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COMPARISON OF CYTOTOXICITY OF FLUOROQUINOLONE ANTIMICROBIAL EYE DROPS AND ITS EFFECT ON THEIR BIOAVAILABILITY

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✧ In addition to the broad spectrum of activities of antibacterial medications and their pharmacokinetic and pharmacodynamic properties, their safety and bioavailability are important aspects of their function. Currently, there is no consensus on fluoroquinolone toxicity. The aim of the present study was to compare the bioavailability and cytotoxic effect of three antibacterial fluoroquinolone eye drops, which are registered in the Russian Federation, on the corneal epithelium: 1) Oftaquix™ [levofloxacin 5 mg/ml; preservative benzalkonium chloride (BAC), 0.05 mg/ml; produced by Santen Oy, Finland], hereafter "levofloxacin (original)"; 2) Signicef® (levofloxacin 5 mg/ml; preservative BAC 0.1 mg/ml; produced by Sentiss Pharma Pvt. Ltd., India), hereafter "levofloxacin (generic)"; and 3) Vigamox® (moxifloxacin® 5 mg/ml; preservative-free; produced by Alcon Laboratories, Inc., USA), hereafter "moxifloxacin." Their cytotoxic effects were evaluated using *in vivo* methods. The effect of different concentrations of the preservative on minimal threshold concentrations of the antibacterial medications in the anterior chamber fluid was determined using high-yield liquid chromatography combined with mass-spectrometric detection. The study revealed that the antibacterial medications exert cytostatic effects on the corneal epithelium *in vivo*, and that they differ in their cytotoxic potential. Confocal microscopy demonstrated that the presence of benzalkonium chloride in Signicef, at a concentration twice that in Oftaquix, affects the corneal epithelium, and this may influence bioavailability of the antibacterial medications.

✧ ***Keywords:*** cytotoxicity; fluoroquinolones; eye drops; bioavailability.

СРАВНИТЕЛЬНАЯ ОЦЕНКА ЦИТОТОКСИЧНОСТИ АНТИМИКРОБНЫХ ГЛАЗНЫХ КАПЕЛЬ ФТОРХИНОЛОНОВОГО РЯДА И ЕЁ ВЛИЯНИЕ НА БИОДОСТУПНОСТЬ ПРЕПАРАТОВ

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✧ Помимо широты спектра активности антибактериальных препаратов (АБП), а также их фармакодинамических и фармакокинетических особенностей, важным аспектом является безопасность лекарственного средства и его биодоступность. В настоящее время нет единого мнения о токсичности фторхинолонов. Цель данного исследования состояла в сравнении общего цитотоксического

действия на эпителий роговой оболочки и биодоступности трёх антибактериальных глазных капель фторхинолонового ряда, зарегистрированных в Российской Федерации: 1) Офтаквикс™ (левофлоксацин 5 мг/мл; консервант бензалкония хлорид (БАХ) 0,05 мг/мл; производитель: АО «Сантэн», Финляндия), далее — «левофлоксацин (оригинальный)»; 2) Сигницеф® (левофлоксацин 5 мг/мл; консервант БАХ 0,1 мг/мл; производитель: «Сентисс Фарма Пвт. Лтд.», Индия), далее — «левофлоксацин (дженерик)»; 3) Вигамокс® (моксифлоксацин 5 мг/мл; без консервантов; производитель: «Алкон Лабораториз, Инк.», США), далее — «моксифлоксацин» с использованием методов *in vivo* и определением возможного влиянии наличия консерванта (в различной концентрации) или его отсутствия на достижение минимальных пороговых концентраций (МПК) антибиотика во влаге передней камеры глаза (ВПКГ), с использованием методов высокоэффективной жидкостной хроматографии (ВЭЖХ) в сочетании с масс-спектрометрическим детектированием (МС). Исследование показало, что протестированные АБП могут оказывать цитостатический эффект в условиях *in vivo* на эпителий роговицы и отличаются по своему цитотоксическому потенциалу. Присутствие бензалкония хлорида в препарате Сигницеф в концентрации, превышающей в два раза концентрацию консерванта основного препарата (Офтаквикс), оказывает воздействие на эпителиальный слой роговицы, что подтверждается данными конфокальной микроскопии, и способно повлиять на биологическую доступность лекарственного средства.

