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Fluoroquinolones
Place in Ocular Therapy

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Abstract

The fluoroquinolones have become widely used antibacterial agents in the treatment of ocular infections, with topical, intravitreal and systemic routes of administration being used. In general, fluoroquinolones (such as ciprofloxacin, ofloxacin, lomefloxacin and norfloxacin) have good activity against Gram-negative and Gram-positive bacteria. Therapeutic concentrations are achieved in the cornea after topical administration so that the fluoroqinolones have largely replaced combination therapy for the treatment of bacterial keratitis. However, a second line agent is needed when resistance is likely, such as in disease caused by streptococcal species. Reversal of resistance to quinolones may not occur with withdrawal of the antibacterial. This stresses the importance of prudent prescribing to reduce the occurrence of resistance to quinolones.

When used in therapeutic topical dosages, corneal toxicity does not occur. Similarly, retinal toxicity is not seen when fluoroquinolones are used at therapeutic dosages, systemically or topically. Corneal precipitation occurs, particu-

larly with ciprofloxacin and to a lesser extent norfloxacin, but does not appear to interfere with healing.

In the treatment of endophthalmitis there is reasonable penetration of systemic fluoroquinolones into the vitreous but sufficiently high concentrations to reach the minimum inhibitory concentration for 90% of isolates (MIC_{90}) of all important micro-organisms may not be guaranteed. Systemic administration may be useful for prophylaxis after ocular trauma.

1. Fluoroquinolones

The fluoroquinolones have become important and frequently used antibacterial agents in medical and surgical specialities, such as ophthalmology. Fluoroquinolones are derived from nalidixic acid, a naphthyridine, which was found during chloroquine synthesis to have sufficient activity against Gram-negative aerobes to treat urinary tract infections. Development has continued in order to produce agents with a broader spectrum of activity and applicability. The common skeleton is 4-oxo-1, 4 dihydroquinoline, simplified to '4 quinolone'[1] (fig. 1). The introduction of a fluorine molecule into this basic nucleus at position R_6 has led to real progress in quinolone development.

Commonly used fluoroquinolones in ophthalmology include ciprofloxacin, ofloxacin, norfloxacin (fig. 1) and lomefloxacin. Other fluoroquinolones such as levofloxacin, sparfloxacin, gatifloxacin, moxifloxacin, pefloxacin and tosufloxacin are starting to gain popularity. The fluoroquinolones have become widely used in ophthalmology predominantly because they have been shown in most situations to be equivalent to combination therapy and because of their effectiveness against polyresistant organisms such as *Pseudomonas aeruginosa* and the Enterobacteriaceae.[2,3] However, they do have some limitations against ocular infections caused by *Streptococci* spp., and this is discussed (section 1.2).

1.1 Mechanism of Action

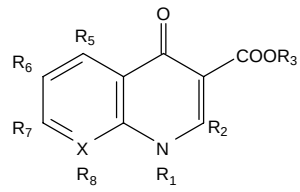
Fluoroquinolones are bactericidal agents.[4] They act by inhibiting DNA topoisomerases, of which DNA gyrase and topoisomerase IV are particularly important. Human cells lack these targeted enzymes and, therefore, the action of quinolones is selective for bacterial cells.

DNA gyrase catalyses the negative supercoiling of DNA and the separation of interlocked, replicated daughter chromosomes. These processes are important for DNA replication, transcription and the segregation of replicated chromosomes.[5] Topoisomerase IV segregates daughter chromosomes at the end of a round of replication through decatenating the daughter replicons. It also causes the relaxation of supercoiled DNA.[5]

DNA gyrase and topoisomerase IV both consist of 2 subunits. The A and B subunits in DNA gyrase are encoded by the genes *gyr*A and *gyr*B, respectively. The subunits in topoisomerase IV are encoded by the genes *grl*A and *grl*B, otherwise known as parC and parE genes, respectively.[5-7] In most Gram-negative bacteria, DNA gyrase is the primary target for fluoroquinolones, but in Gram-positive bacteria it is topoisomerase IV.

Resistance to fluoroquinolones is being seen more frequently and corresponds with their increasing use.[8] The 4 main mechanisms of quinolone resistance are: point mutations in *gyr*A and *gyr*B, point mutation in the *grl*A gene, membrane-associated efflux proteins (norA), and a locus (*cfx*B – *ofx*C or *flq*A) which confers quinolone resistance in *Staphylococcus aureus*.[8,9] Those areas of the genome in which mutations are most commonly seen are known as quinolone resistance determining regions.[10] Efflux mechanisms have been shown to make an important contribution to fluoroquinolone resistance. The main gene involved in fluoroquinolone efflux is *nor*A. This encodes a protein that is predicted to contain 12 membrane-spanning domains and to show significant homology with other transport proteins. All the quinolones share the

a



b

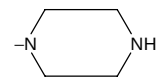
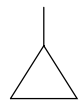
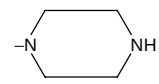
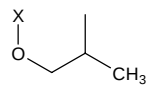
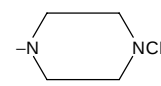
Quinolone	Substituents at position				
	R_2	R_3	R_6	R_7	X
Nalidixic acid	C_2H_5	H		CH_3	N
Norfloxacin	C_2H_5	H	F		CH
Ciprofloxacin		H	F		CH
Ofloxacin		H	F		CH

Fig. 1. Chemical structure of the fluoroquinolones. (**a**) Basic structure of the fluoroquinolones. (**b**) Substituents at positions.[1]

same topoisomerase and gyrase target sites, which themselves are homologous among different organisms.[11]

1.2 Spectrum of Activity

Therapy of an infection must often be started before the causative microbe is identified. The spectrum of activity of the drug and knowledge of potentially resistant micro-organisms is therefore important.

