Aqueous humor concentrations of topical fluoroquinolones alone or in combination with a steroid

Concentração de fluorquinolonas no humor aquoso após instilação tópica das associações com corticosteroides

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ABSTRACT

Purpose: To compare the aqueous humor (AH) concentrations of moxifloxacin 0.5% and gatifloxacin 0.3% solutions alone or when treatment was combined with steroids, and to correlate these concentrations with the minimum inhibitory concentrations (MIC) for the most common endophthalmitis-causing organisms.

Methods: Patients undergoing phacoemulsification were enrolled to receive one drop of one of the following solutions: moxifloxacin (G1), moxifloxacin + dexamethasone (G2), gatifloxacin (G3), or gatifloxacin + c (G4), every 15 min, 1h before surgery. AH samples were collected before surgery and analyzed using HPLC-tandem mass spectrometry.

Results: The mean antibiotic concentrations in the AH were: G1= 1280.8 ng/mL; G2= 1644.3 ng/mL; G3= 433.7 ng/mL; and G4= 308.1 ng/mL. The mean concentrations statistically differed between G1 and G2 (p=0.01), and G3 and G4 (p=0.008). All samples achieved the MIC for *Staphylococcus epidermidis*; 100% of the samples from G1 and G2, and 97% from G3 and G4 reached the MIC for fluoroquinolone-sensitive *Staphylococcus aureus*; 100% of the samples from G1 and G2, 88% from G3, and 72% from G4 reached the MIC for enterococci (p<0.001); and 100% of samples from G1 and G2, 59% from G3, and 36% from G4 reached the MIC for *Streptococcus pneumoniae* (p<0.001). For fluoroquinolone-resistant *S. aureus*, 23% from G1, 44% from G2, and no samples from G3 or G4 achieved the MIC (p<0.001).

Conclusions: Moxifloxacin + dexamethasone demonstrated a higher concentration in the AH than the moxifloxacin alone. Gatifloxacin + steroids demonstrated less penetration into the anterior chamber than gatifloxacin alone. Moxifloxacin was superior to gatifloxacin considering the MIC for enterococci, *S. pneumoniae*, and fluoroquinolone-resistant *S. aureus*.

Keywords: Aqueous humor; Ophthalmic solutions; Antibiotic prophylaxis; Fluoroquinolones; Steroids; Adrenal cortex hormones; Anti-bacterial agents; Comparative study

RESUMO

Objetivos: *Comparar a concentração no humor aquoso entre as soluções de moxifloxacina 0,5% e gatifloxacina 0,3% sozinhas ou combinadas com corticosteroides, e correlacionar a concentração com a concentração inibitória mínima (MIC) para os agentes microbianos mais comumente relacionados a endoftalmites.*

Métodos: *Pacientes que seriam submetidos a cirurgia de catarata foram selecionados para receber 1 gota a cada 15 min, 1 hora antes do procedimento de uma das seguintes soluções: moxifloxacina (G1), moxifloxacina + dexametasona (G2), gatifloxacina (G3) ou gatifloxacina + prednisolona (G4). Amostras do humor aquoso foram coletadas antes do início da cirurgia. Espectrofotometria de massa por HPLC determinou a concentração do antibiótico nas amostras.*

Resultados: *A concentração media de antibiótico nas amostras foram: G1= 1280,8 ng/mL; G2= 1644,3 ng/mL; G3= 433,7 ng/mL; G4= 308,1 ng/mL. Concentração média entre G1 e 2 (p=0,01), e G3 e 4 (p=0,008). Todas as amostras alcançaram MIC para* S. epidermidis*; 100% das amostras do G1 e 2, e 97% do G3 e 4 atingiram o MIC para* S. aureus *fluoroquinolona-sensível; 100% das amostras do G1 e 2, 88% do G3 e 72% do G4 atingiram o MIC para* Enterococci *(p<0,001); e 100% das amostras do G1 e 2, 59% do G3 e 36% do G4 atingiram o MIC para* S. pneumoniae *(p<0,001). Para o* S. aureus *resistente a fluoroquinolona, 23% do G1, 44% do G2, e nenhuma das amostras G3 e 4 atingiram o MIC (p<0,001).*

