Pharmacokinetics of linezolid in human non-inflamed vitreous after systemic administration

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Objectives: To determine the concentration–time curves of linezolid in serum and vitreous from 24 patients undergoing vitrectomy.

Methods: Vitrectomy was performed 1, 2, 4, 8 and 12 h after infusion of 600 mg of linezolid in 20 patients divided into groups of four. Four additional patients were studied 12 h after two separate oral doses of 600 mg of linezolid. Serum samples were obtained 1 h after linezolid administration to determine $C_{\text{max}}$; vitreous and a second serum sample were taken simultaneously during the vitrectomy in all patients, and the concentrations of linezolid in vitreous ($C_v$) and serum ($C_s$) were determined.

Results: Among patients who received one intravenous dose of 600 mg of linezolid, the highest mean $C_v$ was observed at 4 and 8 h following linezolid administration (3.4 and 3.7 mg/L). The highest mean $C_v$ was observed in patients who received two oral doses of 600 mg of linezolid separated by 12 h (4.5 mg/L), which was higher than the MIC 90 for Staphylococcus epidermidis. The highest $C_v/C_s$ ratio was reached 12 h after administration of one and two doses (2.4 and 1.5, respectively).

Conclusions: Microbiologically significant concentrations of linezolid can be achieved in the vitreous of the non-inflamed human eye after intravenous administration of 600 mg, and it is even better after two doses of 600 mg. It appears that linezolid accumulates in the vitreous, achieving potentially useful steady-state concentrations. An evaluation of clinical efficacy is needed to confirm the perceived utility based on the pharmacokinetics.

Keywords: oxazolidinones, eye, penetration

Introduction

Bacterial endophthalmitis, with an estimated incidence of 0.07% to 0.3% after cataract surgery, is one of the most severe complications of intraocular surgery and may result in significant vision loss.1–3 Post-operative endophthalmitis is most frequently due to infection with Gram-positive bacteria, particularly coagulase-negative staphylococci.4 In post-traumatic endophthalmitis, Gram-positive bacteria also play an important role.2 Direct intraocular injection of antibiotics is necessary to treat infectious endophthalmitis because penetration into the eye from the bloodstream is restricted by the blood–ocular barrier for the majority of antistaphylococcal antimicrobials.6 Newer fluoroquinolones (levofloxacin and moxifloxacin) reach the vitreous rapidly in the uninflamed phakic eye following systemic administration.7,8 However, currently, the spectrum of coverage does not appropriately encompass the most common causative organisms in endophthalmitis, especially Staphylococcus epidermidis.9,10 Linezolid is a synthetic oxazolidinone antimicrobial that is highly active against Gram-positive bacteria including meticillin-resistant Staphylococcus aureus and coagulase-negative staphylococci.11 After several oral or intravenous doses of 600 mg/12 h, linezolid reaches maximum concentrations ($C_{\text{max}}$) in serum of 15–20 mg/L with a serum $C_{\text{min}}$ of 4–6 mg/L. As protein binding...
Pharmacokinetics of linezolid in vitreous humour

Table 1. Concentrations of linezolid in vitreous (Cv) and serum (Cs)

<table>
<thead>
<tr>
<th>Time following linezolid administration</th>
<th>Cv (mg/L), mean (range; SD)</th>
<th>Cs (mg/L), mean (range; SD)</th>
<th>Mean ratio (=Cv/Cs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 h</td>
<td>12.7 (11.6–13.5; 0.9)</td>
<td>1.00 (0.9–1.0; 0.06)</td>
<td>0.07</td>
</tr>
<tr>
<td>2 h</td>
<td>8.0 (7.6–8.6; 0.5)</td>
<td>2.2 (0.7–3.6; 2.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>4 h</td>
<td>6.9 (1.7–9.8; 3.5)</td>
<td>3.4 (2.4–4.4; 1.1)</td>
<td>0.49</td>
</tr>
<tr>
<td>8 h</td>
<td>6.0 (4.1–7.8; 2.6)</td>
<td>3.7 (2.8–5.3; 1.4)</td>
<td>0.61</td>
</tr>
<tr>
<td>12 h</td>
<td>1.0 (0.4–1.4; 0.4)</td>
<td>2.4 (1.8–2.8; 0.4)</td>
<td>2.40</td>
</tr>
<tr>
<td>12 h following two oral doses</td>
<td>3.9 (2.7–5.5; 1.3)</td>
<td>4.5 (3.6–5.2; 0.8)</td>
<td>1.15</td>
</tr>
</tbody>
</table>