The susceptibilities of various micro-organisms to the different fluoroquinolones is based on *in vitro* studies (table I). Periodic susceptibility testing of clinical bacterial isolates is needed,[17] because of the development of bacterial resistance. Ideally such testing should be done at least every 2 to 3 years.[17]

Jensen et al.[17] tested 1291 ocular isolates between 1993 and 1994 using disc-diffusion and broth-dilution methods. [The minimum inhibitory concentration (MIC) using a broth-dilution method

Table I. *In vitro* activity of ciprofloxacin, norfloxacin, ofloxacin and lomefloxacin . Data compiled from studies by McDermott et al.,[30] Neu,[17] Wise et al.,[79] Bower et al.[16] and Prosser and Beskid[15]

Bacteria	Fluoroquinolone	MIC range (mg/L)	MIC_{90} (mg/L)	MIC_{50} (mg/L)	Susceptibility (%)
Streptococcus pneumoniae	Ciprofloxacin	≤0.03 - 4	2.0	1 - 2	75-100
	Norfloxacin	2 - 16	16	8	54-81
	Ofloxacin	≤0.03 - 4	2	2	63-96
	Lomefloxacin	≤0.03 - 8	8	4	
Streptococcus epidermidis	Ciprofloxacin	≤0.06 - ≥8	0.5	0.25	
	Norfloxacin	0.25 - 1	1	1	84-86
	Ofloxacin	≤0.06 - ≥8	0.5	0.5	96
	Lomefloxacin	≤0.06 - ≥8	1	1	94
Staphylococcus aureus	Ciprofloxacin	≤0.06 - ≥8	0.5 - 1	0.5 – 0.57	67
	Norfloxacin	0.25 - 4	4	2	90-95
	Ofloxacin	≤0.06 - ≥8	1	0.5	41-96
	Lomefloxacin	≤0.06 - ≥8	1	0.5	94
Enterococci spp.	Ciprofloxacin	0.12 - 8	2 - 8	2	34-81
	Norfloxacin	4 - 8	8	8	44-84
	Ofloxacin	0.25 - 8	8	4	48-84
	Lomefloxacin	0.5 - 8	8	8	4
Escherichia coli	Ciprofloxacin	≤0.06 - ≥8	0.12	≤0.06	88-98
	Norfloxacin	0.03 - 8	0.25	0.12	88-91
	Ofloxacin	≤0.06 - ≥8	0.25	0.12	88-99
	Lomefloxacin	≤0.06 - ≥8	0.25	0.12	98
Proteus mirabilis	Ciprofloxacin	≤0.06 -8	0.12	≤0.06	94-100
	Norfloxacin	0.06 – 0.5	0.5	0.06	100
	Ofloxacin	≤0.06 -8	0.25	0.12	98-100
	Lomefloxacin	≤0.06 -8	0.5	0.25	97
Klebsiella pneumoniae	Ciprofloxacin	≤0.06 -8	0.12	≤0.06	86 - 100
	Norfloxacin	0.064 - 64	8	0.5	94-100
	Ofloxacin	≤0.06 -8	2	0.25	93-100
	Lomefloxacin	≤0.06 -8	2	0.25	90
Pseudomonas aeruginosa	Ciprofloxacin	≤0.06 -8	0.5 - 4	0.25 – 0.5	83-100
	Norfloxacin	0.25 - 1	0.5	0.5	99-100
	Ofloxacin	≤0.06 -8	8	1	69-94
	Lomefloxacin	≤0.06 -8	8	2	64

MIC = minimum inhibitory concentration.

is the lowest antibacterial concentration that inhibits bacterial growth, with a disc-diffusion method it is based on zones of inhibition of growth around antibacterial-impregnated discs under standard growth and media conditions.] The antibacterial agents tested included ofloxacin, ciprofloxacin and norfloxacin. The 3 agents were equally potent against Gram-negative bacteria and all were very effective against most commonly isolated Gram-negative bacteria. The relative activities against Gram-positive organisms were in decreasing order, ofloxacin, ciprofloxacin and norfloxacin. All 3 agents were highly effective against most commonly isolated *Staphylococci* spp. (*S. aureus*, *Staphylococcus epidermidis*). Ofloxacin had similar efficacy against Gram-positive and Gram-negative organisms whereas norfloxacin and ciprofloxacin were more effective against Gram-negative bacteria.[17] Bower et al.[16] found similar susceptibility percentages against Gram-positive organisms (ofloxacin: 84.1%, ciprofloxacin: 76.1%, norfloxacin: 73.4%).

Jensen et al.[17] also tested the susceptibility to oxacillin, as an indicator of multiple antibacterial resistance. Resistance to oxacillin occurred in 18% of the staphylococcal strains tested. The fluoroquinolones used, along with most of the antibacterials tested, were notably less effective against the oxacillin-resistant than the oxacillin-sensitive *Staphylococci* spp.[17]

Everett et al.[18] found similar results to those of Jensen et al.[17] The *in vitro* efficacy of the fluoroquinolones was greater than that of either the aminoglycosides or erythromycin. In addition, they found that more isolates were susceptible to ofloxacin than to ciprofloxacin or norfloxacin.