Conclusão: *Moxifloxacina + dexamethasona demonstrou maior concentração no humor aquoso comparado com a moxifloxacina sozinha. Gatifloxacina + esteróide demonstrou menor penetração na câmara anterior comparado a solução de gatifloxacin sem corticóide. A moxifloxacina foi superior a gatifloxacina considerando o MIC para* Enterococci, S. pneumoniae *e* S. aureus *fluorquinolona resistente.*

Descritores: *Humor aquoso; Soluções oftálmicas; Antibioticoprofilaxia; Fluoroquinolonas; Esteroides; Corticosteroides; Antibacterianos; Estudo comparativo*

INTRODUCTION

Fourth-generation fluoroquinolones are the antibiotics of choice for many ophthalmologists as a result of their bactericidal properties and broad-spectrum coverage against Gram-positive and Gram-negative organisms. Quinolones are bactericides that prevent bacterial DNA replication by inhibiting bacterial DNA gyrase and topoisomerase. Ocular penetration requires the pH of ophthalmic solutions to be around 7, which favors unionized drugs and higher lipid solubility of drugs[1].

The topical use of ophthalmic drops is the oldest and easiest method of administering medications for treating ocular diseases. When instilled on the ocular surface, most of the drug is rapidly washed out as a result of the usual volume of the drop and the eye's drainage system, although viscosity enhancers can increase this length of time. The limited tissue penetration with this method means that the topical delivery is ideal for external, corneal, and anterior segment diseases, but not for retinal or vitreous diseases[2,3]. Topical administration is simple, and patients are generally able to self-administer eye drops, although compliance with daily regimens can be low[4,5].

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Human studies have shown that moxifloxacin 0.5% results in high concentrations in the anterior chamber[6-8]. Treatment with a combination of steroids and antibiotic drops is as effective as conventional treatment for controlling inflammation after phacoemulsification and intraocular lens (IOL) implantation[9-12]. These drug combinations help reduce costs and also improve patient compliance by decreasing the number of applications.

The purpose of the present study was to compare aqueous humor (AH) concentrations of fluoroquinolones after topical instillation of moxifloxacin and gatifloxacin ophthalmic solutions alone or in combination with steroids, and to correlate these concentrations with the minimum inhibitory concentrations (MIC) for the most common endophthalmitis-causing organisms.

METHODS

This prospective clinical study was conducted from January 2012 to February 2013 at the Federal University of São Paulo and Hospital de Olhos Paulista according to the tenets of the Declaration of Helsinki. Institutional review board/ethics committee approval was obtained, and each patient provided written informed consent before enrolment in the study.

Patients scheduled for routine phacoemulsification and IOL implantation were enrolled in this study. Exclusion criteria were patients with ocular surface diseases and those using topical and systemic steroids and antibiotics. Prior to surgery for cataract, they received one of the following commercially available solutions: Group 1: moxifloxacin 0.5% (Vigamox; Alcon, Fort Worth, TX, USA); Group 2: moxifloxacin 0.5% combined with dexamethasone (Vigadexa; Alcon); Group 3: gatifloxacin (Zymar; Allergan, Dublin, Ireland); and Group 4 gatifloxacin combined with prednisolone (Zypred; Allergan). Table 1 shows the pharmacological features of the solutions.

Patients received one drop four times, 1 h before surgery (15-min intervals), instilled by a person designated for that. Approximately 0.150 mL of AH was obtained immediately before paracentesis and transferred to a propylene recipient before storage at -20°C until analysis.