✧ ***Ключевые слова:*** цитотоксичность; фторхинолоны; глазные капли; биодоступность.

Choosing antibacterial eye drops is an important step in the prevention of postoperative infectious complications. All generations of fluoroquinolones play significant roles in the prevention of endophthalmitis after ophthalmic surgery. Eye drops containing ciprofloxacin, ofloxacin, or levofloxacin have been used in ophthalmic practice since a long time. However, a rapid development of microbial resistance to first-generation fluoroquinolones during the last few years has led to the use of fourth-generation fluoroquinolones, namely moxifloxacin, gatifloxacin, and besifloxacin (their use is currently limited to the North American region), by ophthalmic surgeons in several regions of the world [4]. There are several important issues that should be taken into account while choosing antibacterial eye drops for the prevention of postoperative complications after ophthalmic surgery, including the spectrum of antibacterial activity, pharmacodynamics and pharmacokinetic factors, the presence of preservatives, and the speed of the achievement of minimum threshold concentration (MTC) in the anterior chamber (AC), which may depend on the cytotoxic effect of the preservative on corneal epithelial cells. According to the standards of good laboratory practice (GLP), the assessment of drug cytotoxicity is a necessary stage in preclinical trials [19]. Cytotoxicity is the quality of being toxic to cells, i. e., the ability to cause pathological changes exerted by several physical, chemical, and biological agents. There is a wide spectrum of possible changes depending on the impact intensity, from cytostatic to cytocidal effects and leading to cell death [18, 20].

Currently, there is no consensus on the cytotoxic effect of ophthalmic fluoroquinolones on different structures of the eye [8]. Some authors attribute the cytotoxicity of antibacterial eye drops to benzalkonium chloride (BAC), which is often added to such drugs. BAC has been shown to have a cytotoxic effect on the corneal epithelium [13, 17]. Other authors believe that the antibiotic molecule itself exerts cytotoxicity [6].

The aim of this study was to compare the bioavailability and general cytotoxic effect of three fluoroquinolone-containing antibacterial eye drops, registered in the Russian Federation, on the corneal epithelium: 1) Oftaquix™ (levofloxacin, 5 mg/mL, preservative BAC, 0.05 mg/mL, Santen, Finland), hereafter "original levofloxacin"; 2) Signicef® (levofloxacin, 5 mg/mL, preservative BAC, 0.1 mg/mL, Sentiss Pharma Pvt. Ltd., India), hereafter "generic levofloxacin"; and 3) Vigamox® (moxifloxacin, 5 mg/mL, preservative-free, Alcon Laboratories, Inc., USA), hereafter "moxifloxacin." Besides, we aimed to evaluate the possible impact of the preservative (at different concentrations) on the achievement of MTC in the AC of the eye.

MATERIALS AND METHODS

No standard methods for the assessment of the cytotoxicity of eye drops (including antibacterial eye drops) are currently available. Historically, toxicological examinations have been based on acute, sub-acute, chronic, and other special experiments performed on warm-blooded animals [3]. Until recently, animal experiments were considered as the

gold standard; however, these studies are costly and time consuming and cause harm to the animal and may lead to their death. Currently, a strategy based on a new concept of rational combination of *in vivo*, *in vitro,* and *in silico* (computer modelling) experiments is used to optimize the assessment of drug cytotoxicity [2]. There is a growing interest in *in silico* studies because they allow reducing the number of animals used in biological testing. Computer modelling is a highly informative method for the assessment of drug cytotoxicity, which provides a quantitative estimation and has a high practical value in terms of the choice of drugs, although it cannot be used for investigating the exact molecular mechanisms underlying the drug activity because of the structural and functional heterogeneity of cells.

