacteria [1]. Drugs of this group exhibit dose-dependent bactericidal activity and produce a post-antibiotic effect, i.e. have the capacity to inhibit bacterial growth even after a decrease in antibiotic concentration in blood serum [1].

Fluorinated quinolones are currently classified into four groups based on the scope and potency of action, degree of tissue penetration, and development of drug resistance. First-generation fluoroquinolones (nalidixic acid introduced in 1962) are agents used in the treatment of urinary tract infections, showing activity predominantly against Enterobacteriaceae [1]. Fluoroquinolones were first used in the management of ophthalmic infections in the 1990s, when second-generation topical agents were introduced into therapeutic practice, including ciprofloxacin, ofloxacin, and norfloxacin[2]. Since 2000, third-generation (levofloxacin) and fourth-generation (moxifloxacin) fluoroquinolones have been available. Third- and fourth-generation fluoroquinolones are preferred because of their increased activity against Gram-positive organisms and some atypical mycobacteria, better drug penetration into the anterior segment of the eye, and lower predisposition toward the development of antibiotic-resistant strains [1, 2].

PHARMACOKINETICS AND BIOAVAILABILITY

Levofloxacin, the L-isomer of the racemic fluoroquinolone ofloxacin, is significantly more potent than the D-isomer representing the active ingredient of ofloxacin [3]. In addition, levofloxacin is at least 10 times more soluble than ofloxacin and 400 times more soluble in water than ciprofloxacin at neutral pH [4]. The concentration of the clinically available topical formulation of levofloxacin is 0.5%, and ofloxacin/ciprofloxacin – 0.3% [5]. A higher concentration of levofloxacin for topical ophthalmic use might be expected to help achieve greater corneal and aqueous humor penetration. Kawashima *et al.* demonstrated that 0.5% levofloxacin achieved a significantly higher maximum concentration in the aqueous humor than 0.3% ofloxacin after the topical application of three drops of each agent at 15-minute intervals [6]. According to Yamada *et al.* topical levofloxacin achieves superior penetration into the aqueous humor compared to lomefloxacin and norfloxacin [7]. Table I presents a summary of tissue penetration rates of the most commonly used fluoroquinolones in Poland [7, 8].

Levofloxacin readily penetrates into ocular tissues, where it reaches concentrations exceeding the MIC90 (minimum inhibitory concentration required to inhibit the growth of 90% of bacteria *in vitro*; lower MIC90 values correspond to higher antibiotic efficacy) for key pathogens known to play a role in ophthalmic diseases. For fluoroquinolones, the MIC90 against

CORRESPONDING AUTHOR

Michał Post, MD, PhD, FEBO, Department of Ophthalmology, Independent Public Clinical Ophthalmology Hospital, 24/26 Marszałkowska St., 00-576 Warsaw, Poland, email: michalpost.md@gmail.com

the majority of ocular pathogens is ≤ 2 μg/ml [8]. Following the administration of 0.5% levofloxacin to the conjunctival sac in healthy volunteers, the concentration of the agent in tears peaked (221.06 μg/ml) after a quarter of an hour, after which it decreased down to 6.57 μg/ml 6 hours after application [9]. At the same time, 24 hours after administration, the antibiotic concentrations in tears remained at levels > 2 μg/ml in one-third of the subjects. The above findings suggest that 0.5% levofloxacin has a sustained effect which may be beneficial in the treatment of patients with adherence problems.

CLINICAL APPLICATION

Ocular bacterial infections are among the most prevalent ophthalmic disorders. The most common risk factors for severe inflammation include old age, decompensated diabetes mellitus, immunosuppression, local steroid therapy, and other ophthalmic diseases – Sicca syndrome, corneal transplant, corneal dystrophies, and tear duct obstruction. Bacterial infections are estimated to account for 32-74% of all eye infections worldwide [10]. Table II lists the most common pathogens causing anterior eye segment infections in the United States (2011-2015) [10]. Of the ten most prevalent pathogens, eight are bacteria showing sensitivity to levofloxacin. However, it needs to be kept in mind that certain strains of *S. aureus*, *Corynebacterium*, and *S. marcescens* may exhibit resistance to fluoroquinolones depending on the geographic region [10].

In a four-year multicenter study by Kanda *et al.*, clinical response in bacterial anterior segment inflammation was observed in 95.5% of 5,929 patients receiving levofloxacin [11]. The therapy response rates varied from 97.4% in keratitis and 95.5% in conjunctivitis to 88.3% in dacryocystitis (Table III). The response rate was lower in patients with dacryocystitis, in the elderly, and in individuals with prolonged and recurrent disease (all $p < 0.001$).