Moxifloxacin and gatifloxacin concentrations in the AH samples were determined by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) using an API 3200 AB Sciex mass spectrometry detector coupled to a Symbiosis Pharma HPLC system (Spark® Holland, Emmen, the Netherlands) and an ACE® C18 (100 × 4.6 mm, 5 µm) column. The mobile phase was composed of methanol: 0.1% formic acid (v/v), 43:57 (v/v) in the isocratic mode. The monitored mass transitions (precursor ion → product ion) were *m/z* 402.1 → *m/z* 358.2 for moxifloxacin and *m/z* 376.1 → *m/z* 289.2 for gatifloxacin, in the positive electrospray ionization mode. The method was developed using gatifloxacin as the internal standard (IS) for moxifloxacin and moxifloxacin as the IS for gatifloxacin. The validated range was 5-2,000 ng/mL for both analytes, and for samples exceeding the upper limit of quantification, a previously validated dilution process was performed. Linearity, accuracy, precision, and stability were determined in a validation procedure in accordance with ANVISA's bioanalytical guidelines.

The samples were prepared using 50 µL of AH spiked with the IS solution, and the samples were cleaned up using the protein precipitation method with 10% perchloric acid. Moxifloxacin and gatifloxacin were quantified in the samples using a duplicated seven-point calibration curve that was constructed using 60 mg/dL of bovine serum albumin as a surrogate matrix and defined using the linear regression method with 1/x.x ponderation. For all sample analyses, we included 5% quality control (QC) samples at low, medium, and high concentrations. Run acceptance was based on the performance of the calibration standards and QC samples.

We evaluated whether each sample achieved the MIC for pathogens commonly related to endophthalmitis. The standard MICs considered were published by McCulley et al.[8].

Statistical analysis was performed with Stata 14 software (StataCorp. 2015. *Stata Statistical Software: Revision 23*. College Station, TX: StataCorp LP). The Mann-Whitney test was used to compare means between groups, and Fisher's test was used to compare the categorical data (MIC).

RESULTS

A total of 139 samples were collected, and table 2 shows the patients' demographics. The mean antibiotic concentrations in the

Table 1. Pharmacological characteristics of the moxifloxacin solutions (Vigamox® and Vigadexa®) and gatifloxacin solutions (Zymar® and Zypred®)

	Vigamox®	Vigadexa®	Zymar®	Zypred®
Active principle(s)	Moxifloxacin hydrochloride 0.5%	Moxifloxacin hydrochloride 0.5% Dexamethasone 0.1%	Gatifloxacin 3 mg/mL	Gatifloxacin 3 mg/mL Prednisolone 10 mg/mL
pH	6.88	7.95	5.5-6.3	6.5-7.1
Solution	Isotonic solution		Isotonic non-tamponaded	Isotonic non-tamponaded
Vehicle	Boric acid	Edetate disodium	Benzalkonium chloride	Benzalkonium chloride
	Sodium chloride	Boric acid	Edetate disodium	Sodium phosphated dibasic dihydrate
	Sodium hydroxide and/or hydrochloric acid	Sodium chloride	Sodium chloride	Edetate disodium
	Boric acid	Sorbitol	Sodium hydroxide and/or hydrochloric acid	Hypromellose
	Purified water	Tyloxapol	Purified water	Sodium hydroxide and/or hydrochloric acid
			Sodium hydroxide and/or hydrochloric acid	Purified water
			Purified water	

Table 2. Patient demographics of the groups receiving fluoroquinolones

	Group				Comparison-P value	
Variable	**1**	**2**	**3**	**4**	**Group 1 vs. 2**	**Group 3 vs. 4**
Number of eyes	35	34	34	36		
Age (years), mean (SD)	68.5 (12.3)	71.3 (9.8)	65.6 (12.4)	67.6 (11.7)	0.23*	0.69*
Gender, male (%)	13.0 (37.0)	12.0 (35.0)	15.0 (44.0)	15.0 (42.0)		

SD= standard deviation; *= Mann-Whitney test.

AH were: Group 1= 1280.8 ng/mL; Group 2= 1644.3 ng/mL; Group 3= 433.7 ng/mL; and Group 4= 308.1 ng/mL. The differences between the mean concentrations were statistically significant for groups 1 and 2 (p=0.01), and groups 3 and 4 (p=0.008).