Assessment of the impact of antibacterial drugs on cells

Following methods were used for the quantitative and qualitative assessments of the toxicity of antibacterial eye drops on epithelial cells:

1. Quantitative assessment: confocal microscopy using the ConfoScan4 confocal microscope (Nidek, Inc., Freemont, CA)
2. Qualitative assessment: the analysis of pleomorphism and polymegathism using the ConfoScan4 confocal microscope by the photofixation of one point with subsequent image construction by scanning.

Thirty patients underwent confocal microscopy examination before and after the instillation of antibacterial drops in the conjunctival cavity. Patients were divided into three groups (10 patients in each): those in the first group received 0.5% moxifloxacin solution (Vigamox®) and those in the second and third groups received 0.5% levofloxacin solution (Oftaquix™ and Signicef®, respectively). The first examination was conducted prior to the instillation of eye drops and the second was conducted after the instillation according to a fixed schedule. We evaluated the quantitative parameters of corneal epithelial cells, pleomorphism, and polymegathism. Demographic data of the examined patients are shown in Table 1.

Assessment of MTC of antibacterial drugs in the anterior chamber

We used high-performance liquid chromatography (HPLC) combined with mass spectrometry (MS) to assess the MTC of the studied antibacterial agents.

The analysis of the AC fluid requires the detection of very low concentrations of tested substances; however, a small volume of a sample with no possibility to concentrate it creates substantial difficulties for the procedure. Hence, we used an effective method for the quantitative assessment that allowed working with a small volume of biomaterial [4]. The bioavailability of antibacterial drugs was evaluated by measuring their concentrations in the AC fluid.

A total of 90 patients were included in the MTC assessment. They were divided into three groups (30 in each). The first group received 0.5% moxifloxacin solution (Vigamox®) and the second and third groups received 0.5% levofloxacin solution (Oftaquix™ and Signicef®, respectively). Antibacterial eye drops were instilled on the day of surgery in all patients according to the following schedule: one drop every 15 min 1 hour prior to surgery (total four times). Before the phacoemulsification of cataract (PEC), we took a 0.1-mL sample of the AC fluid using an insulin syringe for further assessment of the concentration of antibacterial agent. We performed the HPLC/MS analysis of

Table 1

Age and gender distribution of the examined patients

Таблица 1

Распределение пациентов, участвующих в исследовании по возрасту и полу

Patients	Antibacterial eye drops		
	Group 1 Vigamox® (moxifloxacin, 0.5%)	**Group 2 Oftaquix™ (levofloxacin, 0.5%)**	**Group 3 Signicef® (levofloxacin, 0.5%)**
Mean age (max/min)	68.1 (43/85)	60.3 (39/73)	68.2 (40/89)
Females, *n* (%)	22 (73.3)	14 (46.7)	12 (40)
Males, *n* (%)	8 (26.7)	16 (53.3)	18 (60)

specimens using the Shimadzu LCMS-2010 EV liquid chromatography mass spectrometer (electrospray ionization) with the Agilent Extend-C18 column.

Conditions of the chromatographic separation were as follows: flow rate, 0.25 cm^3/min; volume of injected sample, 0.005 cm^3; column temperature, 40 °C; and mobile phase composition: component A, 0.2% formic acid water solution and component B, acetonitrile.

Conditions of MS were as follows: pressure of drying gas, 0.1 MPa; velocity of the spray gas, 1.5 l/min; heater temperature, 200 °C; curved desolvation line (CDL) temperature, 200 °C; spray voltage, 4000 V; electron multiplier voltage, 1500 V; and single ion monitoring (SIM) positive mode.

Data were analyzed using the Statistica 6.0 software.

RESULTS

Mass chromatogram and mass spectra of levofloxacin and moxifloxacin are shown in Figure 1.