*aSerum and vitreous simultaneously obtained.

is low (30% to 35%), free serum concentration and interstitial fluid are above the MIC for Gram-positive pathogens during the entire interval between doses. Linezolid has shown significant penetration into the aqueous humour in human non-inflamed eyes. However, data concerning human vitreous penetration of linezolid are scarce. If linezolid reaches sufficient concentration in this compartment, it would be highly useful for the treatment of infectious endophthalmitis and even for prophylaxis in high-risk ocular surgical patients. The aim of this study was to establish the vitreous penetration of linezolid following systemic administration in patients with non-inflamed vitreous.

Patients and methods

The study was performed at the Hospital Clínic in Barcelona (Spain), a 600 bed tertiary care hospital. Twenty-four patients who underwent pars plana vitrectomy from March 2004 to September 2004 were included. Twenty patients received one dose of a 30 min intravenous infusion of 600 mg of linezolid. Later, two blood vials were obtained (one 1 h after the intravenous dose and the other at the time of the vitrectomy) and vitreous was extracted during the vitrectomy. Vitrectomy was performed at 1, 2, 4, 8 and 12 h after infusion in 20 patients divided into groups of four. Four additional patients received two oral doses of 600 mg of linezolid separated by 12 h. Vitrectomy was then performed 12 h after the second dose. Exclusion criteria were arterial hypertension, pheochromocytoma, therapy with adrenergic or serotoninergic drugs or serotonin reuptake inhibitors, pregnancy, renal insufficiency (serum creatinine >1.8 mg/dL) and active diabetic vitreoretinopathy with recent (<1 month) haemovitreous. The study was approved by the Institutional Review Board at the Hospital Clinic. All patients gave informed consent to take part in the study.

Concurrently, serum (3–4 mL) samples were obtained 1 h after the end of intravenous linezolid administration (Cmax). Afterwards, serum (3–4 mL) and vitreous (0.2–0.3 mL) samples were obtained simultaneously during surgery in groups of four patients each, at 1, 2, 4, 8 and 12 h after linezolid administration. Four additional patients received two oral doses of 600 mg of linezolid separated by 12 h. Vitrectomy was then performed 12 h after the second dose, obtaining serum and vitreous samples at the same time. All samples were stored immediately at −80°C until processing.

Concentrations of linezolid were determined by HPLC, as previously reported. Several variables were analysed, including the mean Cmax and the mean concentration of linezolid in vitreous (Cv) and serum (Cs) samples taken simultaneously from different groups of patients.

Descriptive statistical analysis was done using the SPSS version 14.0 package.

Results

Fifteen men (62.5%) and nine (37.5%) women were studied. Mean (SD) age was 62 (15.4) years (range 32–86). All were white Caucasian. Indications for vitrectomy were: retinal detachment, 17 (70.8%); macular hole, 2 (8.3%); lens subluxation, 2 (8.3%); diabetic retinopathy without haemovitreous, 2 (8.3%); and epiretinal membrane, 1 (4.2%).