Prosser and Beskid[15] investigated the activities of 4 fluoroquinolones against 25 129 bacterial isolates. They tested bacterial isolates from different infections and found the fluoroquinolones: fleroxacin, ciprofloxacin, ofloxacin and lomefloxacin were all equally effective against Gram-negative bacteria, but ofloxacin and ciprofloxacin were more active than the other fluoroquinolones against the Gram-positive *Streptococci* spp. Antibacterial susceptibilities for isolates from patients with bacterial keratitis gave an overall susceptibility to ofloxacin, ciprofloxacin and norfloxacin, of 88.2%, 82.3% and 80.4%, respectively.

Levofloxacin is potent and has lower MIC_{90} (MIC for 90% of isolates) values than ofloxacin against all ocular pathogens. Levofloxacin is the S-isomer of ofloxacin, it has greater binding affinity to the bacterial DNA-DNA gyrase complex and thus is more potent in inhibiting bacterial DNA synthesis.[13]

Goldstein et al.[8] reviewed 825 patients with bacterial keratitis from 1993 to 1997. They found that between 31.6 and 61.1% of streptococcal species were resistant to fluoroquinolones. Some streptococcal species continue to show a high degree of resistance to the fluoroquinolones, raising concern about the proposed use of monotherapy in the treatment of infectious keratitis.

Fluoroquinolones have also been shown to inhibit many intracellular pathogens, such as *Chlamydia trachomatis, Chlamydia pneumoniae, Mycoplasma pneumoniae, Mycoplasma hominis, Legionella pneumoniae*[19] and *Mycobacterium tuberculosis*.[20]

With regard to *Mycobacteria* spp., excellent bactericidal activity has been found against most strains of *M. tuberculosis, Mycobacterium leprae, Mycobacterium bovis, Mycobacterium kansasii, Mycobacterium marinum* and *Mycobacterium xenopi* with MIC values for ciprofloxacin or ofloxacin ranging from 0.5 mg/L to 2.0 mg/L. Strains of *Mycobacterium avium intracellulare* complex are less susceptible to the fluoroquinolones.[21] Ciprofloxacin and ofloxacin are the quinolones most often evaluated and recommended in mycobacterial diseases.[12] Resistance of *Mycobacteria* spp. to fluoroquinolones is relatively rare but the ready emergence of resistance can occur if the agents are used as a monotherapy. When used in the treatment of mycobacterial diseases, these drugs should be used in combination with at least one other active agent and they should be used only when effective alternative drugs are not available.[21]

Quinolones have not, so far, been considered the drugs of choice for anaerobic infections, although recent studies suggest that they may be more effective than previously thought. Smith et al.[14] demonstrated good activity for ciproflocacin, sparfloxacin and oflocaxin against *Propionibacterium acnes*, a Gram-positive, non-spore-forming, anaerobic bacillus, which has been associated with infections of intraocular lens implants. However, other antibacterials, such as newer β-lactam agents and cephalosporins are more active than the fluoroquinolones against *P. acnes*.[14]

2. Pharmacokinetics

2.1 Systemic

The fluoroquinolones are rapidly absorbed after oral doses with peak serum concentrations appearing 1 to 2 hours after administration. There is a linear dose-response relationship that aids in predicting serum concentrations. Serum concentrations after intravenous doses overlap with those

from oral doses of the same size 2 to 3 hours after administration.[1] After oral administration ofloxacin appears to have a greater than 90% availability with little biotransformation and good tissue penetration.[22]

All quinolones bind divalent cations, especially magnesium, which may lead to a reduced absorption if, for example, they are consumed with magnesium containing antacids.[1]

Fiscella et al.[13] compared the vitreous concentrations of levofloxacin achieved after one 500mg tablet with those achieved after two 500mg tablets given 12 hours apart. At approximately 120 minutes the inhibitory vitreous concentrations against a variety of Gram-negative organisms were reached in the group receiving one tablet. Approximately 120 minutes after the second tablet, inhibitory concentrations in the vitreous were achieved against most organisms responsible for endophthalmitis, except *Enterococcus faecalis* and *P. aeruginosa*.

Studies assessing intravenous antibacterial administration in treating endophthalmitis have not established their effectiveness, especially since many do not produce inhibitory concentrations in the vitreous cavity. Levofloxacin is usually administered orally once daily. In a few studies, twice-daily administration has been used but generally it is not required to ensure a clinical cure. The half-life of levofloxacin is long enough for once daily administration. The length of treatment and whether more than one daily dose would be required to produce continuous intraocular inhibitory concentrations remains to be determined.[13]

2.2 In Tears

The concentration of topically applied drugs in the tear film is very variable. This reflects the effects of the small size of the conjunctival sac (7 to 10ml), dilution of the drug by fresh tears during normal blinking and reflex tearing secondary to irritation. The pH values of the different formulations of the fluoroquinolones as eye drops may affect tear dynamics. Ciprofloxacin is the most acidic and ofloxacin the least. It would be expected, but has not been proven, that the induction of tear flow caused by local pH related irritations, should be lowest with ofloxacin eye drops.[23]

Green et al.[24] studied ciprofloxacin concentrations in rabbit tears after topical administration. The tear samples were collected and analysed at 5, 10 and 30 minutes and 1, 2, 4 and 6 hours after topical drug application. Peak ciprofloxacin concentrations were seen 5 minutes after administration and then declined. The ciprofloxacin concentrations in tears were substantially higher throughout the length of the study than the MIC_{90} for most ocular pathogens including *S. aureus* and *P. aeruginosa*.[24]