In the discussed study, the response rates to levofloxacin therapy by the most common pathogens were: *Staphylococci* (93.5%), *S. pneumoniae* (95.9%), *H. influenzae* (98.9%), *Corynebacterium* spp. (93.5%), *Pseudomonas* spp. (100%), *P. aureginosa* (80.8%), *Serratia* (100%), and *Moraxella* spp. (96.7%).

Conjunctivitis

Acute conjunctivitis is inflammation of the conjunctiva without concurrent corneal involvement. In most cases, conjunctivitis is bilateral and presents clinically as painless diffuse conjunctival congestion ("pink eye") with intense tearing, discharge, and sensation of "sand in the eye". According to Petrick *et al.*, patients with bacterial conjunctivitis account for 15% of all patients visiting an ophthalmologist [12]. The most common pathogens causing acute bacterial conjunctivitis include *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Moraxella catarrhalis*, and *Haemoph-*

Table I. Concentration of fluoroquinolones in different segments of the eye after topical administration

	Tear film (μg/ml)	Conjunctiva (μg/g)	Cornea (μg/g)	Aqueous humor (μg/ml)	Vitreous body (μg/ml)	Solubility in water (%)	Lipophilicity (c-7, π)
Levofloxacin	221.06	2.34	18.23	0.49-4.4	0.03	1.85	0.06
Ofloxacin	73.3	1.26	8.01	0.31-1.44	0.07-0.37	0.35	–0.35
Ciprofloxacin	11.28	2.65	4.15	0.07-0.44	0.08-0.22	0.02	0.06
Moxifloxacin	366	18.0	21.3	0.88-2.28	0.06-0.28	> 6.43	0.24

Table II. Most common pathogens isolated from patients with ocular anterior segment infection in the USA in 2011-2015. All bacterial pathogens (marked in bold) show sensitivity to levofloxacin

No.	All infections ($n = 4649$)			Conjunctivitis ($n = 876$)			Keratitis ($n = 1498$)			Endophthalmitis ($n = 198$)		
	pathogen	*n*	%	pathogen	*n*	%	pathogen	*n*	%	pathogen	*n*	%
1	*S. aureus*	1027	22.1	*S. aureus*	311	25.5	*P. aureginosa*	405	27	*S. epidermidis*	60	30.3
2	*P. aureginosa*	639	13.7	*H. influenzae*	65	7.4	*S. aureus*	234	15.6	*S. viridans*	28	14.1
3	*S. epidermidis*	312	6.7	*P. aureginosa*	55	6.3	*Fusarium* spp.	117	7.8	*Candida* spp.	18	9.1
4	*S. viridans*	222	4.8	*Adenovirus*	43	4.9	*Serratia* spp.	78	5.2	*S. aureus*	15	7.6
5	*S. marcescens*	177	3.8	*S. viridans*	39	4.5	*S. viridans*	63	4.4			
6	*Fusarium* spp.	175	3.8	*C. trachomatis*	33	3.8	*S. epidermidis*	59	3.9			
7	*S. pneumonie*	113	2.4	*S. pneumonie*	32	3.7	HSV 1	56	3.7			
8	*H. influenzae*	113	2.4	*Candida* spp.	22	2.5	*S. pneumonie*	39	2.6			
9	*C. albicans*	92	2	*Corynebacterium*	20	2.3	*C. albicans*	31	2.1			
10	*Corynebacterium* spp.	67	1.4	*Serratia* spp.	20	2.3	*Acabthamoeba* spp.	20	2			

Table III. Evaluation of levofloxacin efficacy in the treatment of different inflammations of the anterior eye segment. Four-year follow-up

Condition	Number of patients	Number of treatment responses	Treatment response rate (%)	Median daily doses	Median duration of treatment (days)
Zapalenie brzegów powiek	279	269	96.4	4	10
Zapalenie woreczka łzowego	265	234	88.3	4	29
Jęczmień	1013	954	94.2	4	8
Zapalenie spojówek	3446	3292	95.5	4	9
Zapalenie gruczołów Meiboma	146	139	95.2	4	10
Zapalenie rogówki	1190	1159	97.4	4	8
Wrzód rogówki				4.64	8

ilus influenzae [12]. The most common pathogens causing conjunctivitis in children are *H. influenzae* and *S. pneumoniae*, while in adults the main pathogenic agent is *S. aureus* [12].