We observed that the mean concentration of levofloxacin in the AC fluid was 1.5 μg/mL in patients in the third group and 0.9 μg/mL in those in the second group (Figure 2), whereas that of moxifloxacin (Vigamox®) in patients prior to PEC was 1.0 μg/mL (Figure 1). Maximum concentrations of levofloxacin (Signicef®) were 1.55 ± 0.86 μg/mL (detected 30–60 min post instillation) and 1.29 ± 1.08 μg/mL (detected 60–120 min post instillation). The preventive instillation of antibacterial eye drops up to 30 min prior to PEC and 120–240 min prior to surgery revealed lower concentrations of antibiotics in the AC fluid: 0.96 ± 0.81 μg/mL and 0.99 ± 0.72 μg/mL, respectively. The results of the quantitative assess-

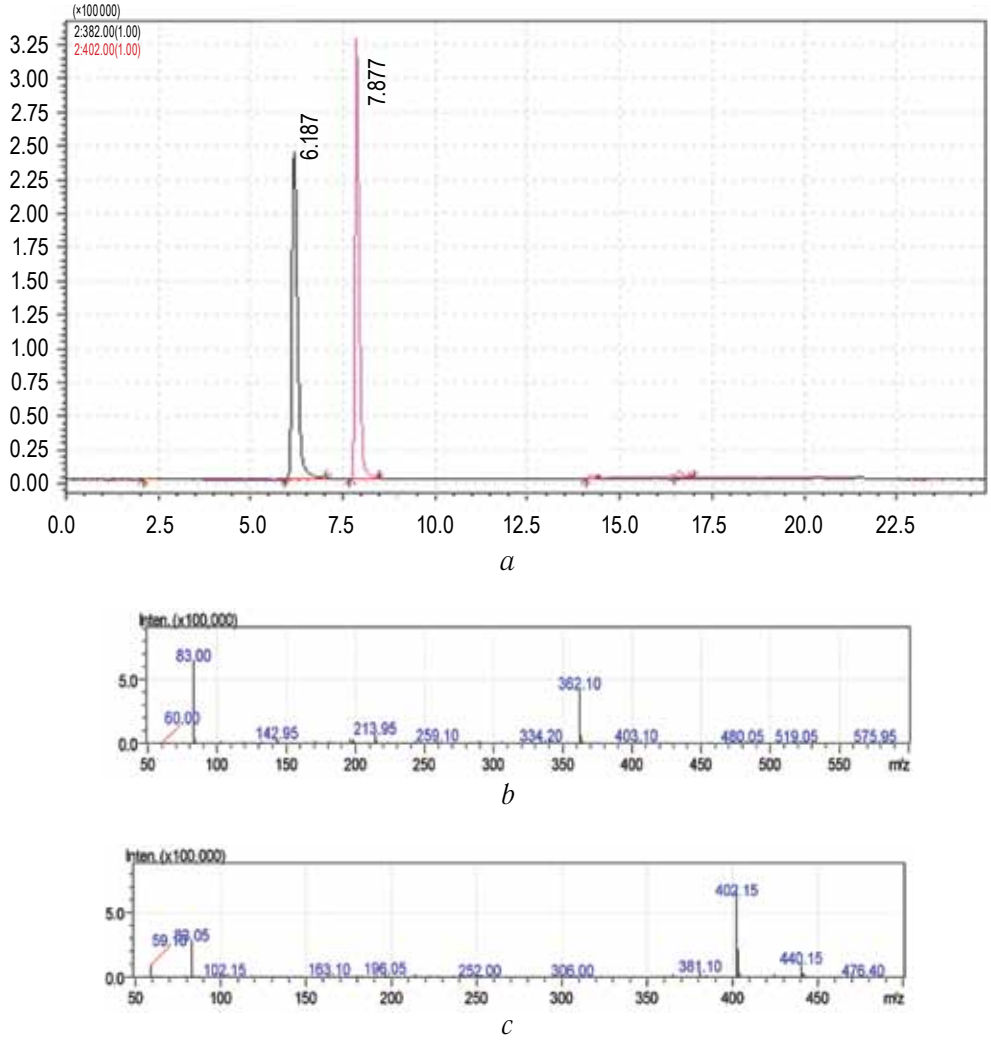

Fig. 1. Mass-chromatogram and mass-spectres of levofloxacin and moxifloxacin. *a*) Mass-chromatogram of levofloxacin and moxifloxacin, *b*) Levofloxacin mass-spectrum, *c*) Moxifloxacin mass-spectrum