Borrman et al.[25] found that the concentration of ofloxacin in the tear film ranged from 5.7 to 3.1 mg/L over 40 minutes after topical administration.[25]

2.3 Corneal Pharmacokinetics

The cornea acts as a barrier to the penetration of many topically applied substances. It consists of a hydrophilic stroma between a hydrophobic epithelium and endothelium. Corneal and aqueous fluoroquinolone pharmacokinetics can be considered simultaneously since, after topical administration, aqueous concentrations reflect processes ongoing in the cornea. Reports on the concentration of the fluoroquinolones in the cornea and aqueous humour have shown wide variation. This variability has been attributed to the frequency of application, drug formulation, concentration, presence or absence of an epithelial defect, mode of fluoroquinolone application, and the measurement technique.

Diamond et al.[26] investigated the intracorneal concentrations of ciprofloxacin, norfloxacin and ofloxacin after topical administration. After applying 4 drops of each agent over a 1-hour pre-operative period they found concentrations of ciprofloxacin, norfloxacin and ofloxacin in the cornea of 0.60, 0.54 and 0.81 mg/kg, respectively. All 3 agents achieved corneal concentrations above or close to the MIC_{90} values for most of the Gram-negative organisms they listed. The exceptions were for *Acinetobacter* spp. and *P. aeruginosa*, for which only ciprofloxacin reached the MIC_{90}. Corneal concentrations of norfloxacin were below the

MIC_{90} values for all the Gram-positive bacteria tested and none of these fluoroquinolones achieved corneal concentrations equivalent to the MIC_{90} values for *Streptococci* spp. or *E. faecalis*. They concluded that ciprofloxacin and ofloxacin have a clear advantage over norfloxacin.[26] Von Keserlingk et al.[23] and Donnenfeld et al.[27] investigated the concentrations of the same 3 agents in the aqueous humour after topical administration.[23,27] Donnenfeld et al.[27] found aqueous ofloxacin concentrations to be 4.5 times greater than those of norfloxacin or ciprofloxacin. Von Keyserlingk et al.[23] obtained similar results. This difference has been attributed to the greater solubility of ofloxacin and its higher pH of 6.4 compared with pH values of 4.5 and 5.3, respectively, for ciprofloxacin and norfloxacin.

Frequency of application is clearly important in attaining adequate antibacterial concentrations. For example, Donnenfeld et al.[27] obtained concentrations in the aqueous of 0.078 to 0.625 mg/L after the application of 2 drops of ofloxacin into the fornix, 90 and 30 minutes before sampling, with a mean of 0.338 mg/L, whereas Grayson et al.[28] used 4 drops over 1 hour prior to sampling at surgery and obtained mean concentrations of 0.888 mg/L (range 0.107 to 1.49). Bouchard et al.[29] achieved high concentrations of 0.143 to 2.4 mg/L (mean 0.793 mg/L) at the time of surgery after using one drop every 5 minutes for 5 doses before surgery and every 2 hours the day before surgery.

The techniques used to measure fluoroquinolone concentration may also account in part for some of the differences between studies assessing corneal fluoroquinolone concentration. Donnenfeld et al.[27] found a mean ofloxacin concentration of 4.51 mg/L, lower than the 5.28 mg/kg found by McDermott et al.[30] for ciprofloxacin. Donnenfeld et al.[27] enzymatically digested the corneas prior to analysing them, whereas McDermott et al.[30] mechanically ground the corneas. It is unclear however, what portion of the ciprofloxacin and ofloxacin concentrations were from antibacterial precipitated on the corneal surface.[27] Corneal precipitation occurs most commonly with ciprofloxacin followed by norfloxacin. The lower pH values of these substances allow them to crystallize out on the corneal surface.

Even higher aqueous concentrations can be obtained if different drug concentrations are used (see section 2.3). For example, Reidy et al.[31] used ciprofloxacin 0.75% every 15 minutes and then every 30 minutes for a total of 22 doses and obtained an aqueous concentration of ciprofloxacin at 1 hour of 30.5 mg/L (standard deviation 5).

Higher fluoroquinolone concentrations may also be achievable in the presence of an ulcerative keratitis where there is an epithelial defect. Price et al.[32] compared corneal tissue ciprofloxacin concentrations in patients exposed to 3 ciprofloxacin administration regimens before undergoing penetrating keratoplasty. The results are shown in table II and demonstrate well the effect of a denuded epithelium allowing increased fluoroquinolone corneal penetration. O'Brien et al.[33] also found a 3-fold increase in aqueous ciprofloxacin concentrations in rabbits after debridement of the corneal epithelium. The integrity of the corneal epithelium is obviously an important consideration in the treatment of patients with bacterial keratitis and other causes of corneal epithelial irregularity.