In over 60% of cases, the condition resolves spontaneously within one to two weeks, and severe complications are extremely rare [13]. However, the presence of a large bacterial population in the conjunctival sac puts the patient at greater risk of keratitis, particularly in conditions associated with corneal epithelial defects such as dry eye syndrome. In a meta-analysis involving a total of 3,673 patients from 11 randomized clinical trials, antibiotic treatment was shown to have increased the rate of clinical improvement by 10% compared to placebo [13, 14]. Even though highly virulent bacteria have the potential to induce severe damage to the ocular surface, no vision-threatening complications were reported in any of the placebo groups in the above-mentioned metaanalysis. According to the literature review by Azari *et al.* (2020) all eye drops containing broad-spectrum antibiotics (including levofloxacin) show efficacy in the treatment of bacterial conjunctivitis [13]. There were no significant differences in clinical cure rates for various antibiotic dosing frequencies [15]. However, the use of topical steroids as well as combination drugs (antibiotic + steroid) should be avoided in view of the prolonged course of the disease and increased severity of infection [16].

In their randomized study, Schwab *et al.* evaluated the efficacy of fluoroquinolones in 208 patients (levofloxacin n = 109; ofloxacin n = 99) [17]. The pathogen eradication rates were significantly higher in the group treated with 0.5% levofloxacin compared to the group treated with 0.3% ofloxacin (90% vs. 81%; p = 0.038). The difference in pathogen eradication rates was largely due to the higher efficacy of levofloxacin in eradicating *S. pneumoniae* (86% vs. 68%) and *H. influenzae* (93% vs. 89%) which accounted for 62% of all bacteria cultured at baseline. The two species are the most common pathogens causing bacterial conjunctivitis, especially in children. At the same time, treatment with 0.5% levofloxacin was found to be considerably more effective in reducing photophobia (94% vs. 73%, p = 0.006). Both study drugs were well tolerated, and the incidence of adverse events was low.

In a multicenter, randomized, double-blind study, Lichtenstein *et al.* analyzed the efficacy of levofloxacin and ofloxacin in 167 children with bacterial conjunctivitis [18]. The eye drops were instilled every two hours on days 1 and 2, and every four hours on days 3 to 5. At the study endpoint (mean 6.5 days for 118 evaluable patients), treatment with levofloxacin demonstrated higher rates of pathogen eradication (i.e. proportion of patients with no causative organisms initially cultured at baseline) as compared with 0.3% ofloxacin or placebo. In children aged 2 to 11 years, the result was statistically significant in favor of 0.5% levofloxacin (87% vs. 62%, p = 0.032, compared to 0.3% ofloxacin; and 88% vs. 24%, p = 0.001, compared to placebo). In other age subgroups, no significant differences were identified between the groups in terms of pathogen eradication rates.

In a study by Szumiński, which was conducted in a population of infants with bacterial conjunctivitis, positive cultures were obtained in 140 (90.9%) conjunctival sac smears [19]. In most cases (88.6%), infantile conjunctivitis was caused by Gram-positive bacteria, among which *Streptococcus pneumoniae* was found to be the most frequently isolated pathogen (36.7%). Gram-negative bacteria were identified in 18 cases (11.4%). In this group, the most common bacterial pathogen was *Haemophilus influenzae* (9.5%). Levofloxacin 0.5% used in monotherapy was found to be effective in 86 children (93.5%). The efficacy of two levofloxacin treatment regimens was compared in a study of the Polish adult population of patients with acute conjunctivitis [20]. In one regimen, the drug was used three times a day. In the other one, levofloxacin was administered every two hours during the first two days of treatment, followed by every four hours in the next three days. Both regimens were associated with a similar reduction in ophthalmic symptoms and high microbiological efficacy (92.7% vs. 95.6%, p = 0.67), though patients treated with the former regimen showed a better adherence to therapy.

Keratitis

A total of 71,000 cases of infectious keratitis (bacterial, fungal, and caused by *Acanthamoeba*, etc.) are diagnosed annually in the United States, with a growing frequency in recent years [21]. Bacterial keratitis rarely occurs in the healthy eye, as the human cornea is naturally resistant to infections. However, certain predisposing factors, such as wearing contact lenses, trauma, corneal surgery, ocular surface diseases, systemic conditions and immunosuppression, may impair the natural de-

fense mechanisms of the ocular surface, allowing bacteria to invade the cornea. Retrospective analyses performed in the UK and Italy showed that the most common risk factor for bacterial keratitis was the use of contact lenses [22].