Рис. 1. Масс-хроматограмма и масс-спектры левофлоксацина и моксифлоксацина: *a*) масс-хроматограмма левофлоксацина и моксифлоксацина; *b*) масс-спектр левофлоксацина; *c*) масс-спектр моксифлоксацина

ment of corneal epithelial cells in patients from the first group are shown in Figure 2.

Figures 3 and 4 demonstrate the results of the quantitative assessment of corneal epithelial cells in the second and third groups.

According to our results, cytotoxicity of the drugs tested in the study may be presented as generic levofloxacin cytotoxicity > moxifloxacin cytotoxicity > original levofloxacin cytotoxicity.

DISCUSSION

Our results suggest that all antibacterial eye drops are cytotoxic to corneal epithelial cells, but they exhibit different levels of cytotoxicity and MTCs, which correlate with the degrees of cytotoxicity evaluated by confocal microscopy.

The penetration of antibiotics into the AC depends on several factors. Corneal epithelium has strong intercellular connections; hence, a drug must be able

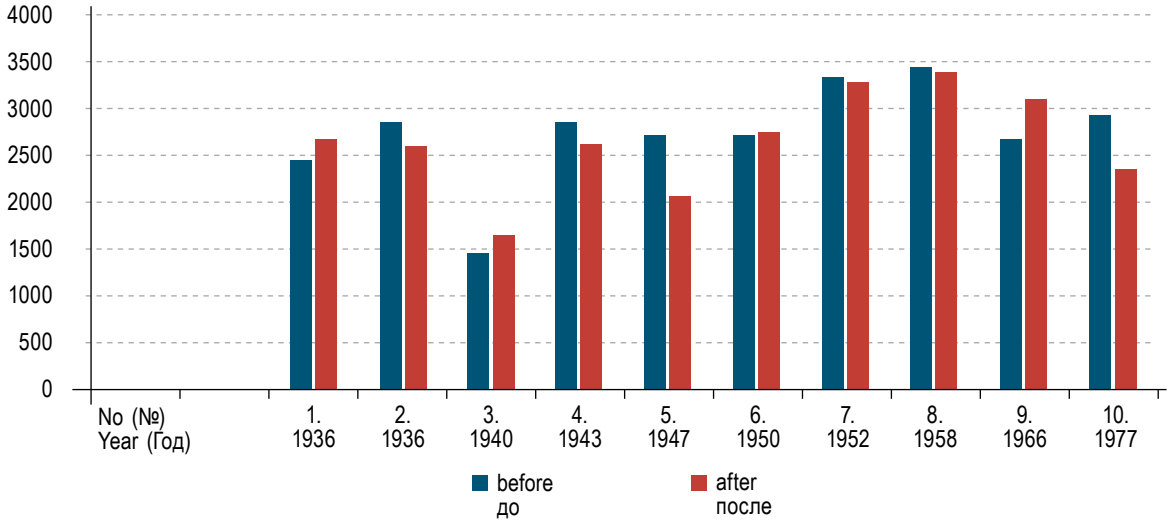

Fig. 2. Quantitative assessment of corneal epithelial cells before and after antibiotic drop (Moxifloxacin) instillation in 1st group patients according to confocal microscopy data

Рис. 2. Данные количественной оценки состояния клеток эпителия роговицы до и после закапывания антибактериального препарата (Моксифлоксацин) у пациентов 1-й группы по данным конфокальной микроскопии