The mode of antibacterial application is a further issue determining tissue drug concentrations. Pamel and Perl[34] investigated the use of a collagen shield delivery system and found them successful in achieving a higher antibacterial concentration in the corneal stroma (mean ciprofloxacin concentration 22.09 mg/L) compared with a standard dropper system. Adequate concentrations of ciprofloxacin can also be achieved in the anterior chamber following oral, intravenous or topical administration.[33] Higher concentrations have been achieved with ofloxacin with better therapeutic action against *S. epidermidis* and *S. aureus*,[27,35] than ciprofloxacin and norfloxacin.[35]

Usually, the efficacy of an ophthalmic antibacterial agent is determined using non-ocular bacterial isolates and interpreting susceptibilities from standards based on the concentrations achieved in the blood, serum and urine.[36] However, the effi-

Table II. Summary of corneal and aqueous pharmacokinetics of fluoroquinolones[26,27,29,31,32]

Fluoroquinolone used	Strength (%)	Integrity of corneal epithelium	Frequency of drop administration	Corneal concentration
Ciprofloxacin	0.3	Intact	4 drops, 1h pre sampling	0.6 mg/kg
Norfloxacin	0.3	Intact	4 drops, 1h pre sampling	0.54 mg/kg
Ofloxacin	0.3	Intact	4 drops 1h pre sampling	0.81 mg/kg
Ciprofloxacin	0.3	Intact	1 drop, every 4h for 24 hrs pre sampling	0.00882 mg/kg
Ciprofloxacin	0.3	Intact	2 drops, every 15 mins for 4 hrs pre sampling	0.1662 mg/kg
Ciprofloxacin	0.3	Denuded	2 drops, every 15 mins for 4 hrs pre sampling	0.9383 mg/kg
				Aqueous concentration
Ofloxacin	0.3	Intact	2 drops at 90 and 30 mins pre sampling	0.078-0.625 mg/L
Ofloxacin	0.3	Intact	4 drops over 1h pre sampling	0.888 mg/L
Ofloxacin	0.3	Intact	1 drop every 2h and then every 5 mins for 5 doses pre sampling	0.143-2.4 mg/L
Ciprofloxacin	0.75	Intact	1 drop every 15 mins and then every 30 mins for 22 doses pre sampling	30.5 mg/L

cacy of an antibacterial in the cornea is dependent, not only on the MIC_{90} for the organism, but also on the stromal drug concentration. Ellner and Nev[37] proposed the use of the inhibitory quotient (IQ) as a means of determining antimicrobial efficacy. The IQ is the concentration of a specific antimicrobial reached in the tissue (cornea) divided by the MIC_{90} of the antimicrobial. The antimicrobial efficacy increases with the IQ.[37] A time-kill study determines both the overall killing capability and the time required to kill. Thus the contact time is important as well as the concentration. Under ideal conditions a steady state concentration from 8 to 24 hours is required to eradicate bacteria from an infected cornea. Sub-optimal concentrations may support continued bacterial growth, so that positive cultures may be obtained in the presence of treatment.

Kowalski et al.[36] proposed using bacterial susceptibility to the concentrations achieved in the cornea, that is the $Cornea_{99}$. The $Cornea_{99}$ is the concentration of an antimicrobial within the cornea that can be exceeded in 99% of human corneas after topical administration.[36] This value can be compared with the MIC_{90} for a given micro-organism. Using previously published reports of corneal fluoroquinolone concentrations, the $Cornea_{99}$ of ciprofloxacin is 3.57 mg/L and for ofloxacin it is 2.22 mg/L. The reported serum concentrations are 1.0 mg/L and 2.0 mg/L. The maximal attainable human corneal concentrations after topical administration are 25.3 mg/L and 21.87 mg/L.[12,27,30,36]

Importantly, metal ions can significantly reduce the bioavailability of fluoroquinolones. Such ions are present both in ocular fluids and many irrigating fluids, for example BSS-Plus. Osato[38] showed that the clinical efficacy of ciprofloxacin against deep ocular infections may not be as good as laboratory antibacterial susceptibility testing would indicate because of the interaction of the drug with the metal ions in ocular fluids. This was not the case with ofloxacin which seemed unaffected by the ionic composition. For an overview of corneal pharmacokinetics, please see table II.

3. Superficial Ocular Infections

3.1 Conjunctivitis and Blepharitis

Bacterial conjunctivitis and blepharitis are common external ocular infections that can be caused by many types of micro-organisms. Everett et al.[18] found 92% of bacterial strains isolated from 173 patients with blepharitis were Gram-positive compared with 8% that were Gram-negative. They also found that 75% of micro-organisms (289 of 385 bacterial isolates) isolated from patients with conjunctivitis were Gram-positive. These authors compared the *in vitro* susceptibility of these bacterial isolates recovered from patients with conjunctivitis and blepharitis to new topical antibacterials,

such as ofloxacin, ciprofloxacin and norfloxacin with established topical antibacterials, such as chloramphenicol. Chloramphenicol was ranked highest in terms of percent susceptibility of recovered isolates to single agents or combinations. Of the fluoroquinolones tested, ofloxacin appeared to provide the broadest coverage with 88% of isolates susceptible, compared with 85% for ciprofloxacin and 82% for norfloxacin.[18] However, *in vitro* efficacy does not necessarily correlate with clinical outcome measures, such as time to resolution of clinical signs or time to clearance of bacteria from the eye.

Agius-Fernandez et al.[39] investigated the use of topical lomefloxacin versus topical chloramphenicol in the treatment of acute bacterial conjunctivitis. They concluded that lomefloxacin 0.3% eye drops instilled twice daily were as effective and well tolerated as chloramphenicol 0.5% eye drops instilled 5 times daily in the treatment of acute bacterial conjunctivitis.[39]

Friedlander[40] found that topical ofloxacin use in patients with blepharitis and conjunctivitis resulted in a significant clinical improvement in symptoms. He determined that ofloxacin eye drops could be used either 2 or 4 times per day with good effect. Despite these findings the author is still a proponent of lid scrubs/hygiene as the first line treatment in blepharitis.