Permanent visual impairment may occur either due to corneal scarring or topographic abnormalities. Either untreated or severe bacterial keratitis may result in corneal perforation, and lead to endophthalmitis and ultimately loss of the eye. Since the inflammatory process may follow a fulminant course (24 hours if the infection is caused by a virulent organism), optimal management requires rapid diagnosis, prompt initiation of treatment, and appropriate patient follow-up. According to the 2019 American Academy of Ophthalmology guidelines, antibiotic eye drops are capable of reaching high levels in tissues and represent the preferred treatment option in the majority of cases[23]. In patients with central or severe keratitis (e.g. deep stromal involvement or an infiltrate exceeding 2 mm with extensive suppuration), a loading dose is suggested, e.g. every 5-15 minutes, followed by frequent instillations, e.g. every hour. Single-agent therapy with a fluoroquinolone has been shown to be as effective as combination therapy with antibiotics fortified in concentrations beyond commercially available topical antibiotics [AAO: strong recommendation I+] [23]. Fortified topical antibiotics should be considered in the treatment of patients with extensive and/or significant corneal infiltrates, especially if hypopyon is present. Ciprofloxacin, ofloxacin, and levofloxacin have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of bacterial keratitis [23]. At the same time, some pathogens (e.g. MRSA, streptococci, anaerobes) have variable susceptibility to fluoroquinolones [24], and the prevalence of antibiotic resistance (particularly to second-generation fluoroquinolones: cipro- and ofloxacin) seems to be on the increase [25]. Interestingly, moxifloxacin (a fourth-generation fluoroquinolone) is not approved by the FDA in the USA for the treatment of bacterial keratitis despite the drug's high efficacy proven in clinical trials.

In their literature review and metaanalysis, McDonald *et al*. evaluated the efficacy of topical antibiotic therapy (fluoroquinolones vs. aminoglycosides in combination with cephalosporins) in the treatment of bacterial keratitis [2]. A total of 16 randomized clinical trials involving 1,823 patients were analyzed. The review found no evidence for any differences in the efficacy of the ophthalmic antibiotics listed above. However, combination therapy, particularly tobramycin and cefazolin, was associated with an increased risk of ocular discomfort by up to 78% compared with fluoroquinolones. Furthermore, there is evidence that combination therapy increases the risk of chemical conjunctivitis by 80% in comparison with fluoroquinolones, while ciprofloxacin causes a 24-fold increase in the risk of white corneal precipitates compared to combination therapy. Levofloxacin was not associated with an elevated risk of chemical conjunctivitis or corneal precipitate formation. The authors of the metaanalysis emphasize that patient adherence is an important determinant of treatment success. Clinical trials are conducted under ideal conditions, with eye drop storage, administration and regimen being closely monitored and well documented. However, in real-life conditions patients may be more inclined to closely adhere to the treatment with fluoroquinolones rather than combination therapy, as the former are associated with a lower risk of discomfort/chemical conjunctivitis, and can be stored at room temperature. In addition, just one drop per dose is required.

Perioperative prophylaxis/endophthalmitis

Postoperative endophthalmitis is an inflammatory condition of the eye caused by an infectious process induced by bacteria, fungi or, in rare cases, parasites which enter the eye during the perioperative period. The initial incubation phase lasting from 16-18 hours to several days is followed by acceleration and destruction phases of infection. The prophylaxis of postoperative bacterial ocular infections such as endophthalmitis consists of intraocular administration of antibiotics during surgery, mainly into the anterior chamber or subconjunctivally. Topical pre- and postoperative applications are another commonly used prophylactic modality. A broad-spectrum antibiotic is indicated to achieve greater efficacy, and topical quinolones may be a reasonable therapeutic choice, given their bactericidal activity against both Gram-positive and Gram-negative bacteria. The incidence of endophthalmitis after cataract surgery has been reported to range from 0.014 to 0.048% [26]. The incidence of bleb-associated endophthalmitis (BAE) after anti-glaucoma surgery varies between 0.12 and 1.2% [27]. For intravitreal injections, the incidence of endophthalmitis depends on the type of drug injected; for anti-VEGF injections the rate reaches 0.019%, while for intravitreal steroid injections it is higher, around 0.13% [28, 29].

Based on a 2017 Cochrane database review, the efficacy of perioperative antibacterial prophylaxis was analyzed on the basis of five clinical trials, with 132 cases of endophthalmitis among 101,000 patients undergoing cataract surgery [30]. The authors note that the injection of cefuroxime into the anterior chamber during the procedure clearly reduces the risk of endophthalmitis, and the use of levofloxacin eye drops is likely to have an additional risk-lowering effect [30].