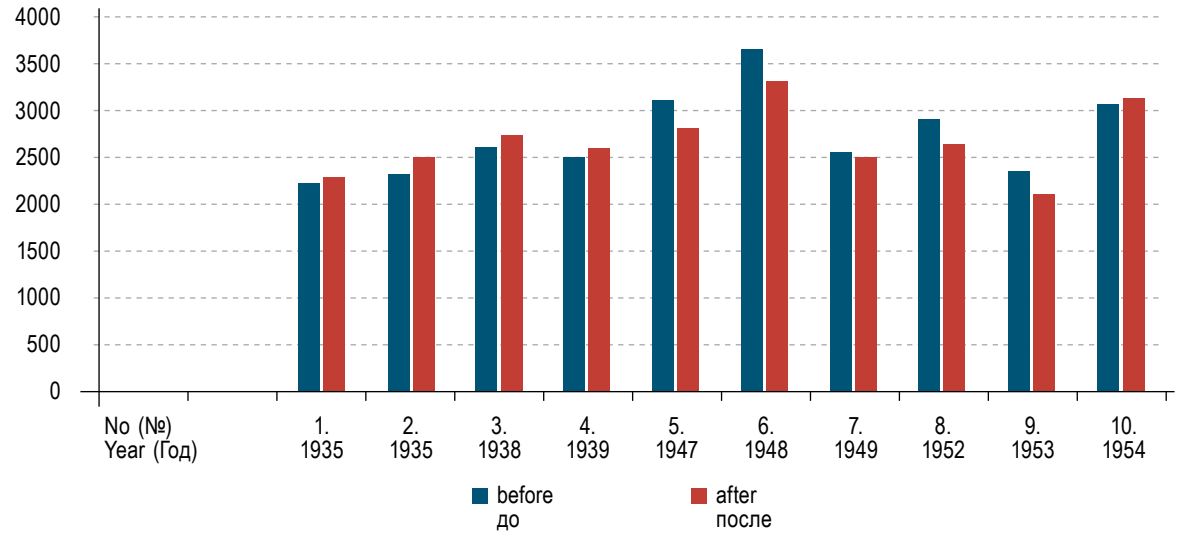

Fig. 3. Quantitative evaluation (by confocal microscopy) of the corneal epithelium cells state of health before and after antibacterial medication instillation (branded levofloxacine) in patients of the 2nd group

Рис. 3. Данные количественной оценки состояния клеток эпителия роговицы до и после закапывания антибактериального препарата (Левофлоксацин оригинальный) у пациентов 2-й группы по данным конфокальной микроскопии

