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Review Article

Ciprofloxacin: Rationale for Use in Intraocular Infections

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Abstract

Achieving an effective antimicrobial concentration of a broad spectrum drug by conventional oral or topical route is limited by the barriers of the eye. Systemic drugs are often underused or exploited for ocular use without rationalizing the penetration characteristics of the drug. Lack of clarity or consensus about the underlying mechanisms of drug penetration into the eye translates into attenuated enthusiasm among pharmaceutical researchers and ophthalmic clinicians. This review summarizes the available literature on intraocular penetration of ciprofloxacin following different application routes, mainly systemic administration, and the rationale for its use in intraocular infections.

INTRODUCTION

Ciprofloxacin is a synthetic fluoroquinolone antibacterial active against a broad spectrum of Gram-positive and Gram-negative ocular pathogens. It has proved to be an effective topical and systemic antimicrobial as a single agent for treating ocular infections [1-3]. Ciprofloxacin has been suggested for anti-bacterial prophylaxis of endophthalmitis following intraocular surgery as it has demonstrated in vitro activity against Staphylococcus and Bacillus species and most Gram-negative organisms, including Pseudomonas species [4,5]. Like other fluoroquinolone anti-infective agents, ciprofloxacin blocks DNA synthesis in bacteria by inhibiting DNA gyrase [6]. It has demonstrated excellent penetration into tissues such as meninges and bone that are poorly accessible to many other antibiotics. In adults, the toxicity of ciprofloxacin is lower than that of many other commonly used antibiotics, and it has less renal toxicity than the aminoglycosides or vancomycin and fewer allergic reactions than the cephalosporins [7]. However, it can occasionally cause central nervous system excitation [4]. The broad spectrum of activity, low serum protein binding, adequate tissue penetration, favourable pharmacokinetics and relative safety in adults and in the aged following systemic administration provide evidence of the effectiveness of ciprofloxacin for the treatment of bacterial ocular infections [8-10].

Ocular penetration of a drug is affected by the physiological processes involved in guarding the eye against xenobiotics. The presence of blood ocular barriers at the topical, aqueous and retinal routes determines the intraocular concentration of antimicrobial agents in the ocular humours. Because of these barriers, reaching and sustaining an adequate concentration of antimicrobial substances above the minimum inhibitory concentration (MIC) of the invading microbe becomes a formidable task in the treatment of ocular infections. Penetration of most substances from the blood into the vitreous is blocked by the zonula occludens and zonula adherens of the retinal pigment epithelium and the non-fenestrated retinal capillary bed [11]. Most systemically administered antimicrobials used in the treatment of endophthalmitis do not penetrate well into the non-inflamed vitreous humour [12-14]. Data on intravitreal antibiotic levels reached following systemic administration of antibiotics are sparse and comprehensive recommendations for systemic use have yet to be established. This review summarizes the available literature on intraocular penetration of ciprofloxacin following different routes of application mainly systemic administration and the rationale for its use in intraocular infections.

FACTORS INFLUENCING THE INTRAOCULAR PENETRATION OF ANTIBIOTICS

The intravitreal penetration of antibiotics into the eye after systemic administration is limited by two blood-retinal barrier mechanisms: the retinal pigment endothelial cells located within the retinal cell layers (outer barrier) and the retinal capillary endothelial cells (inner barrier) [15]. Penetration into the anterior segment of the eye is limited by the blood-aqueous

barrier, which is characterized by less restrictive properties, resulting in different aqueous and vitreous drug concentrations.

The aqueous bioavailability of most topically applied antibiotics is less than 5% of the applied dosage. One of the critical factors affecting corneal penetration is the degree of ionization of the drug in the tear film pH. Non-specific irritation caused by the drug on the corneal nerves stimulates reflux tear flow, which can substantially decrease corneal penetration. The volume of the eye drop (low volume having better bioavailability) and formulation factors (irritant preservatives, osmolarity, viscosity, bioadhesive nature and pH) are other indicators that govern the intraocular penetration of topically applied antibiotics [16].The lipophilic property of topical antibiotics is enough to penetrate into ocular humours, and the concentration of antibiotic after penetration into the aqueous humour was dependent on the number of doses instilled in human eyes without infection [17-20].

The subconjunctival injection has been reported to be an effective route to reach a higher antimicrobial concentration in the anterior segment of the eye. Subconjunctivally, a given antibiotic was reported to penetrate the eye by direct diffusion [21].The highest drug concentrations in the cornea after subconjunctival injection were reached adjacent to the injection site, and levels were reported to decrease as the distance from the injection site increased [22]. However, subconjunctivally given antibiotics reached exceedingly low levels in the non-inflamed vitreous in humans [23].