In a prospective randomized study, Kaspar *et al*. compared the efficacy of reducing the physiological flora in the conjunctival sac prior to cataract surgery between two groups of patients treated with the following regimens: 1) povidone only before the procedure, 2) levofloxacin the day before surgery + povidone before the procedure[31]. After the surgery, positive cultures were obtained in 15 (23.1%) of 65 eyes in group 1, and 6 (9.0%) of 67 eyes in group 2 ($p = 0.027$). This study confirmed an enhanced effect of topical levofloxacin in combination with povidone irrigation in reducing bacterial populations in the conjunctival sac in patients undergoing intraocular surgery.

One of the most recent randomized studies evaluating the bioavailability and efficacy of levofloxacin was published in 2020 by Figus *et al*. [32]. Antibiotic levels in the anterior chamber were assessed in 125 patients undergoing cataract surgery. The results were compared against the MIC90 (minimum inhibitory concentrations required to inhibit the growth of 90%

of bacteria *in vitro*). Levofloxacin concentrations in the aqueous humor peaked 90-150 minutes after drug administration and significantly exceeded MIC90 values, the only exceptions being MSSA and some *Enterococcus* spp. The ESCRS Guidelines for Prevention and Treatment of Endophthalmitis Following Cataract Surgery highlight that from a clinical point of view the ratio between the anterior chamber concentration of antibiotic and MIC90 is more important for lowering the risk of endophthalmitis than both parameters considered separately. The optimal aqueous humor antibiotic concentration/MIC90 ratio should be > 30 for multiple strains of Gram (+), and > 100 for Gram (–) bacteria. The study confirmed that this level can be achieved by the administration of levofloxacin in the vast majority of isolated strains.

SAFETY

ADRs and tolerance

Levofloxacin is a safe and well-tolerated drug. Kanda et al. collected information on 6,760 patients receiving levofloxacin for the treatment of various ocular infections [11]. Adverse drug reactions (ADRs) were reported in 42 of 6,686 patients (0.63%). No serious ADRs were observed. The most commonly reported ADRs included blepharitis, ocular irritation, and punctate keratitis. The incidence of ADRs was not found to vary significantly with age, but it was significantly higher in women (0.82%) than in men (0.36%; $p = 0.028$). However, as Kanda *et al.* note, the observation does not appear to be specific to 0.5% levofloxacin solution. This study collected data on the use of the drug in 1,259 children, showing that levofloxacin can be used safely in the pediatric population. Adverse reactions were reported only in 0.32% of children, which was not higher than the rates determined in patients in other age groups. A study conducted by Lichtenstein *et al.* in a group of 167 children also showed favorable safety and tolerability profiles of 0.5% ophthalmic levofloxacin solution, which were similar to those observed with placebo [18]. The five-day dosing regimen of levofloxacin was found to be safe in children from 1 year of age.

Wound healing

In their prospective, randomized, double-blind comparative study, Park *et al.* analyzed 47 eyes of 47 patients with primary pterygium. They were randomly divided into three treatment groups (0.5% levofloxacin, 0.3% gatifloxacin, and 0.5% moxifloxacin) [33]. Following pterygium surgery performed with the same technique using conjunctival autograft, each patient followed a treatment schedule based on randomly assigned fluoroquinolone eye drops. The moxifloxacin group showed a slower rate of re-epithelialization of conjunctival epithelial defects at the harvesting site than those observed in the levofloxacin ($p = 0.003$) and gatifloxacin groups ($p = 0.019$). According to Park *et al.*, the finding can be explained by two factors: different inhibitory effects on topoisomerase II and differences in the penetration of fluoroquinolones into the ocular tissues. Kim *et al.* also suggested that moxifloxacin might show a higher toxicity than levofloxacin [34]. The authors found that moxifloxacin was characterized by significantly greater penetration into normal and abnormal ocular tissues than other fluoroquinolones. Higher drug concentrations may provide high efficacy in eradicating bacteria, but at the same time may increase toxicity due to the abundance of fluoroquinolone potentially delaying re-epithelialization [35]. This aspect is particularly important if the drug used for treatment additionally contains preservatives and the infection is accompanied by corneal/conjunctival epithelial defects.

Patel *et al.* found ciprofloxacin to be the least soluble of all available fluoroquinolones, which is attributed to its low pH [36]. It can precipitate in the corneal epithelium, delaying the process of its reconstruction by blocking epithelial migration or inhibiting regeneration. Similarly, Oum *et al.* showed that fluoroquinolones with a relatively low pH – such as 0.3% tosufloxacin – induced delayed corneal epithelial migration compared to 0.5% levofloxacin [37]. The same study evaluated the effects of various fluoroquinolones (ofloxacin, levofloxacin, tosufloxacin, moxifloxacin) on corneal epithelial cells *in vitro*. Moxifloxacin was shown to exhibit the most potent cellular cytotoxicity. It is thought that impaired corneal wound regeneration after the administration of 0.5% moxifloxacin is not due to the low pH (6.0-6.8) but may be an effect of corneal cell damage caused by the drug itself. This finding suggests that fourth-generation fluoroquinolones may be more cytotoxic than their second- or third-generation counterparts after prolonged exposure of human corneal epithelial cells to the effects of the drugs. Therefore, in patients receiving long-term treatment with fourth-generation fluoroquinolones – or in the event of an overdose – the possibility of toxic effects on the human corneal epithelial cells should be considered on an initial basis.