The mean linezolid Cmax was 13.4 mg/L (range 9.4–20.5; SD 2.8). The mean Cv and Cs and the mean Cv/Cs ratio at different times following linezolid administration are shown in Table 1. Linezolid concentration versus time curves are shown in Figure 1. The highest mean Cv of linezolid was observed in patients who received two oral doses of 600 mg of linezolid separated by 12 h (4.5 mg/L; range 3.6–5.2; SD 0.8). Among patients who received one intravenous dose of 600 mg of linezolid, the highest mean Cv was observed at 4 and 8 h following linezolid administration:

![Figure 1. Pharmacokinetic curves (concentration versus time) showing linezolid concentrations in serum and vitreous following one and two doses of 600 mg of linezolid. Filled circles, observed serum concentration; open circles, observed vitreous concentration; continuous line, serum concentration–time curve after the first intravenous (iv) dose; dotted line, 'expected' serum concentration–time curve after the second dose [iv or oral (smaller curve)]; dashed line, vitreous concentration–time curve; horizontal line, MIC90 of linezolid for S. epidermidis and S. aureus (4 mg/L).](image-url)
3.4 mg/L (range 2.4–4.4; SD 1.1) and 3.7 mg/L (range 2.8–5.3; SD 1.4), respectively. All patients had a $C_v$ of $\geq 2$ mg/L 4 h after antibiotic administration, and all patients but one had a $C_v$ $\geq 4$ mg/L 12 h after administration of two oral doses of linezolid administered 12 h apart. The highest $C_v/C_s$ ratio was reached 12 h after administration of one and two doses of the antibiotic (2.4 and 1.15, respectively) (Table 1).

Linezolid-related adverse effects were not detected. None of the patients developed infection after surgery.

Discussion

Results from this study show that microbiologically significant concentrations of linezolid can be achieved in the vitreous humour of the non-inflamed human eye after intravenous administration of 600 mg, and it is even better after two doses of 600 mg.

Coagulase-negative staphylococci are the causative agents of $\sim 70\%$ of post-cataract surgery endophthalmitis, followed by $S. aureus$. Enterococci and Streplococcus pneumoniae are less frequent; however, endophthalmitis due to these microorganisms is severe. In post-traumatic endophthalmitis, Bacillus cereus and Gram-positive bacteria are the most frequent causative agents. All these bacteria are susceptible to linezolid.

Two hours after administration of one dose of the antibiotic, the concentrations achieved in the vitreous were higher than the MIC at which 90% of Streplococcus spp. strains are inhibited, including enterococci (2 mg/L). Furthermore, 12 h after two separate doses of 600 mg, concentrations achieved in the vitreous were higher than the MIC at which 90% of $S. epidermidis$ and $S. aureus$ are inhibited (4 mg/L). Taking this finding into account, as well as the fact that the $C_v/C_s$ ratio is higher 12 h after administration of the antibiotic, it appears that linezolid accumulates in the vitreous, achieving potentially useful steady-state concentrations. This is a relevant pharmacokinetic advantage of linezolid as this is a time-dependent antibiotic.

Two previous studies, with somewhat different methodologies, have also shown penetration of linezolid into the vitreous. One study determined vitreous linezolid concentration 1–3 h after administration, and found a higher concentration in patients in whom vitrectomy was performed later, suggesting an upsurge of vitreous linezolid as serum concentration increased, as we have demonstrated. The other study analysed vitreous linezolid concentrations $\sim 100$ and 220 min after one dose, and 350 min after two separate doses, and found concentrations of linezolid $> 2$ mg/L at 3 h after administration, and even higher concentrations (5.7 mg/L) $\sim 4$ h after the administration of the two doses. In our study, patients were scheduled to be operated on at pre-fixed times in order to establish an accurate concentration–time curve after pooling all data. Our data confirm previous results. Moreover, our study analyses a wider period of time including 12 h after two separate doses of linezolid, demonstrating a good steady-state of this drug in the vitreous. An evaluation of clinical efficacy is needed to confirm the perceived utility based on the pharmacokinetics of linezolid in vitreous fluid.

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Transparency declarations

None to declare.

References