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Fluoroquinolone Resistance in Ophthalmology and the Potential Role for Newer Ophthalmic Fluoroquinolones

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Abstract. The three topical ophthalmic fluoroquinolones recently introduced into the U.S. market—levofloxacin, gatifloxacin, and moxifloxacin—offer several advantages over the previously available fluoroquinolones (norfloxacin 0.3%, ciprofloxacin 0.3%, and ofloxacin 0.3%). These include enhanced spectrum and potency for Gram-positive cocci and possibly atypical mycobacterial species, improved penetration into the anterior segment, and reduced propensity to promote the development of resistance. Although published data and clinical experience with these agents is quite limited given their relatively recent entry into the U.S. market, this perspective will attempt to provide an understanding of the potential role of these newer fluorquinolones in addressing the problem of increasing fluoroquinolone resistance amongst bacterial ocular isolates. (**Surv Ophthalmol 49(Suppl 2)**:S79–S83, 2004. © 2004 Elsevier Inc. All rights reserved.)

Key words. antimicrobial resistance • endophthalmitis • fluoroquinolones • gatifloxacin keratitis • levofloxacin • moxifloxacin

In the 1990s, three topical fluoroquinolones were introduced for topical ophthalmic use in the United States: ciprofloxacin 0.3%, ofloxacin 0.3%, and norfloxcin 0.3%. Although norfloxacin 0.3% never achieved widespread use due to its relatively poorer antimicrobial activity, both ciprofloxacin 0.3% and ofloxacin 0.3% rapidly achieved widespread use for the treatment and prophylaxis of ocular infections. Both ciprofloxacin and ofloxacin are indicated for the treatment of generally self-limited external eye infections such as bacterial conjunctivitis, as well as more serious infections such as bacterial keratitis.[8,12,14,16] Although no randomized clinical trial has been performed in an attempt to investigate the role of topical antibiotics in ophthalmic surgical prophylaxis,[9,10] presumably due to the large cohort size that such a study would require, topical antibiotics, including topical fluoroquinolones, are routinely used for surgical prophylaxis.

Recently, three fluoroquinolones were introduced in the U.S. for topical ophthalmic use: levofloxacin 0.5%, gatifloxacin 0.3%, and moxifloxacin 0.5% (Table 1). The most important attribute of these compounds (hereinafter referred to as "newer fluoroquinolones") is their enhanced Gram-positive activity relative to ciprofloxacin and ofloxacin (hereinafter referred to as "older fluoroquinolones"). Additionally, other potentially beneficial features shared by some or all of these compounds include enhanced drug delivery into the anterior segment, improved activity against certain strains of atypical mycobacteria, and lowered likelihood of selecting for resistant bacterial strains. The clinical benefits of these newer fluoroquinolones have yet to be fully established, but their attributes suggest a potential role in addressing at least one emerging and important problem in ocular infectious disease: the observation of a rising