All samples from the four groups achieved the MIC for *Staphylococcus epidermidis*; 100% of the samples from groups 1 and 2, and 97% samples from groups 3 and 4 reached the MIC for fluoroquinolone-sensible *Staphylococcus aureus*, with no statistically significant difference (p=0.087) between the two antibiotics; 100% of the samples from groups 1 and 2, 88% sample from group 3, and 72% sample from group 4 reached the MIC for enterococci, with a statistically significant difference (p<0.001) between the two antibiotics; and 100% of the samples from groups 1 and 2, 59% samples from group 3, and 36% samples from group 4 reached the MIC for *Streptococcus pneumoniae*, with a statistically significant difference between the two antibiotics (p<0.001). Conversely, for fluoroquinolone-resistant (FQR) *S. aureus*, 23% from group 1, 44% from group 2, and no sample from groups 3 and 4 achieved the MIC, with a statistically significant difference found between the two antibiotics (p<0.001).

Table 3 shows the antibiotic concentrations in the AH in all groups and the percentage of samples that achieved the MICs.

DISCUSSION

In the present study, we compared the ability of antibiotic drops alone and in combination with steroids to penetrate the anterior chamber before cataract surgery. The mean concentration in the group that received moxifloxacin 0.5% with dexamethasone was 1644.3 ng/dL, which was higher than that of the group that received moxifloxacin 0.5% alone (p=0.01). Between the gatifloxacin groups, the opposite results were observed: the mean concentration was higher in the group that received gatifloxacin without steroids (p=0.008).

The AH concentrations of moxifloxacin that we found are compatible with the MICs for the most common pathogens related to endophthalmitis. The samples from the gatifloxacin groups achieved the MICs for fluoroquinolone-sensible (FQS) *S. epidermidis* and FQS *S. aureus*. There was a statistically significant difference between gatifloxacin and moxifloxacin regarding the MICs for enterococci, *S. pneumoniae*, and FQR *S. aureus*. Fewer samples from the gatifloxacin group achieved the MICs for these pathogens. Interestingly, other studies have also reported the inferiority of gatifloxacin in achieving the MICs for enterococci, *S. pneumoniae,* and FQR *S. aureus*[8]; therefore, surgeons should opt for moxifloxacin over gatifloxacin.

A clinical study by Kim et al. showed AH concentrations of 1800 ng/mL for moxifloxacin after instilling one drop of antibiotic every 10 min, with four doses, beginning 1h before cataract surgery[7]. Katz et al. reported an AH moxifloxacin concentration of 1740 ng/mL with four-times-daily dosing the day before surgery plus one drop every 15 min for four doses before surgery[6]. Further, Solomon et al. showed an AH moxifloxacin concentration of 1310 ng/mL after four-times-daily dosing for 3 days before surgery and one dose every 15 min for three doses 1h before surgery[13]. These clinical studies demonstrated AH moxifloxacin concentrations similar to those found in our study.

Kim et al. and McCulley et al. also reported gatifloxacin concentrations in AH after topical instillation of the drug without steroids. Kim et al. showed an AH concentration of 480 ng/mL for gatifloxacin after instilling one drop of antibiotic every 10 min for four doses beginning 1h before cataract surgery[7,8]. Additionally, McCulley et al. reported an AH gatifloxacin concentration of 940 ng/mL[8]. The concentrations found in the present study are similar to those reported by Kim et al. and Solomon et al., which showed two-fold higher AH concentrations for moxifloxacin over gatifloxacin: 1310 ng/mL and 630 ng/mL, with four-times-daily dosing for 3 days before surgery and one dose every 15 min for three doses 1 h before surgery, respectively[7,13].

