Improved penetration of aminoglycosides and fluoroquinolones into the aqueous humour of patients by means of Acuvue contact lenses

Abstract Objectives: In order to improve the penetration of topically applied drugs in ophthalmology, the suitability of hydrophilic contact lenses (Acuvue, Vistacon, power −1.0 D) as a drug delivery system for antibiotics was tested. A prospective study was undertaken to determine the transcorneal penetration of five topically applied aminoglycosides and fluoroquinolones into the aqueous humour of patients.

Methods: Two hundred and sixty-five patients undergoing cataract extraction received 0.3% gentamicin, kanamycin, tobramycin, ciprofloxacin or ofloxacin solution by two different modes of administration: either as eye drops (nine drops every 15 min, starting 2 h prior to surgery) or by means of a drug delivery system (Acuvue contact lenses soaked for 1 h in eye drop solution without preservatives, 1–5 h prior to surgery). At the beginning of cataract extraction, 50–100 μl aqueous fluid was aspirated from the anterior chamber and immediately stored at −80 °C. Antibiotic concentrations were measured using fluorescence polarisation immunoassays (aminoglycosides) or high-performance liquid chromatography (fluoroquinolones).

Results: After soaking for 1 h in 0.3% eye drop solutions, Acuvue contact lenses released about 190–250 μg aminoglycoside and ofloxacin and 1000 μg ciprofloxacin. These amounts are considerably lower or in the same order of magnitude than obtained with application of eye drops (1350 μg).

From the aminoglycosides tested, only gentamicin and tobramycin, but not kanamycin, were able to penetrate into the aqueous humour of patients. After the wearing of antibiotic-soaked lenses, mean aqueous humour concentrations were higher than after the use of eye drops. This difference reached significance in tobramycin (1.09 (1.30) μg·ml⁻¹ vs 0.49 (0.79) μg·ml⁻¹), ciprofloxacin (1.23 (0.60) μg·ml⁻¹ vs 0.38 (0.33) μg·ml⁻¹) and ofloxacin (5.55 (2.53) μg·ml⁻¹ vs 0.56 (0.37) μg·ml⁻¹).

The percentage of patients with aqueous humour concentration above the MIC₉₀ of Staphylococcus epidermidis, the most common cause of postoperative endophthalmitis, was 92% and 100% after wearing ciprofloxacin- or ofloxacin-soaked lenses, respectively.

Conclusion: Gentamicin and tobramycin penetrated into the aqueous humour of patients, whereas kanamycin was not able to overcome the corneal barrier. Acuvue contact lenses soaked in 0.3% eye drop solutions can release sufficient amounts of gentamicin, ciprofloxacin and ofloxacin to produce bacteriostatic concentrations in the humor aquosus. Acuvue contact lenses can be recommended as a drug delivery system for fluoroquinolones.

Key words Aqueous humour penetration · Fluoroquinolones · Aminoglycosides

Introduction

Current means of ocular drug delivery include drops and ointments, subconjunctival injections, and intraocular injections. Commercially prepared antibiotic drops, applied topically, are generally satisfactory for the treatment of mild superficial infections, but may not be sufficient in delivering high concentrations of antibiotics to the anterior chamber. Subconjunctival injections are painful, can result in injury to the eye and deliver non-uniform concentrations of drug to the cornea. The pharmacological and microbiological characteristics of aminoglycosides and fluoroquinolones make them suitable for prophylaxis and therapy of intraocular infections. But clinical data on the disposition of these
antibiotics after topical application into the aqueous humour of patients showed that sufficient concentrations could be obtained, even with frequent instillation of eye drops, only in some of the patients treated [5, 6, 11, 18]. Therefore, the aim of this study was to measure the penetration of topically applied aminoglycoside and quinolone eye drops into the aqueous humour of humans and to test whether penetration could be improved with hydrophilic soft contact lenses (Acuvue) serving as a drug delivery system.

Material and methods

Contact lenses as a drug delivery system

Acuvue contact lenses (Vistacon, Johnson & Johnson, Norderstedt, power −1.0 D), consisting of Etafilcon A, with a water content of 58%, were tested for suitability as a drug delivery system. Lenses were soaked in 1 ml eye drops of different antibiotics for various time intervals (three lenses for 15 min, 1, 2 and 24 h, respectively). Afterwards drugs were washed out by incubating the lenses four times in 3 ml sterile 0.9% NaCl solution. The drug concentrations were detected (see below) and the amount of released antibiotic per lens was calculated (Table 1).