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TABLE 1

Antibacterial Activity of Fluoroquinolones

Agent	Indication	Date Introduced	Susceptible Organisms[a]	MIC_{90} (Range)	MIC_{50} (Range)
Norfloxacin 0.3%	Conjunctivitis	Pre-1990	Gram-Positive Aerobes: *Bacillus* spp., *E.faecalis, S.aureus, S.epidermidis, S.saprophyticus, S.warnerii, S.pneumoniae* Gram-Negative Aerobes: *A.calcoaceticus, A.hydrophila, C.koseri, C.freundii, E.tarda, E.aerogenes, E.cloacae, E.coli, H.alvei, H.aegyptius, H.influenzae, K.oxytoca, K.pneumoniae, K.rhinoscleromatis, M.morganii, N.gonorrhoeae, P.mirabilis, P.vulgaris, P.alcalifaciens, P.aeruginosa, P.rettgeri, P.stuartii, S.typhi, S.marcescens, V.cholerae V.parahemolyticus, Y.enterocolitica* Other: *U.urealyticum*	0.5–16 µg/ml (16 µg/ml reported for *S.pneumoniae)*	0.06–8 µg/ml (8 µg/ml reported for *S.pneumoniae)*
Ciprofloxacin 0.3%	Conjunctivitis, Keratitis	Dec 1990	Gram-Positive Aerobes: *Bacillus* sp., *Corynebacterium* spp., *E.faecalis, S.aureus, S.epidermidis, S.haemolyticus, S.hominis, S.pneumoniae,* Viridans group *Streptococcus* spp. Gram-Negative Aerobes: *A.calcoaceticus, E.aerogenes, E.coli, H.influenzae, H.parainfluenzae, K.pneumoniae, M.catarrhalis, N.gonorrhoeae, P.mirabilis, P.aeruginosa, S.marcescens*	0.5–32 µg/ml (32 µg/ml reported for *S.pneumoniae*)	0.25–32 µg/ml (32 µg/ml reported for *S.pneumoniae*)
Ofloxacin 0.3%	Conjunctivitis, Keratitis	July 1993	Gram-Positive Aerobes: *E.facealis, L.monocytogenes, S.aureus, S.capitis, S.epidermidis, S.hominis, S.simulans, S.pneumoniae, S.pyogenes* Gram-Negative Aerobes: *A.lwoffii, A.anitratus, C.koseri, C.freundii, D.acidovorans, E.aerogenes, E.cloacae, E.coli, H.influenzae, H.parainfluenzae, K.oxytoca, K.pneumoniae, M.catarrhalis, M.lacunata, M.morganii, N.gonorrhoeae, P.agglomerans, P.mirabilis, P.aeruginosa, P.fluorescens, S.marcescens, S.sonnei* Anaerobes: *P.acnes* Other: *C.trachomatis*	0.25–8 µg/ml (8 µg/ml reported for *P.aeruginosa*)	0.12–2 µg/ml (2 µg/ml reported for *S.pneumoniae)*
Levofloxacin 0.5%	Conjunctivitis	Aug 2000	Gram-Positive Aerobes: *Corynebacterium* spp., *E.facealis, S.aureus, S.epidermidis, S.saprophyticus, S.agalactiae, S.pneumoniae, S.pyogenes,* Viridans group *Streptococcus* spp., *Streptococcus* Groups C,F,G Gram-Negative Aerobes: *A.lwoffii, A.anitratus, A.baumannii, C.koseri, C.freundii, E.aerogenes, E.cloacae, E.coli, H.influenzae, H.parainfluenzae, K.oxytoca, K.pneumoniae, L.pneumophila, M.catarrhalis, M.morganii, N.gonorrhoeae, P.agglomerans, P.mirabilis, P.vulgaris, P.rettgeri, P.stuartii, P.aeruginosa, P.fluorescens, S.marcescens*	0.03–8 µg/ml (8 µg/ml reported for *S.epidermidis)*	0.03–2 µg/ml[b] (2 µg/ml reported for *S.pneumoniae*)
Gatifloxacin 0.3%	Conjunctivitis	Mar 2003	Gram-Positive Aerobes: *C.propinquum, L.monocytogenes, S.aureus, S.epidermidis, S.saprophyticus, S.mitis, S.agalactiae, S.pneumoniae, S.pyogenes,* Viridans group *Streptococcus* spp., *Streptococcus* Groups C,F,G	0.25–2 µg/ml (2 µg/ml reported for *S.epidermidis*)	0.08–0.5 µg/ml[b] (0.5 µg/ml reported for *S.pneumoniae*)

(continued)

TABLE 1

Continued

Agent	Indication	Date Introduced	Susceptible Organisms[a]	MIC_{90} (Range)	MIC_{50} (Range)
Moxifloxacin 0.5%	Conjunctivitis	Apr 2003	Gram-Negative Aerobes: *A.lwoffii, C.freundii, C.koseri, E.aerogenes, E.cloacae, E.coli, H.influenzae, H.parainfluenzae, K.oxytoca, K.pneumoniae, M.catarrhalis, M.morganii, N.gonorrhoeae, N.meningitidis, P.mirabilis, P.vulgaris, S.marcescens, V.cholerae, Y.enterocolitica* Anaerobes: *B.fragilis, C.perfringens* Other: *C.pneumoniae, L.pneumophila, M.marinum, M.fortuitim, M.pneumoniae* Gram-Positive Aerobes: *Corynebacterium* spp., *M.luteus, S.aureus, S.epidermidis, S.haemolyticus, S.hominis, S.warnerii, pneumoniae, S. pyogenes,* Viridans group *Streptococcus* spp. Gram-Negative Aerobes: *A.lwoffii, E.coli, H.influenzae, H.parainfluenzae, K.oxytoca, K.pneumoniae, M.catarrhalis, P.mirabilis* Anaerobes: *Fusobacterium* spp., *Prevotella* sp. Other: *C.trachomatis*	0.03–1 μg/ml† (1 μg/ml reported for *K.pneumoniae*)	0.03–0.13 μg/ml[b] (0.13 μg/ml reported for *S.pneumoniae*)

Sources of data for the table: (Long M, Jensen HG: Ocular bacteria from conjunctivitis patients: susceptibility to gatifloxacin and older fluoroquinolonesl[abstract]. Association for Research in Vision and Ophthalmology, Annual Meeting, 2003) FDA-approved product labeling, and references[3,5,13,14].