The effectiveness of fluoroquinolones in improving conditions such as blepharitis must be balanced against the potential for causing resistance.

Some of the fluoroquinolones are suitable agents for the treatment of chlamydial infection. Sparfloxacin and tosufloxacin are the most effective against *Chlamydia* spp. (MIC values of 0.063 to 0.125 mg/L), ofloxacin and ciprofloxacin have moderate activity but norfloxacin is ineffective.[41]

3.2 Bacterial Keratitis

Fluoroquinolone use has become particularly predominant in the treatment of presumed bacterial keratitis, an important cause of ocular morbidity and visual loss. After specimen collection, treatment of a presumed bacterial ulcerative keratitis is usually commenced with an antibacterial before identification and bacterial sensitivity testing. A wide range of organisms can be responsible and as such it is important to have broad-spectrum antibacterial cover. In the patient where no specific organism has been identified, the choice of antibacterials with good broad spectrum activity, such as the fluoroquinolones where there is an 85 to 95% bacterial susceptibility,[11] has increased their use in the treatment of ocular infections. In our unit, ciprofloxacin is first choice in the treatment of corneal ulcers in combination with teicoplanin if there is clinical suspicion of a Gram-positive organism or if there is no sign of clinical improvement after 48 hours.

Bower et al.[16] investigated the use of ciprofloxacin, norfloxacin and ofloxacin as single therapy and as a combination therapy with cefazolin, in the treatment of bacterial keratitis. They found the cefazolin-fluoroquinolone combination had greater predicted susceptibility than any of the single agent therapies. The cefazolin/fluoroquinolone combination was comparable to a cefazolin/gentamicin combination. In contrast, fluoroquinolone monotherapy has shown equivalence to fortified tobramycin/cefazol in the treatment of bacterial keratitis.[33]

However, single agent therapy with fluoroquinolones is limited because of a level of resistance seen in Gram-positive organisms. In the study of Bower at al.,[16] ofloxacin was found to have the greatest activity against Gram-positive organisms with 84.1% susceptible, 76.1% were susceptible to ciprofloxacin and 73.4% to norfloxacin. Gram-negative organisms were 100% susceptible.

The fluoroquinolones are less effective against *Streptococcus pneumoniae*.[33,42-45] In the study by O'Brien et al.,[33] ulcers caused by *S. pneumoniae* failed to respond in 2 out of 5 patients receiving ciprofloxacin 0.3% compared with 1 out of 10 receiving fortified tobramycin 1.3% and cefazolin 5% as combination therapy. Leibowitz found that 9.1% of 148 patient ulcers did not respond to ciprofloxacin.[42] Donnenfeld et al.[35] advocates that patients at risk of having an ulcer infected with *S.*

pneumoniae should also receive a penicillin or β-lactam antibacterial, or bacitracin or vancomycin. We have found topical teicoplanin to be an effective agent in these situations. Infections of the eye known to be associated with *S. pneumoniae* include suture abscesses after penetrating keratoplasty, dacryocystitis, filtering bleb infection,[45] and infections associated with pseudophakic bullous keratopathy and crystalline keratopathy.[46] Similarly, patients with suspected methicillin resistant *S. aureus* should be treated with fortified vancomycin.[27,45,46]

Enterococci spp. and anaerobes may also be less susceptible.[47]

Ciprofloxacin and ofloxacin appear to have similar effectiveness in the treatment of Gram-negative keratitis.[33,48]

As with the treatment of conjunctivitis, higher corneal and aqueous concentrations are achieved with more frequent applications. More frequent application in the initial period of an infection with shorter duration of treatment is likely to be beneficial with fewer subsequent adverse effects. This is apparent when fluoroquinolones are compared with fortified antibacterials in the treatment of bacterial corneal ulcers. In this situation, treatment with a fluoroquinolone (ciprofloxacin) required an average of 4 days compared with 6 days with a fortified antibacterial (tobramycin 1.3% and cefazolin 5%) combination.[49] However, fluoroquinolones may be associated with more complications in patients with large corneal ulcers.[49]

3.3 Safety and Toxicity

Four fluoroquinolones are currently available for topical ophthalmic use: ciprofloxacin 0.3% (Alcon), norfloxacin 0.3% (Merck Sharp & Dohme), ofloxacin 0.3% (Allergan) and lomefloxacin 0.3% (CIBA Vision). These are available in Europe and North America.

3.3.1 Corneal Epithelium

It is established that preservatives in antimicrobial solutions have adverse effects on corneal epithelial wound healing,[50-52] often leading to a toxic keratitis manifested as punctate lesions with a persistent epithelial defect. Mechanisms of toxicity include membrane injury due to a detergent effect, drug binding to membrane sterols and drug-induced free radicals causing peroxidative damage to membrane lipids. Although fortified drops do not contain preservatives, they may also be toxic to the epithelium and delay healing. The use of fortified antibacterials is controversial[53] as the increased tonicity causes reflex tearing which may lead to reduced corneal penetration[54] and may result in epithelial toxicity with reduced healing.[55]

Fluoroquinolones have become a potential replacement to combination antibacterial treatment of keratitis. For example, when comparing fortified tobramycin/cefazolin with ciprofloxacin, Hyndiuk et al.[53] used ciprofloxacin every 30 minutes for 6 hours, then hourly up to day 4, 2-hourly for days 4 and 5, and 4-hourly days 6 to 14. They found that ciprofloxacin was equivalent to fortified tobramycin/cefazolin both in terms of clinical efficacy (resolution of clinical signs and symptoms), 91.5% *vs* 86.2%, and time to cure. Importantly, ciprofloxacin caused less discomfort.

