Penetration of cefpirome into the anterior chamber of the human eye after intravenous application

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The penetration of intravenously administered cefpirome into the anterior chamber of the non-inflamed human eye was investigated in this study. A total of 42 patients, all hospitalized for cataract extraction, received a dosage of 1 g or 2 g of cefpirome by iv infusion 1, 2 or 6 h preoperatively. An aqueous humour sample was collected immediately after paracentesis and a blood specimen was simultaneously obtained from each patient. All samples were analysed for cefpirome concentrations using high-pressure liquid chromatography. Mean aqueous humour levels of cefpirome in patients receiving a dosage of 1 g were 1.33 mg/L (1 h), 1.67 mg/L (2 h) and 1.29 mg/L (6 h after application), respectively. When patients received a dosage of 2 g cefpirome the resulting mean aqueous humour concentrations were 1.60 mg/L (1 h), 2.27 mg/L (2 h) and 2.39 mg/L (6 h after application), respectively. A statistically significant difference in aqueous humour concentrations between patients receiving 1 g or 2 g of cefpirome could not be proven. In conclusion, cefpirome penetrates well into the anterior chamber of the non-inflamed human eye in concentrations that are therapeutic for many Gram-positive and Gram-negative organisms, frequently responsible for anterior segment eye infections.

Introduction

Cefpirome is a cephalosporin composed of a β-lactam ring fused with a six-membered dihydrothiazine ring—as with other cephalosporins—but additionally has a positively charged quaternary ammonium molecule at the carbon-position 3 of this dihydrothiazine ring. This confers the distinctive advantages of both higher permeability across the outer bacterial membrane and low affinity for chromosomal cephalosporinases compared with the third-generation cephalosporins that lack this quaternary ammonium moiety. These unique properties have also led to the suggestion that this antibiotic—together with some others—represents a ‘fourth-generation’ of cephalosporins.1

From clinical and bacteriological data it is evident that cefpirome is extremely effective against Gram-positive and Gram-negative bacteria,2-5 with cure rates similar to or better than those obtained with ceftazidime, cefotaxime and ceftriaxone.2

As many of these susceptible organisms are frequently the causative agents in intraocular infections, information on the ability of cefpirome to penetrate into the aqueous humour is clearly important. This study was designed to determine the penetration characteristics of cefpirome into the aqueous humour of the non-inflamed human eye.

Materials and methods

A total of 42 patients (22 females and 20 males), aged 58-87 years, all hospitalized for cataract extraction, were included in this study. Exclusion criteria were all other ocular diseases, previous ocular surgery, topical or systemic antibiotic treatment up to 4 weeks preoperatively, hepatic disease, renal function impairment, diseases of the central nervous system and allergy to antibiotics.

All patients gave informed consent to take part in this study. The study protocol followed the tenets of the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the County Government of Salzburg.

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Patients were randomly assigned to one of six groups, with seven patients in each group. Twenty-one patients received a dosage of 1 g cefpirome, administered intravenously over a period of 10 min ending 1 h (group 1a), 2 h (group 1b) and 6 h (group 1c) before aqueous humour collection. An additional 21 patients received a dosage of 2 g cefpirome, administered in an identical fashion (groups 2a, 2b and 2c).

Immediately before surgery, patients routinely received tropicamide 0.5% eye drops (5 mg tropicamide preserved in 0.01 mg phenylmercuric nitrate). Patients were prepared for surgery with topical application of 0.4% tetracaine hydrochloride, retrobulbar injections of 2% lidocaine hydrochloride and one drop of povidone-iodine 5%. Eyelids, brow, nose, cheek and forehead were scrubbed with povidone-iodine 10%. After draping, a paracentesis was performed and 0.05–0.1 mL of aqueous humour were aspirated using a 30 gauge blunt cannula. A blood specimen was collected simultaneously with the aqueous humour aspiration from all patients. All samples were stored immediately at –80°C until processing.

All samples were analysed for cefpirome concentration by high-pressure liquid chromatography (HPLC) according to the following procedures. For the assay of aqueous humour and serum a Shimadzu SIL6B auto injection port, a Shimadzu LC9A pump and a UV-VIS, SPD-10AV Shimadzu workstation (Shimadzu, Tokyo, Japan) were used. Chromatography was performed at room temperature on a C18 column (4.0 mm × 150 mm i.d., 5 μm particle size, M & W, Berlin, Germany). The mobile phase consisted of 750 mL 0.05 mol/L sodium acetate trihydrate (Merck, Darmstadt, Germany), 8 mL tetrabutylammonium hydroxide (20% w/w) and 250 mL methanol adjusted to pH 5.0–5.5. The flow rate was 1 mL/min. Cefpirome concentration was measured by UV absorption at 240 nm. Details concerning internal standard and calibration curves, and regression equation have been described previously.6

The samples were thawed at room temperature directly before analysis. We added 300 μL of internal standard to the specimen and stirred it for c. 60 s. After centrifugation at 7500 g for 2.5 min the supernatant was filtered through a 0.2 μm filter (Watermillipore, Molsheim, France), and 20 μL were injected into the HPLC column through the auto injector. With this HPLC method, the minimum detectable cefpirome concentration was 0.45 mg/L.