[a]Susceptibility defined by in vitro MICs of ≤2 μg/ml against ≥90% of strains.

[b]Antibacterial activity of ocular isolates is presented where available. Select data, marked by (†), indicate non-ocular isolate MIC data for common ocular pathogens.

incidence of fluoroquinolone resistance amongst bacterial ocular isolates.

Increasing Fluoroquinolone Resistance in Ocular Infections

Since the introduction of the older fluoroquinolones for ophthalmic use, the reported incidence of in vitro resistance to older fluoroquinolones among bacteria isolated from cases of bacterial keratitis and endophthalmitis has been steadily increasing.[1,4,6,15]

A number of recent studies have reported emerging resistance to fluoroquinolones among ocular isolates, particularly among Gram-positive organisms. Goldstein et al studied all cases of bacterial keratitis at the Eye and Ear Institute of Pittsburgh presenting from 1993 to 1997 and found that resistance of *Staphylococcus aureus* isolates to ciprofloxacin and ofloxacin increased 6–7-fold over the 5-year study period. Significant resistance to these older fluoroquinolones among *Streptococcus* and coagulase-negative *Staphylococcus* species was also found.[6] A retrospective study at Bascom Palmer Eye Institute in South Florida that examined the susceptibility trends of bacterial keratitis isolates during the period from 1990 to 1998 also demonstrated increased in vitro resistance to older fluoroquinolones among Gram-positive species, particularly *S.aureus*.[1] In recent years, up to 30% or more of *S.aureus* strains were found to be fluoroquinolone-resistant based on in vitro criteria.[1,6] Fluoroquinolone resistance has not only been reported in isolates causing ocular infection, but also in the normal flora of asymptomatic individuals, albeit at a lower frequency. In a study conducted in Japan, bacterial isolates were sampled from the eyes of healthy individuals between 1994 and 1997. In this study, 6.7% of coagulase-negative *Staphylococcus* and 49.2% of aerobic Gram-positive rods were resistant to ofloxacin.[15] Emerging fluoroquinolone resistance among Gram-negative isolates such as *Pseudomonas aeruginosa* has also been reported in several centers.[4]

To evaluate the clinical significance of fluoroquinolone resistance, it is helpful to quantify the level of resistance. Low-level in vitro resistance may not necessarily translate into a clinical treatment failure since the tissue levels that can be achieved with topical dosing may be much higher than that typically achieved after systemic dosing. By contrast, a high-level resistant isolate is more likely to be associated

with a treatment failure because the minimum inhibitory concentration (MIC) of the isolate may not be achievable even with a topical route of delivery. Whereas the more commonly employed Kirby-Bauer disk diffusion testing is designed only to characterize an isolate into categories of "susceptible," "intermediate," or "resistant," rapid methods of quantitatively determining the MIC of an isolate, such as the E-test or microbroth dilution techniques, can provide useful information as to whether the resistance is low-level or high-level.

Low-level fluoroquinolone-resistant bacterial isolates have generally acquired a single chromosomal mutation, and are thus called "single-step" mutants. Mutations can occur in the genes encoding for the two principal enzymes targeted by fluoroquinolones, topoisomerase II (also known as DNA gyrase) and topoisomerase IV, as well as in other genes such as those encoding for efflux pumps and membrane permeability proteins, which affect transport of fluoroquinolones across the bacterial cell membrane.

On the other hand, high-level fluoroquinolone-resistant isolates typically will have acquired two or more mutations conferring resistance, and are thus termed "multi-step" mutants. Extrachromosomal (e.g., plasmid-mediated) transfer of fluoroquinolone resistance genes has not been reported, so high-level resistant strains have presumably serially acquired multiple chromosomal mutations that confer fluoroquinolone resistance. Thus multi-step mutants are more likely to arise after exposure of a bacterial subpopulation to repeated rounds of sublethal doses of fluoroquinolone, as from intermittent or tapered dosing over a prolonged interval. Indeed, one study has demonstrated the frequent recovery of high-level fluoroquinolone-resistant staphylococci from eyes treated with a four-week tapering dose of ciprofloxacin (Hodge WG, Bui DP, Cevallos V, Dang SB, Moore T, Hwang DG: Frequency of recovery of ciprofloxacin-resistant ocular isolates following topical ciprofloxacin therapy [abstract]. Invest Ophthalmol Vis Sci 36:S155, 1995).