Infrequent ocular adverse effects associated with quinolones are discomfort, chemosis, hyperaemia, eyelid oedema and superficial punctate keratitis.[42,45,56] The fluoroquinolones, however, appear to have minimal toxicity to the epithelium. Although ciprofloxacin precipitation is relatively common, occurring within 24 hours to 16 days in between 13%[42] and 16%[45] of patients, it appears to have no effect on treatment outcome. Resolution usually occurs within 5 days in 50% of patients and within 2 weeks in the rest. Crystalline corneal deposits representing drug precipitation have also been seen with norfloxacin.[48] The lower pHs of ciprofloxacin and norfloxacin allow them to precipitate out when administered into the near neutral tear sac. Konishi et al.[56] reported a case of corneal ulceration associated with norfloxacin deposit. Factors thought to be of importance in the causation of this antibacterial precipitate, in addition to the low solubility at neutral pH of norfloxacin, were frequent administration of the antibacterial, corneal exposure and poor tear mixing attributable

to incomplete blinking, and low reflex tearing attributable to decreased corneal sensation. The precipitate is unrelated to the gender, organism cultured, size or depth of ulcer, or time to resolution.[42,45]

In situations where fluoroquinolone-resistant organisms are present, additional therapy, such as with vancomycin or teicoplainin, or replacement therapy should be considered. However there have been conflicting reports regarding vancomycin use since it can damage the corneal epithelium. Petroutsos et al.[57] found retarded healing in 3.1% of patients receiving vancomycin, while Lin and Boehnke[51] found that 5% vancomycin had no effect on epithelial healing. Cefazolin 5% does not appear to retard corneal epithelial healing[52,58] and chloramphenicol 0.5% also was not toxic and did not delay healing.[51,57,59] In the case of gentamicin, however, although 0.3% was not toxic[57] both preserved and nonpreserved 3%, 2%, 1.4% and 1% were toxic.[51,57]

3.3.2 Corneal Endothelium

Kang[60] showed that concentrations of ciprofloxacin, gentamicin or streptomycin at their MIC did not adversely affect endothelial transport in the rabbit. At low concentrations (0.06 to 1 mg/L), fluoroquinolones act by inhibiting bacterial DNA gyrase,[60] but at higher concentrations (>100 mg/L) they can inhibit eukaryotic gyrase as well.[61] Stevens et al.[2] showed that an intravitreal ciprofloxacin concentration of >100 mg/L led to a dose-dependent acute corneal decompensation in aphakic vitrectomised rabbit eyes. Stromal oedema occurred when >25μg (114 mg/L or 308 mmol/L) concentrations were injected into the anterior chamber of rabbits. Using transendothelial electrical potential difference as a reflection of endothelial pump activity, Fischbarg[61] showed that ciprofloxacin had a significantly higher threshold (50 x MIC_{90} 0.03 to 2 mg/L) than gentamicin (40 x MIC_{90} 0.5 to 50 mg/L) and streptomycin (2 x MIC_{90} <200 mg/L.

McDermott et al.[62] found that fluoroquinolones concentrations below 30 mg/L were nontoxic after 3 hours of exposure.

4. Infections of the Vitreous and Retina

4.1 Pharmacokinetics

Data from studies on animals and humans show significant penetration of fluoroquinolones into the vitreous after systemic administration.[42,63-66] Although therapeutic concentrations in the vitreous are achievable, they are less than those attained in the anterior chamber after topical or systemic administration.[35,39,67,68] The intravitreal concentrations attained depend on the species and patient,[42,63-66] the particular fluoroquinolone, the administration regimen,[65,66] previous surgery, and the presence of infection, inflammation, trauma or the breakdown of the blood-retinal barrier.[27,63,66,69]

In an animal model, Ng et al.[70] showed that systemic trovafloxacin reached a mean vitreous peak concentration of 0.55 ± 0.09 mg/L in infected eyes, reflecting a penetration of 36%. Treatment with systemic fluoroquinolones without intravitreal antibacterials improved clearance of organisms from the vitreous but was not sufficient to prevent irreversible retinal damage from infection. Alfaro et al.[65] demonstrated that ocular trauma increased the intravitreal concentration of ciprofloxacin after intravenous administration to a mean between 0.31 to 0.37 mg/L compared with 0.12 to 0.18 mg/L in control animals. However, this required doses of ciprofloxacin above those used in humans on a bodyweight basis.[65]

In humans, after a single oral dose of ciprofloxacin 750mg, El Baba et al.[63] showed a mean vitreous concentration of 0.37mg/L after 5 to 12 hours and Keren et al.[64] found a mean concentration of between 0.17 mg/L to 0.21 mg/L after 4 to 8 hours, depending on the measurement technique. Lesk et al.[66] showed that patients receiving 2 oral doses of ciprofloxacin 750mg 12 hours apart attained mean vitreous concentrations of 0.59 mg/L after 4 to 12 hours and mean sub-retinal fluid concentrations of 0.71 mg/L. These values were approximately 15% of the mean serum value.[66] However, all studies show considerable individual

variation in the achieved intravitreal concentrations.