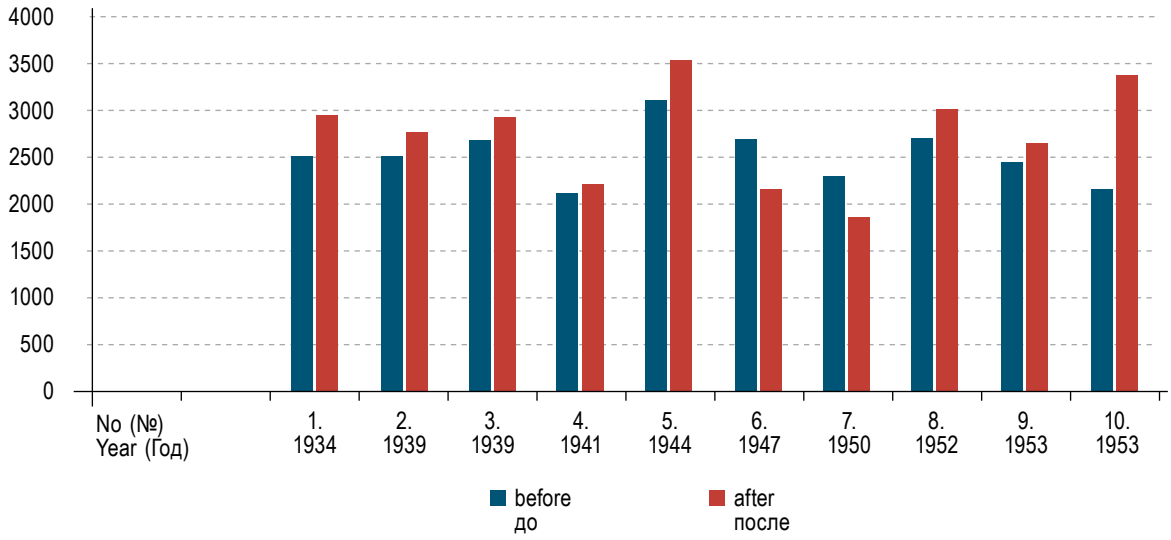

Fig. 4. Quantitative assessment of corneal epithelial cells before and after antibiotic drop (Levofloxacin generic preparation) instillation in 3rd group patients according to confocal microscopy data

Рис. 4. Данные количественной оценки состояния клеток эпителия роговицы до и после закапывания антибактериального препарата (Левофлоксацин дженерик) у пациентов 3-й группы по данным конфокальной микроскопии

Table 2

Quantitative assessment of corneal epithelial cells before and after antibiotic drop instillation in the third group (generic levofloxacin) according to confocal microscopy data

Таблица 2

Данные качественной оценки состояния клеток эпителия роговицы у пациентов 3-й группы (Левофлоксацин дженерик) по данным конфокальной микроскопии

Patient	Polymegathism		Pleomorphism	
	Before eye drop instillation, %	After eye drop instillation, %	Before eye drop instillation, %	After eye drop instillation, %
1	34.3	47.1	44.6	43.0
2	29.5	24.7	53.5	76.7
3	50.2	63.2	34.7	48.9
4	34.0	32.6	54.2	57.0
5	51.3	35.9	28.6	56.4
6	49.7	51.6	35.1	42.2
7	33.0	26.5	55.2	62.3
8	37.2	29.7	56.3	53.3
9	35.5	28.8	59.2	71.2
10	45.8	76.8	43.2	20.3
Number of cells: normally 1650–3200 cells/mm^2. Polymegathism: normally >30%				

Table 3

Quantitative assessment of corneal epithelial cells before and after antibiotic drop instillation in the second group (original levofloxacin) according to confocal microscopy data

Таблица 3

Данные качественной оценки состояния клеток эпителия роговицы у пациентов 2-й группы (Левофлоксацин оригинальный) по данным конфокальной микроскопии

Patient	Polymegathism		Pleomorphism	
	Before eye drop instillation, %	After eye drop instillation, %	Before eye drop instillation, %	After eye drop instillation, %
1	33.4	47.8	59.3	34.3
2	41.5	35.0	52.5	53.4
3	35.2	37.1	48.1	53.3
4	39.6	46.4	53.5	41.4
5	32.8	28.6	59.7	43.1
6	49.0	32.9	37.7	53.9
7	56.5	37.0	31.5	55.1
8	38.8	34.8	47.8	65.2
9	37.5	40.6	52.6	39.7
10	45.8	39.4	49.3	45.3

Table 4

Quantitative assessment of corneal epithelial cells before and after antibiotic drop instillation in the second group (moxifloxacin) according to confocal microscopy data

Таблица 4

Данные качественной оценки состояния клеток эпителия роговицы у пациентов 2-й группы (Моксифлоксацин) по данным конфокальной микроскопии

Patient	Polymegathism		Pleomorphism	
	Before eye drop instillation, %	After eye drop instillation, %	Before eye drop instillation, %	After eye drop instillation, %
1	38.3	45.5	56.1	35.1
2	39.2	48.4	47.5	47.0
3	35.0	42.0	46.2	38.1
4	32.9	38.7	57.3	38.7
5	43.4	63.4	48.1	20.5
6	33.3	49.9	63.4	47.5
7	46.4	42.8	50.7	43.6
8	38.1	28.5	57.5	56.3
9	36.6	31.6	56.2	53.1
10	49.1	42.8	36.0	37.9

to directly penetrate through the hydrophobic epithelium to reach the AC. Therefore, liposoluble drugs have obvious advantages. However, when the corneal epithelium is injured or inflamed, a drug penetrates much quicker.