Recent studies have suggested that by maintaining a fluoroquinolone concentration above a certain level, termed the *mutant prevention concentration* (MPC), the probability of selecting for a single-step mutant can be greatly reduced.[2] For fluoroquinolones, the MPC is generally several-fold above the MIC. Thus, the probability of selecting a single-step resistant mutant can be lowered by maintaining the highest possible ratio between tissue fluoroquinolone concentration and the MIC, preferably at a level equal to or exceeding the MPC.[17] A higher tissue fluoroquinolone concentration can be achieved in a number of ways, including dosing at more frequent intervals, increasing the concentration of drug in the ophthalmic formulation, using adjunctive drug delivery devices or penetration enhancers, or employing fluoroquinolones with enhanced ocular penetration characteristics. The MIC can be lowered by utilizing a fluoroquinolone with heightened activity against the bacterial species of interest.

All three of the newer fluoroquinolones possess characteristics that are conducive to maximizing the tissue concentration relative to the MIC, and thus have a lower theoretical likelihood of encouraging the development of resistance, assuming the fluoroquinolone is properly used and dosed. Levofloxacin achieves up to two-fold higher levels in the cornea and aqueous relative to ofloxacin after topical dosing (Holland EJ, et al: Concentrations of levofloxacin, ofloxacin, and ciprofloxacin in aqueous fluid and corneal tissue after topical ophthalmic administration in human volunteers before penetrating keratoplasty [abstract]. Association for Research in Vision and Ophthalmology, Annual Meeting, 2003). For Gram-positive cocci, which are responsible for a majority of ocular infections, the MICs of levofloxacin are approximately half that of ofloxacin, whereas the MICs of gatifloxacin and moxifloxacin are even lower, typically in the range of one-fourth to one-eighth that of the older fluoroquinolones.[7]

In addition, both gatifloxacin and moxifloxacin, which are 8-methoxyfluoroquinolones, are less prone to resistance developing as the result of single-step topoisomerase mutations. (These fluoroquinolones are sometimes referred to as fourth-generation fluoroquinolones,[11] but this designation is avoided in this discussion because unlike for the beta-lactam antimicrobials, there is no universal agreement on the classification by generation of the fluoroquinolones.) The 8-methoxyfluoroquinolones retain activity against single-step topoisomerase mutants in most strains of staphylococci and certain streptococci. However, they are still susceptible to resistance due to one or more mutations in other genes (a not infrequent event) or due to a double mutation in both topoisomerase II (DNA gyrase) and topoisomerase IV (a highly improbable event).

In terms of forestalling the development of resistance, primary use of the newer fluoroquinolones may actually be a better strategy than initial use of an older fluoroquinolone. Use of a newer fluoroquinolone, particularly one of the 8-methoxyfluoroquinolones such as gatifloxacin or moxifloxacin, may help avoid selection of resistant mutants. On the other hand, the more conventional strategy of reserving the use of a newer antimicrobial only when initial treatment with the older antimicrobial fails may not be a wise strategy if applied to the fluoroquinolone class of antibiotics. Primary use of an older fluoroquinolone is more likely to lead to acquisition of a first-step mutation.

Once a bacterial population is already pre-enriched for first-step mutants, subsequent mutations can be readily acquired, thus vitiating the value of 8-methoxyfluoroquinolones in particular in forestalling the occurrence of double topoisomerase mutations.

Conclusion

Fluoroquinolone resistance in ophthalmology is a growing problem and may portend a trend toward declining efficacy of older fluoroquinolones. Newer fluoroquinolones such as levofloxacin and in particular the 8-methoxyfluoroquinolones gatifloxacin and moxifloxacin offer the opportunity to help address this problem in two ways. First, their enhanced activity against Gram-positive pathogens increases the probability that the strains resistant to an older fluoroquinolone will be susceptible to one of the newer fluoroquinolones. Second, they are less prone to encouraging the development of resistance on a number of fronts, primarily because of their higher activity against Gram-positive pathogens, but also for other reasons (higher penetration in the case of levofloxacin; resistance to single-step topoisomerase mutations in the case of gatifloxacin and moxifloxacin). Primary use of newer fluoroquinolones in preference to initial use of older fluoroquinolones offers a potential strategy for helping to forestall the development of resistance, but this approach must be coupled with the overall strategy of avoiding indiscriminate use and ensuring proper dosing of these antimicrobials.

Method of Literature Search

This article was written based on MEDLINE searches from 1966 to the present, using different combinations of the search terms *fluoroquinolones, ocular penetration, antibacterial activity, gatifloxacin, moxifloxacin, resistance, minimum inhibitory concentration, and mutant prevention concentration.* Relevant journal articles and/or abstracts based on direct search results as well as 'Related Article' searches were selected for review. Searches for abstracts were also conducted using similar terms at relevant ophthalmic society websites such as American Academy of Ophthalmology and Association for Research in Vision and Ophthalmology. Relevant articles cited in the references of articles initially retrieved were also included. An effort to use the most recently available literature was made, concentrating on journal articles and abstracts published in the last decade.

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