Corneal perforation

Both *in vitro* and *in vivo* studies suggest that fluoroquinolones may increase proteolytic activity degrading the stroma of the cornea, inhibit cell metabolism, and induce cellular changes resulting from alterations in cytokine pathways [38]. Ciprofloxacin is recognized as the most cytotoxic fluoroquinolone in this respect. Only isolated cases of corneal perforation secondary to fluoroquinolone therapy have been reported in the literature [39]. A metaanalysis by McDonald *et al.* revealed no differences in the risk of corneal perforation during fluoroquinolone treatment versus combination therapy in a group of 449 patients [2]. The review involved four fluoroquinolones: ofloxacin, ciprofloxacin, gatifloxacin, and moxifloxacin. No corneal perforation was observed in studies comparing lomefloxacin or levofloxacin with combination therapy [2].

ANTIBIOTIC RESISTANCE

Antibiotic resistance can develop when bacteria come into contact with an antibiotic used at a sublethal dose. To prevent it, it is critical that patients adhere to the prescribed dosing and timing regimen of antibiotic therapy. Antibiotic resistance of fluoroquinolones arises from the development of spontaneous mutations in the genes encoding topoisomerase IV and DNA gyrase, i.e. the enzymes whose inhibition forms

the basis of the antibacterial action of these antibiotics [40]. With regard to second- and third-generation fluoroquinolones, a mutation in the gyrase gene is usually enough to induce the development of antibiotic resistance. For moxifloxacin (a fourth-generation fluoroquinolone), mutations in the genes of both enzymes are necessary, with the occurrence of one mutation promoting the development of the other. Resistance can also arise from excessive drug efflux pump activity in bacterial cells, which suppresses drug penetration into the pathogen [40].

Staphylococcus aureus (SA) is the leading cause of keratitis worldwide [41]. *Staphylococcus aureus* is considered to be the most virulent of all *Staphylococcus* species. As estimated, one in three individuals are colonized with the bacteria. Methicillin-resistant *Staphylococcus aureus* (MSSA) is susceptible to levofloxacin in approximately 80-90%, which is superior to the efficacy of ciprofloxacin (2nd generation fluoroquinolone) and comparable to the results obtained for moxifloxacin (4th generation fluoroquinolone) [40]. A clinical problem is an increase in the proportion of keratitis (30-40% in the USA) caused by methicillin-resistant *Staphylococcus aureus* (MRSA) which at the same time demonstrates decreased sensitivity to fluoroquinolones [23, 40]. The issue applies in particular to second-generation drugs (e.g. ciprofloxacin), where the sensitivity of MRSA decreased from 87% to 27.9%, and in keratitis from 79.8% to 5.2% [40]. The process stems from several factors: 1) longer availability of second-generation drugs on the market, 2) the fact that a single mutation in bacterial genotype leads to resistance, 3) physicochemical properties of drugs in this group: small molecule, higher hydrophobicity and lower solubility, which promotes the removal of the drug from bacterial cells via the above-mentioned drug efflux pump. Chang *et al.*, based on their 20-year monitoring of increasing MRSA resistance in the USA, are of the opinion that 2nd generation fluoroquinolones are contraindicated in the treatment of keratitis [41]. In the Ocular TRUST study, which evaluated the build-up of antibiotic resistance in the USA, 81% of MSSA strains were found to be susceptible to levofloxacin [42]. The study also showed 100% sensitivity of *S. pneumoniae* and *H. influenzae* towards levofloxacin [42]. The activity of levofloxacin against *Pseudomonas aeruginosa* in this analysis was superior to that of moxifloxacin and similar to that of oxifloxacin [42].

CONCLUSIONS

Successful treatment of bacterial ocular inflammation must be based on a broad-spectrum antibiotic showing efficacy against both Gram-positive and Gram-negative pathogens. Levofloxacin is a safe antibiotic with good patient tolerance and a broad spectrum of action. Very good penetration through ocular tissues makes it an effective agent for use in perioperative prophylaxis. Despite reports of growing bacterial resistance to fluoroquinolones *in vitro*, most bacteria causing inflammatory conditions of the conjunctiva and cornea remain susceptible to levofloxacin.