Drug permeability across the blood-retinal barrier depends on drug characteristics such as molecular size, lipophilicity, ionization and protein binding. The blood-retinal barrier has been found to be more permeable than the blood-brain barrier owing to morphological differences [15]. Reports say that ocular inflammation following surgery, trauma or infection increases the permeability of antibiotics across the blood-retinal barrier. However, the effects of inflammation on quinolone penetration are not very clear [11].

Elimination of antibiotics from the vitreous occurs via two routes: passive diffusion to the anterior chamber and through the Schlemm's channel (anterior route), and retrograde transport through the blood retinal barrier (posterior route). Clearance pathways from the vitreous depend not only on physicochemical drug properties and ocular inflammation but also on the surgical status [24]. Postoperative aphakia after removal of the lens as well as vitrectomy affect elimination of antibiotics [25].The clearance of intravitreal drugs is faster in aphakic eyes due to the availability of the aqueous pathway for removal of the antibiotic, along with the posterior route [26].

ROLE OF SYSTEMIC ANTIBIOTIC IN ENDOPHTHALMITIS

In the Endophthalmitis Vitrectomy Study 1990, no significant difference in visual acuity was found in patients receiving intravitreal antibiotics followed by intravenous antibiotic therapy compared with patients receiving only intravitreal treatment [27]. However, this finding has been controversial because of the exclusion of patients with severe endophthalmitis and the choice of adjunctive antibiotics such as ceftazidime and amikacin, which have poor activity against the dominant Gram-positive organisms and limited intraocular penetration. After that, only a few studies evaluated the efficacy of systemic antibiotic therapy in endophthalmitis with varying methodologies and results [28,29].

Some recommendations advocate the adjunctive use of systemic antibiotics in severe acute purulent postoperative endophthalmitis, such as vancomycin combined with ceftazidime or imipenem with ciprofloxacin [30,31]. Nevertheless, the use of systemic antibiotics is undisputed for the treatment of endogenous endophthalmitis [32,33].The pharmacokinetic rationale for adjunctive systemic antibiotics is the rapid elimination of intravitreally applied antibiotics with almost complete removal after 24 hours, whereas systemic administration favours intraocular antibiotic accumulation over time.

In contrast to the acute presentation, chronic endophthalmitis cases involving relatively indolent organisms that are difficult to eradicate, such as Propionibacterium acnes, are absolute candidates for systemic antibiotics whose use as adjuncts to vitrectomy has been described [34]. Also, in rare cases progressing to fulminant panophthalmitis, in which there is a risk that the infection may spread to the orbit or other body sites, systemic antibiotics should be administered with consideration of enucleation [35].

PHARMACOKINETICS OF CIPROFLOXACIN IN THE EYE

The pharmacokinetics of antibiotics in the eye is assessed by single concentration measurements in human eyes performed at the time of surgery and rabbit models, allowing for repetitive drug measurements. However, pharmacodynamic index values such as Cmax/ MIC do not necessarily reflect efficacy in the complex microenvironment of the eye. Also, animal studies must be interpreted with caution, as they do not fully reflect the pharmacokinetics in humans. Rabbit ocular pharmacokinetic studies in the literature have shown that the quinolones penetrate into the non-inflamed vitreous better than the beta lactams, aminoglycosides and vancomycin [36-42].

Systemically administered ciprofloxacin has been reported to achieve intravitreal concentrations ranging from 0.2 to 1.4µg/ml. Kowalski and colleagues compared the MIC of bacterial isolates from 66 patients with endophthalmitis and found that ciprofloxacin levels achieved after systemic administration could inhibit all of the Gram negative isolates. Nevertheless, gram-positive pathogens, particularly coagulase negative staphylococci, a much more common cause of endophthalmitis, had more variable susceptibility [11,39]. El Baba et al., in their study, found that following one oral dose of 750 mg of ciprofloxacin before surgery, intravitreal levels above its MIC90 were reached for staphylococcus epidermidis, Bacillus species, and Enterobacteriaceae. However, intravitreal levels never exceeded the MIC90 for Staphylococcus aureus and Pseudomonas [43].

Lesk and colleagues obtained ciprofloxacin levels of 0.51 µg/ml in vitreous, and 0.71 µg/ml in subretinal fluid after two doses of oral ciprofloxacin 750mg, which exceeded the MIC90 of Staphylococcus epidermidis, Propionibacterium species,

Pseudomonasaeruginosa, Proteus mirabilis, and Haemophilus influenzae, as well as the MIC70 of Staphylococcus aureus and Bacillus cereus. They concluded that ciprofloxacin might have a role in the management and prevention of endophthalmitis [4]. Keren and associates demonstrated vitreous ciprofloxacin levels ranging from 0.40 to 0.90 μg/ml, with a mean of 0.56 μg/ml in seven patients who received two doses of ciprofloxacin of 750 mg 12 hours apart [44].