Although the topical administration of drugs is the preferred and most convenient route for treating ocular diseases, it is associated with extremely limited bioavailability. The primaryt causes of drug loss are pre-corneal factors such as drainage; further, the tear turnover rate, and absorption by other tissues result in the loss of the drug to the systemic circulation. Some causes of the low ocular bioavailability may be the lipoidal nature of the corneal epithelium and the water-laden stroma, which work as rate-limiting barriers for hydrophilic and lipophilic molecules. Further, efflux transporters on the corneal epithelium may contribute to the low ocular bioavailability by actively effluxing molecules from the cornea back into the tear film. Multidrug resistance is primarily caused by the cellular extrusion of drugs by P-glycoprotein (P-gp), multidrug resistance-associated proteins (MRPs), and breast cancer resistance protein, which limit absorption across many biologic membranes and restrict entry into important pharmacologic sites[14]. The expression and functional activity of P-gp and MRP2 in the rabbit and human corneal epithelia have been studied[15-17]. In 2009, Hariharan et al. showed that steroids are effective at inhibiting both P-gp- and MRP2-mediated efflux across the rabbit cornea. Thus, steroids improve the ocular absorption of topically administered drugs by inhibiting efflux pumps on the cornea and elevating the cellular concentration of the drug in the cornea as well as the AH[18]. This finding helps explain why the AH moxifloxacin concentration was higher in the group that received the combined solution.

Corneal permeability increases when the corneal integrity is compromised by the high concentrations of formulation excipients such as preservatives and chelating agents[19]. Studies on the effect of formulation additives on transcorneal permeability have revealed that compounds such as benzalkonium chloride (BAC), thiomersal (THM), chlorobutanol (CB), phenylmercuric nitrate, ethylenediamine

Table 3. Mean moxifloxacin and gatifloxacin concentrations for each group; samples that achieved the MIC for the most common pathogens related to endophthalmitis in groups receiving moxifloxacin 0.5% or gatifloxacin 0.3%

	Group				P value	
Variable	**1**	**2**	**3**	**4**	**Group 1 vs. 2**	**Group 3 vs. 4**
Concentration (ng/mL)	1280.8	1644.3	433.7	308.1	0.010*	0.008*
Median (Q1-Q3)	(751.1-1743.1)	(1043.1-2289.9)	(289.4-649.8)	(205.1-495.3)		
MIC, yes (%)					**Groups 1-4**	**Group 3 vs. 4**
FQS *S. epidermidis*	35 (100)	34 (100)	34 (100)	36 (100)	1.000†	1.000†
FQS *S. aureus*	35 (100)	34 (100)	33 (97)	35 (97)	0.870†	0.740†
S. pneumoniae	35 (100)	34 (100)	30 (88)	26 (72)	<0.001†	0.080†
Enterococci	35 (100)	34 (100)	20 (59)	13 (36)	<0.001†	0.130†
FQR *S. aureus*	8 (23)	15 (44)	0 (0)	0 (0)	<0.001†	1.000†

Q1= first quartile; Q3= third quartile; MIC= minimum inhibitory concentration; FQS= fluoroquinolone-sensible; FQR= fluoroquinolone-resistant; *= Mann-Whitney test.

tetra-acetic acid (EDTA), methyl hydroxybenzoate (MHB), and propyl hydroxybenzoate increase the extent of transcorneal permeation at pH 7.4. BAC, THM, CB, and EDTA, have adverse effects on the corneal cell structure and integrity, and also increase drug permeability[20].

Unfortunately, because of the small volume of the AH samples, we could not measure the concentration of steroids that penetrated the anterior chamber. This information could have explained why moxifloxacin penetrated the anterior chamber more than gatifloxacin when associated with steroids. Dexamethasone and prednisolone can have different effects on the corneal absorption of antibiotics.

In conclusion, moxifloxacin in combination with dexamethasone demonstrated a higher concentration in the AH than moxifloxacin alone. Gatifloxacin in combination with steroids showed less penetration in the anterior chamber than the steroid-free gatifloxacin solution. Moxifloxacin was superior to gatifloxacin considering the AH MICs for enterococci, *S. pneumoniae* and FQR *S. aureus*. The commercial association of Vigamox with dexamethasone appears to be the best option for preoperative prophylaxis.

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