DISCLOSURE

The authors declare no conflict of interest.

References

1. Ogawa GS, Hyndiuk RA. The fluoroquinolones: new antibiotics in ophthalmology. Int Ophthalmol Clin 1993; 33: 59-68.
2. McDonald M, Blondeau JM. Emerging antibiotic resistance in ocular infections and the role of fluoroquinolones. J Cataract Refract Surg 2010; 36: 1588-1598.
3. Wimer SM, Schoonover L, Garrison MW. Levofloxacin: a therapeutic review. Clin Ther 1998; 20: 1049-1070.
4. Mitsui Y, Ooishi M, Sasaki K, et al. AQCmax as a pharmacokinetic parameter of ophthalmic solution. J Eye 1995; 12: 783-786.
5. Ross DL, Riley CM. Aqueous solubilities of some variously substituted quinolone antimicrobials. Int J Pharm 1990; 63: 237-250.
6. Kawashima Y, Takashina H, Usui M. Pharmacokinetic parameters of ofloxacin and levofloxacin ophthalmic solutions. Atarasii Ganka 1995; 12: 791-794.
7. Yamada M, Ishikawa K, Mochizuki H, et al. Corneal penetration of simultaneously applied topical levofloxacin, norfloxacin and lomefloxacin in human eyes. Acta Ophthalmol Scand 2006; 84: 192-196.
8. Robertson SM, Curtis MA, Schlech BA, et al. Ocular pharmacokinetics of moxifloxacin after topical treatment of animals and humans. Surv Ophthalmol 2005; 50 Suppl 1: S32-S45.
9. Raizman, MB, Rubin JM, Graves AL Tear concentrations of levofloxacin following topical administration of a single dose of 0.5% levofloxacin ophthalmic solution in healthy volunteers. Clin Ther 2002; 24: 1439-1450.
10. Miller D. Update on the Epidemiology and Antibiotic Resistance of Ocular Infections. Middle East Afr J Ophthalmol 2017; 24: 30-42.
11. Kanda Y, Kayama,T, Okamoto S, et al. Post-Marketing Surveillance of Levofloxacin 0.5% Ophthalmic Solution for External Ocular Infections. Drugs R D 2012; 12: 177-185.
12. Petricek I, Prost M, Popova A. The differential diagnosis of red eye: A survey of medical practitioners from Eastern Europe and the Middle East. Ophthalmologica 2006; 220: 229-237.
13. Azari AA, Arabi A. Conjunctivitis: A Systematic Review. J Ophthalmic Vis Res 2020; 15: 372-395.
14. Hørven I. Acute conjunctivitis. A comparison of fusidic acid viscous eye drops and chloramphenicol. Acta Ophthalmol (Copenh) 1993; 71: 165-168.
15. Tepedino ME, Heller WH, Usner DW, et al. Phase III efficacy and safety study of besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis. Curr Med Res Opin 2009; 25: 1159-1169.
16. Varu DM, Rhee MK, Akpek EK, et al. American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Conjunctivitis Preferred Practice Pattern®. Ophthalmology 2019; 126: 94-169.