If the antibiotic or preserving agent has toxic effects on the corneal epithelium, then permeability may also increase [12].

We found that the instillation of Signicef® ensures the highest concentration of the antibiotic in the AC fluid (1.5 μg/mL) compared with that of other antimicrobial eye drops. This may be attributed to the presence of hypromellose in Signicef®, which is highly viscous and increases the duration of contact between the antibiotic and the surface of cornea and conjunctiva. Signicef® contains twice as much BAC as does Oftaquix™; it has an impact on the corneal epithelium (confirmed by confocal microscopy) and may potentially influence the bioavailability of the drug.

In terms of cytotoxicity, our data largely coincides with those published by foreign authors. Earlier studies have demonstrated that fluoroquinolones could suppress the proliferation of keratocytes [14], while a high concentration of fluoroquinolones may exhibit cytotoxic effect on the corneal epithelium and endothelium [12]. Previous studies have suggested that ciprofloxacin has the lowest cytotoxicity to corneal epithelium compared with norfloxacin, ofloxacin, gentamicin, and tobramycin [9]. More recent studies that evaluated the cytotoxic effect of third- and fourth-generation fluoroquinolones have revealed that levofloxacin is less toxic than are moxifloxacin or gatifloxacin [7]. Other studies have confirmed this by demonstrating that levofloxacin exerts the lowest cytotoxic effect on human corneal endothelium and keratocytes among the five ophthalmic fluoroquinolones, whereas ciprofloxacin exerts the most cytotoxic effect [8]. Kim et al. (2007) have revealed that the viability rate of human corneal epithelial cells after a 24-h incubation with levofloxacin was 64%, whereas that after the incubation with moxifloxacin was only 5%. Besides, the assessment of cellular migration ability showed that the re-epithelialization rate after a 24-h incubation with levofloxacin was 95% (which did not significantly differ from the control), whereas that after an incubation with moxifloxacin was 60%; this is important because quick corneal re-epithelialization helps in preventing secondary infection of the ocular surface and other possible complications [11]. Despite multiple studies suggesting a potential cytotoxicity of fourth-generation fluoroquinolones, some recently published reports have challenged this. R. Watanabe et al. (2010) observed no significant difference in the cytotoxicity and unfavorable effects of levofloxacin and moxifloxacin on the corneal epithelium in healthy volunteers; both drugs were safe and well tolerated. These data correlate with those of another study, which also failed to demonstrate significant differences in the speed of corneal healing in patients receiving moxifloxacin and levofloxacin eye drops after PEC, although re-epithelialization seemed to be faster in patients receiving levofloxacin [11]. The authors concluded that the prophylactic use of eye drops with fourth-generation fluoroquinolones during the postoperative period should not cause serious concerns regarding drug cytotoxicity.

CONCLUSION

We demonstrated that third- and fourth-generation fluoroquinolones may exert cytotoxic effects of various degrees *in vivo*. The results of our analysis should be extrapolated to clinical signs, which are usually non-specific. The cessation of an antibiotic or its substitution by a less toxic one may solve the problem of adverse effects of eye drops.

The mean concentration of third- and fourth-generation fluoroquinolones in the AC in patients receiving Oftaquix™ and Vigamox® was similar (0.9 and 1.0 μg/mL, respectively). Patients receiving Signicef® had a higher (1.5 μg/mL) concentration of the antibiotic in the AC. The optimal time for the instillation of antibacterial eye drops is 30–120 min prior to PEC, which allows the achievement of MTC of the antibiotic in the AC. A broad implementation of antibiotic concentration assessment using HPLC/MS will increase the efficacy and safety of fluoroquinolone therapy in patients after ophthalmic surgery. For all tested eye drops, the concentration of the antibiotic in the AC was several times higher than the MTC measured for 90 bacterial strains recovered from clinical specimens, which ensures postoperative safety and prevention of infectious complications.

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