Antibiotics

The following antibiotics were tested as 0.3% eye drop solutions: gentamicin (Gentamix, Dr. Mann Pharma), kanamycin (Kanamix, Basotherm), tobramycin (Tobramaxin, Alcon-Thilo), ciprofloxacin (Ciloxan, Alcon-Thilo) and ofloxacin (Floxal, Dr. Mann Pharma). Following the warnings by manufacturers not to apply drugs onto the cornea while wearing contact lenses, for use with Acuvue contact lenses as a drug delivery system only eye drops without preservatives were used. If such formulations were not available, eye drops in the appropriate concentration were manufactured in the pharmacy of the University Clinic.

Application modes

On the day of surgery, patients received one of the antibiotics either as eye drops or via Acuvue contact lenses. Drugs and application modes were tested sequentially. Eye drops were applied during a period of 2 h prior to surgery by the same nurse (one drop every 15 min, nine drops in all), starting 2 h prior to incision. Acuvue contact lenses were soaked for 1 h in eye drop solution, were put on the cornea for 1–5 h. Time of application of the lenses and start of surgery was recorded.

Patients and drawing of samples

Two hundred and sixty-five patients undergoing cataract extraction (205 females) were included in the study after informed consent.

Table 1 Cumulative amount of antibiotic released from Acuvue contact lenses after soaking in 1.0 ml 0.3% eye drop solution and washing out in four volumes of 3.0 ml sterile 0.9% NaCl solution

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Released amount</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>186 (17) µg</td>
<td>6</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>230 (56) µg</td>
<td>8</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>239 (31) µg</td>
<td>8</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>246 (24) µg</td>
<td>8</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>998 (34) µg</td>
<td>8</td>
</tr>
</tbody>
</table>

The patients were between 33 and 94 years (mean age 77.5 years) of age. At the beginning of cataract extraction, 50–100 µl aqueous humour was aspirated after paracentesis from the anterior chamber with a 26-gauge cannula attached to an insulin syringe and immediately frozen at −80 °C until analysis.

Analytics

Aminoglycosides

Aminoglycosides were measured with a fluorescence polarisation immuno-assay (FPIA, Abbott Diagnostic Products, Wiesbaden). For gentamicin and tobramycin, reagent-specific kits were used. Kanamycin was quantified with the amikacin kit, using the known cross-reactivity for kanamycin. The method was calibrated with appropriate concentrations of kanamycin (Dr. Karl Thomae GmbH, Biberach a.d.Riss) in 0.9% NaCl solution. Quality controls were carried out by regularly measuring three control samples per set. The quantitation limits were as follows: gentamicin 0.27 µg·ml⁻¹, tobramycin 0.18 µg·ml⁻¹, kanamycin 0.8 µg·ml⁻¹.

Fluoroquinolones

Fluoroquinolones were measured by HPLC with fluorescence detection after extraction of the samples with methylene chloride [15, 18]. The quantitation limits were 10 ng·ml⁻¹ for ciprofloxacin and 12 ng·ml⁻¹ for ofloxacin. Regarding the validation of the method and the quantitative analysis of the various samples, the relevant principles were taken into account [16].

Statistical tests

All concentration data are given as means with SD. The samples were evaluated for normal distribution by the Kolmogorov-Smirnov test. As the distribution of the concentrations was not Gaussian, the nonparametric comparison of concentrations in the independent sample groups was carried out by the H test of Kruskal and Wallis. In case the samples were not derived from the same data set, multiple paired comparison of the mean ranks with the χ² analysis was performed. A P-value of ≤0.05 was considered significant.

Results

In vitro studies

Acuvue contact lenses were able to adsorb all tested aminoglycosides and fluoroquinolones in sufficient amounts. The released amounts of aminoglycosides were comparable for all three substances and for ciprofloxacin (Table 1). Lenses adsorbed significantly more ofloxacin than ciprofloxacin.

Adsorption occurred fast, lenses were loaded to a maximum already after 15 min. Longer soaking times did not considerably increase the amount of released antibiotics (Fig. 1). All aminoglycosides and ofloxacin were released rapidly, about 90% of the adsorbed drug were washed out within the first washing step. Ciprofloxacin was released more slowly so that relatively high amounts were found even in the fourth washing volume (Fig. 2). After the fourth washing step only negligible amounts were released.

Based on these results, for the following clinical study Acuvue contact lenses were soaked for 1 h in the above