17. Schwab IR, Friedlaender M, McCulley J, et al. Levofloxacin Bacterial Conjunctivitis Active Control Study Group. A phase III clinical trial of 0.5% levofloxacin ophthalmic solution versus 0.3% ofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis. Ophthalmology 2003; 110: 457-465.
18. Lichtenstein SJ, Rinehart M; Levofloxacin Bacterial Conjunctivitis Study Group. Efficacy and safety of 0.5% levofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis in pediatric patients. J AAPOS 2003; 7: 317-324.
19. Szumiński M, Bakunowicz-Łazarczyk A, Sielicka D. Effectiveness of levofloxacin therapy in bacterial conjunctivitis in infants = Ocena skuteczności lewofloksacyny w leczeniu bakteryjnego zapalenia spojówek u niemowląt. Kontaktologia i Optyka Okulistyczna 2013; 37: 22–24.
20. Szaflik J, Szaflik JP, Kamińska A , et al. Clinical and microbiological efficacy of levofloxacin administered three Times a day for the treatment of bacterial conjunctivitis. Eur J Ophthalmol 2009; 191: 1-9.
21. Jeng BH, Gritz DC, Kumar AB, et al. Epidemiology of ulcerative keratitis in Northern California. Arch Ophthalmol 2010; 128: 1022-1028.
22. Cruciani F, Cuozzo G, Di Pillo S, et al. Predisposing factors, clinical and microbiological aspects of bacterial keratitis: a clinical study. Clin Ther 2009; 160: 207-210.
23. Lin A, Rhee MK, Akpek EK, et al. American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Bacterial Keratitis Preferred Practice Pattern®. Ophthalmology 2019; 126: 1-55.
24. Wilhelmus KR, Abshire RL, Schlech BA. Influence of fluoroquinolone susceptibility on the therapeutic response of fluoroquinolone--treated bacterial keratitis. Arch Ophthalmol 2003; 121: 1229-1233.
25. Goldstein MH, Kowalski RP, Gordon YJ. Emerging fluoroquinolone resistance in bacterial keratitis: a 5-year review. Ophthalmology 1999; 106: 1313-1318.
26. Barry P, Cordoves L, Gardner S. Wytyczne ESCRS dotyczące profilaktyki i leczenia zapalenia wnętrza gałki ocznej po operacji zaćmy: dane, dylematy i wnioski. 2013.
27. Ang GS, Varga Z, Shaarawy T. Postoperative infection in penetrating versus non- penetrating glaucoma surgery. Br J Ophthalmol 2010;94:1571-6 DOI: 10.1136/bjo.2009.163923
28. Vander-Beek BL, Bonaffini SG, Ma L. The Association between Intravitreal Steroids and Post-Injection Endophthalmitis Rates. Ophthalmology 2015; 122: 2311-2315.
29. Sachdeva MM, Moshiri A, Leder HA , et al. Endophthalmitis following intravitreal injection of anti-VEGF agents: long-term outcomes and the identification of unusual micro-organisms. J Ophthalmic Inflamm Infect 2016; 6: 2.
30. Gower EW, Lindsley K, Tulenko SE , et al. Perioperative antibiotics for prevention of acute endophthalmitis after cataract surgery. Cochrane Database Syst Rev 2017; 2: CD006364.
31. Miño de Kaspar H, Kreutzer TC, Aguirre-Romo I, et al. A prospective randomized study to determine the efficacy of preoperative topical levofloxacin in reducing conjunctival bacterial flora. Am J Ophthalmol 2008; 145: 136-142.
32. Figus M, Posarelli C, Romano D, et al. Aqueous humour concentrations after topical apPlication of combinEd levofloxacin-dexamethasone eye dRops and of its single components: a randoMised, assEssor-blinded, parallel-group study in patients undergoing cataract surgery: the iPERME study. Eur J Clin Pharmacol 2020; 76: 929-937.
33. Park HS, Lee JH, Kim HK. Comparative clinical study of conjunctival toxicities of newer generation fluoroquinolones without the influence of preservatives. Int J Ophthalmol 2015; 8: 1220-1223.
34. Kim SY, Lim JA, Choi JS, et al. Comparison of antibiotic effect and corneal epithelial toxicity of levofloxacin and moxifloxacin in vitro. Cornea 2007; 26: 720-725.
35. Torkildsen G, Proksch JW, Shapiro A, et al. Concentrations of besifloxacin, gatifloxacin, and moxifloxacin in human conjunctiva after topical ocular administration. Clin Ophthalmol 2010; 4: 331-341.
36. Patel GM, Chuang AZ, Kiang E, et al. Epithelial healing rates with topical ciprofloxacin, ofloxacin, and ofloxacin with artificial tears after photorefractive keratectomy. J Cataract Refract Surg 2000; 26: 690-694.
37. Oum BS, Kim NM, Lee JS et al. Effects of fluoroquinolone eye solutions without preservatives on human corneal epithelial cells in vitro. Ophthalmic Res 2014; 51: 216-223.
38. Reviglio VE, Hakim MA, Song JK, et al. Effect of topical fluoroquinolones on the expression of matrix metalloproteinases in the cornea. BMC Ophthalmol 2003; 3: 10.
39. Mallari PL, McCarty DJ, Daniell M, et al. Increased incidence of corneal perforation after topical fluoroquinolone treatment for microbial keratitis. Am J Ophthalmol 2001; 131: 131-133.
40. Aramă V. Topical antibiotic therapy in eye infections - myths and certainties in the era of bacterial resistance to antibiotics. Rom J Ophthalmol 2020; 64: 245-260.
41. Chang VS, Dhaliwal DK, Raju L, et al. Antibiotic Resistance in the Treatment of Staphylococcus aureus Keratitis: a 20-Year Review. Cornea 2015; 34: 698-703.
42. Asbell PA, Colby KA, Deng S , et al. Ocular TRUST: nationwide antimicrobial susceptibility patterns in ocular isolates. Am J Ophthalmol 2008; 145: 951-958.