Topical ofloxacin every 30 mins for 4 hours in patients with bullous keratopathy associated with aphakia or anterior chamber lenses resulted in mean anterior vitreous humour concentrations of 0.37 mg/L (range 0.05 to 0.9). Higher vitreous concentrations (2.55 mg/L, range 0.28 to 4.97) were achieved with topical and oral ofloxacin (400mg 12 hourly for 3 doses up to 2 hours preoperatively).[27] These high vitreous concentrations may reflect improved posterior diffusion in the absence of the crystalline lens or lens capsule, particularly with a high concentration of ofloxacin in the anterior chamber due to an enhanced penetration of ofloxacin through an abnormal cornea. However, posterior vitreous concentrations may be much lower.

Fluoroquinolones appear to bind to melanin well. Important issues arising from this are whether or not this causes a toxic effect in the short or long term and does it change the antimicrobial activity of the fluoroquinolones? These issues are still under investigation. Mochizuki et al.[68] researched the effects of norfloxacin on the retina in rabbits. They used a comparison of albino and pigmented rabbits and found much higher norfloxacin levels in the iris, ciliary body and chorioretinal tissues of the pigmented rabbits than the albino ones. In addition, electronretinographic changes were found in albino rabbits suggesting that norfloxacin bound with melanin in the pigment epithelium has less effect in pigmented rabbits than nonpigmented ones in an acute phase.[68]

4.2 Safety and Toxicity

In animal models, fluoroquinolones (ciprofloxacin and norfloxacin) have been used intravitreally with both good effectiveness[66] and safety.[2,71,72] Stevens et al. used intravitreal doses of ciprofloxacin 100μg in rabbit eyes (equivalent to approximately 200μg in the larger human eye) without toxicity.[2] Loss of outer rod segments and atrophy of inner rods in rabbits only occur with intravitreal doses of ciprofloxacin 1000μg (550 mg/L).

Although ciprofloxacin is not currently licensed for intravitreal use in humans, it is being used in our unit in most patients with endophthalmitis.

5. Endophthalmitis

Penetration of systemic fluoroquinolones into the vitreous is relatively good compared with other antibacterials.[73] Studies suggest that the mean concentrations attained in the vitreous are above the MIC_{90} for most of the likely causative organisms.[63,66,74] However, the concentrations are variable and not predictably above the MIC_{90} of probable organisms causing post-surgical endophthalmitis (*S. aureus, S. epidermidis* and *S. pneumoniae*).[36,75,76] In addition, these concentrations may only be attained on repeat doses.[65,66]

It seems reasonable to aim for a concentration of antibacterial well above the MIC_{90} in view of the poor host response in the vitreous and the potential for rapid retinal damage as a result of infection.[2] Extrapolation from the treatment of meningitis suggests effective treatment requires a concentration 2 to 10 times the MIC_{90} for most bacteria.[74] Even with the fluoroquinolones, systemic treatment alone would not achieve these concentrations. Even though there has been success in treating endophthalmitis caused by less virulent organisms, such as *S. epidermidis*, without intravitreal antibacterials,[77] it is still necessary to use intravitreal antibacterials in the initial treatment of endophthalmitis.[36] A variety of antibacterial agents are used for intravitreal injection. Ciprofloxacin 0.2mg in 0.1ml may be used in conjunction with teicoplanin 1mg in 0.1ml to ensure good cover of Gram-negative and Gram-positive organisms, respectively.

The Endophthalmitis Vitrectomy Study showed that after the initial use of intravitreal antibacterials, there was no benefit from additional intravenous agents.[77] This may have been the result of limited penetration into the vitreous of effective concentrations of the antibacterials used (amikacin and ceftazidime).[73] Additional oral ciprofloxacin after intravitreal ciprofloxacin may help maintain intravitreal concentrations to reduce the need for further intravitreal injections. Peak vitreous con-

centrations occur approximately 4 to 8 hours after administrations of systemic fluoroquinolones.[63,70]

There have been no randomised clinical trials to show whether prophylactic systemic antibacterials are of benefit in penetrating ocular trauma. *Bacillus cereus* is often associated with traumatic bacterial endophthalmitis and ciprofloxacin is effective against this organism with an MIC_{90} of 1mg/L.[78] It is also effective against Enterobacteriaciae and *P. aeruginosa*, with MIC_{90} values of 0.01 to 0.13 mg/L and 0.004 to 2.0 mg/L, respectively.[78] Systemic fluoroquinolones such as ciprofloxacin would therefore be useful because of their penetration into the vitreous and spectrum of activity against probable causative organisms in penetrating ocular trauma.[63,65,66,70]

6. Conclusion

Fluoroquinolones have changed the treatment of ocular infections markedly since their introduction. They are likely to continue to do so as research progresses and newer derivatives with broader spectrums of activity and less likelihood of resistance become available.

The fluoroquinolones have become accepted as effective single antibacterial agents for the treatment of ulcerative bacterial keratitis, except in some cases of presumed streptococcal or methicillin resistant-staphylococcal disease where additional therapy may be needed.

Their use in the treatment of endophthalmitis is well established. It is likely that as fluoroquinolone formulations are further modified, there will be enhanced ocular penetration, particularly after systemic administration.

Acquired resistance to fluoroquinolones is not lost after withdrawal of the antibacterial, suggesting that fluoroquinolones should not be used injudiciously or in subtherapeutic doses.

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