In the study by Cekiç et al., a vitreous ciprofloxacin level of 0.64 ± 0.06 μg/ml was attained following a single 1000 mg oral dose given six hours before surgery. Six initial doses of 2 drops of 0.3% ciprofloxacin ophthalmic solution instilled at a 30 minutes interval followed by three doses at a 60 minutes interval yielded a mean concentration of 0.44 ± 0.07 μg/ml in the aqueous humour, which was comparable with concentrations produced by a single oral dose of 1000 mg ciprofloxacin. The data indicated that topical application of 0.3% ciprofloxacin solution has the potential to achieve microgram levels of drug in the aqueous humour depending on the dosing schedule. However, topical ciprofloxacin yielded a concentration in the vitreous humour of 0.22 ± 0.04 μg/ml after a total of nine doses. They observed that the local administration of ciprofloxacin yielded a vitreous humour concentration of approximately one half the concentration in the aqueous humour. The authors attributed the reduced concentration in vitreous humour to the additional barriers that the drug must penetrate to reach the vitreous space and the larger volume of drug distribution through the vitreous compared with the aqueous space. Nevertheless, the difference in concentration between the two spaces disappeared after oral administration [45].

Madu et al., studied the penetration of ciprofloxacin into the aqueous and vitreous humour following three different modes of systemic administration. Pharmacokinetic analysis was performed using RSTRIP II, a non-linear, least square regression model analysis program. The serum area under the concentration ± time curve (AUC) values for each mode of drug administration were similar: 32.9 μghr ml^{-1} for single dose, 31.9 μghr ml^{-1} for intermittent dose, and 33±8 μghr ml^{-1} for continuous infusion modes. Serum concentrations of ciprofloxacin are observed to be higher after oral administration of 750 mg than after intravenous administration of 400 mg per dose. The percentage penetration into the aqueous and vitreous was also similar (30.5% and 6.5% for a single dose, 31.6% and 7.4% for intermittent doses and 30.0% and 7.5% for continuous infusion). The penetration into the aqueous and vitreous humours was not influenced by the mode of administration. Nevertheless, ciprofloxacin shows only 5-7% penetration into the non-inflamed vitreous. Hence, the drug would need to be given intermittently at high doses to help ensure that concentrations exceeding the MIC are achieved. Vitreous humour ciprofloxacin concentrations achieved were below levels which inhibit most isolates of Staphylococcus epidermidis, the most common isolate in patients with postoperative endophthalmitis [11]. In a study by Morlet et al., the concentrations of ciprofloxacin in both aqueous and vitreous were lower than the MIC90 (0.5 μg/ml) for common bacterial ocular pathogens in many patients after administrationof two doses of 750 mg ciprofloxacin 12 hours apart [46].