Statistical methods
To detect differences in serum and aqueous humour cephalosporin concentrations within the six groups, we performed a MANOVA based on the bootstrap. We computed our statistical results based on simultaneous confidence intervals to assess which means could be regarded as statistically significant.7,8

Results
Concentrations of cefpirome after iv injection of 1 g or 2 g found in aqueous humour and serum are shown in Figure 1 (aqueous humour concentrations) and Figure 2 (serum concentrations).

**Figure 1.** Aqueous humour concentrations of cefpirome after iv administration. Vertical bars indicate mean ± s.d.; large boxes indicate mean ± s.e.; small boxes indicate mean.
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After infusion of 2 g cefpirome the serum concentration resulting 1 h after injection is statistically significantly higher when compared with a dosage of 1 g ($P < 0.05$). This difference is not reflected in the aqueous humour concentrations. At the 2 and 6 h sampling time points a statistically significant difference between the patients receiving a dosage of 1 g or 2 g cefpirome could not be shown, either in serum or in aqueous humour concentrations.

A statistically significant decrease of cefpirome over a period of 6 h was not detectable in aqueous humour or serum samples.

Discussion

For an antibiotic to be effective a therapeutic concentration must be reached in an infected tissue and has to be maintained for an adequate period of time. This study clearly demonstrates that clinically significant levels of cefpirome are achieved in the aqueous humour of the non-inflamed human eye after infusion of 1 or 2 g.

The levels obtained are greater than the MIC$_{90}$ (minimal inhibitory concentration required to inhibit 90% of the isolates tested) for many bacteria that are frequently responsible for serious infections of the anterior segment of the eye.

Cefpirome is particularly active against Enterobacteriaceae such as Proteus mirabilis (MIC$_{90} < 0.12$ mg/L), Proteus vulgaris (MIC$_{90} 1$ mg/L), Aeromonas spp. (MIC$_{90} 0.25$ mg/L) and Serratia marcescens (MIC$_{90} 1$ mg/L). Pneumococci (MIC$_{90} < 0.12$ mg/L), group A streptococci (MIC$_{90} < 0.12$ mg/L) and group B streptococci (MIC$_{90} < 0.25$ mg/L) are also very susceptible, as is Staphylococcus aureus (MIC$_{90} 1$ mg/L).

The anti-staphylococcal activity of cefpirome seems to be a distinct advantage of cefpirome compared with other cephalosporins frequently used in the treatment of ocular infections. Sader & Jones have shown in their study that cefpirome was eight-fold to 64-fold more active than ceftazidime against seven different staphylococcal species.

Cefpirome is effective against Pseudomonas aeruginosa also, but requires a considerably higher minimal inhibitory concentration (MIC$_{90} > 16$ mg/L). MIC$_{90}$ for Staphylococcus epidermidis (4 mg/L) is also higher than the cefpirome concentration achievable in the anterior chamber after iv application. For the treatment of intraocular infections caused by these bacteria a combination with another antibiotic more effective against P. aeruginosa and S. epidermidis seems to be mandatory. This requirement of a rather high tissue concentration is a disadvantage that cefpirome shares with other cephalosporins, e.g. cefotaxime.

As the anterior chamber concentrations of cefpirome 1, 2 and 6 h after iv application do not differ in a statistically significant manner, it can be safely concluded that an infusion every 6 h is sufficient to produce therapeutic aqueous humour concentrations. Further studies are required to show whether administration at shorter intervals can increase anterior chamber concentrations to the MIC$_{90}$ for S. epidermidis.

Figure 2. Serum concentrations of cefpirome after iv administration. Vertical bars indicate mean ± s.d.; large boxes indicate mean ± s.e.; small boxes indicate mean.
A s shown by the results of this study, 2 g cefpirome seems to confer no benefit for the attainable anterior chamber concentration when compared with a dosage of 1 g.

Kanski et al. have shown a three-fold increase of aqueous humour concentration for cefoxitin in inflamed eyes, as compared with non-inflamed eyes. A s our study was carried out in ‘quiet’ eyes, it is reasonable to assume that in the presence of anterior-segment inflammation the breakdown of the blood–aqueous humour barrier permits an easier diffusion, resulting in higher antibiotic levels.

In conclusion, cefpirome is able to penetrate the blood–aqueous humour barrier, and therapeutic concentrations for many bacteria that are frequently responsible for ocular infections are achievable. Further studies will have to investigate penetration into the vitreous humour and resulting intraocular levels of cefpirome, both in the non-inflamed, native eye and under conditions of intraocular infection.

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References


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