Azad, Ravi, and Talwar et al., described a paradigm of management of endophthalmitis consisting of radical vitrectomy, in which complete vitrectomy with shaving of vitreous upto the posterior vitreous base and as close as possible to the ora was carried out followed by injection of silicone oil at the end of the procedure for medium term tamponade [47].They hypothesized that intraocular antibiotic level reached in silicone oil filled eyes would be higher than that reached in non-vitrectomized eyes or vitrectomized eyes without silicone oil. Talwar and colleagues also evaluated the penetration of oral ciprofloxacin in the retrosilicone oil space fluid (RSOF) in silicone oil (SO) filled eyes. The technique for obtaining uncontaminated and undiluted retrosilicone fluid has also been described by them. One dose of 750 mg ciprofloxacin was given to two groups of five patients with vitrectomized eyes with SO endotamponade, 4 hours (group I) and 8 hours (group II) before SO removal. In ten vitrectomized eyes with SO endotamponade (group III) and another ten patients scheduled for vitrectomy for the first time (group IV), two 750-mg doses had been given every 12 hours, with the last dose 12 hours before surgery. The mean drug concentration in the RSOF was 0.34 ±0.09, 0.37± 0.04, 0.84 ± 0.29, and 0.44 ± 0.11 μg/mL in groups I, II, III, and IV, respectively. Ciprofloxacin level of 0.8 ug/mL was considered as the MIC90 for common ocular pathogens, including Staphylococcus aureus, Streptococcus, and Pseudomonas, based on the results of previous studies. Intraocular ciprofloxacin levels greater than the MIC90 for these pathogens were reached in 6 of the 10 eyes in group III. In contrast, none of the eyes in group IV (non-vitrectomized eyes) reached an intraocular concentration more than 0.8 ug/mL. This is despite the fact that eyes in group III were aphakic except one, which was pseudophakic, compared with group IV where all eyes were phakic. It is well known that clearance of drugs from the vitreous is faster in aphakiceyes due to the availability of the aqueous pathway for removal of the antibiotic, along with the posterior route. However, despite this, the antibiotic concentrations were higher in the RSOF of silicone oil filled eyes. The mean serum concentration was 1.29 ± 0.63, 1.08 ± 0.14, 1.93 ± 0.84, and 1.34 ± 0.55 μg/mL in groups I, II, III, and IV, respectively, with no statistically significant difference between groups III and IV. The ratio of intraocular to serum antibiotic levels in patients with SO-filled eyes was observed to be 0.46 ± 0.11 in patients in group III and was greater than the ratio of the concentration of ciprofloxacin in the vitreous to the serum concentration in group IV (0.35 ± 0.10). It was 31% greater than that in non-vitrectomized eyes, which suggested that eyes with SO endotamponade were likely to have significantly higher intraocular levels of antibiotic than non-vitrectomized eyes in the presence of similar serum antibiotic levels, due to accumulation of the drug in the retro-SO space in SO-filledeyes. Ciprofloxacin levels in the RSOF in SO-filled eyes after oral administration of two doses of 750 mg of ciprofloxacin were found to exceed the MIC90 for most bacterial species and were higher than levels reached in the vitreous in non-vitrectomized eyes. The presence of silicone oil in the vitreous cavity decreases the volume available for dilution of the intraocular antibiotic. It was hypothesized that this compartmentalization of the vitreous cavity by SO would help to maintain therapeutic antibiotic levels of ciprofloxacin in the RSOF after systemic administration and might have a role in managing intraocular infection in patients

with SO-filled eyes [48].The study also suggested that it takes two doses of 750 mg of ciprofloxacin given at 12 hourly intervals to reach high intraocular concentrations of the antibiotic even in silicone oil filled eyes.

Table 1 shows the MIC90 of different bacterial species for ciprofloxacin studied by various investigators.[44,49] Ciprofloxacin vitreous levels have good activity against Staphylococcus aureus, Staphylococcus epidermidis, Bacillus, Pseudomonas, Klebsiella, and Propionibacterium species.

Table 1: MIC90 of different bacterial species for ciprofloxacin

Species of bacteria	MIC90 (µg/ml)
Staphylococcus aureus	0.57 – 0.79
Pseudomonas	0.50 – 0.62
Streptococcus pyogenes	0.78
Staphylococcus epidermidis	0.25 – 0.37
Propionibacterium acnes	0.35
Klebsiella	0.295
Proteus	0.06 – 0.26
Bacillus cereus	0.25
Enterobacter	0.20
Serratia	0.12
Escherichia coli	0.02-0.08
Hemophilus influenzae	0.01

CONCLUSION

Existing literature on the intravitreal concentration of systemic ciprofloxacin following systemic administration suggests that the values reached are not consistently higher than the MIC90 values for most common ocular pathogens. Use of silicone oil endotamponade seems to increase the intraocular antibiotic levels reached substantially. Further studies are needed to validate this hypothesis completely. Future research is needed to assess the intravitreal penetration of oral ciprofloxacin and other newer fluoroquinolones like Moxifloxacin and their clinical outcomes. While the Endophthalmitis Vitrectomy Study postulated that there was no significant role of systemic antibiotics in the management of postoperative endophthalmitis in patients being treated with intravitreal antibiotics, it suffered from a serious lacuna as almost 49% of the patients in the study received ceftazidime or amikacin for use as systemic antibiotics which have a poor intraocular penetration after systemic use. Furthermore, in more severe cases of endophthalmitis managed by complete vitrectomy with silicone oil endotamponade, systemic antibiotics if effective, could prove to be a very useful adjunctive treatment for ensuring better outcomes. Further studies including those on newer antibiotics may well demonstrate significant capability to effectively manage intraocular infections without or with use of silicone oil as intraocular tamponade. Till then, the choice of the adjunctive systemic antibiotic agent in situations considered relevant for treatment must be made on an individual basis, taking into account the clinical situation, suspected or detected organisms(with gram negative bacteria being especially more virulent and recalcitrant to treatment), operative status, intraocular inflammatory activity and the drug's side effect profile.

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