High dose intravitreal ganciclovir injection provides a prolonged therapeutic intraocular concentration

N Morlet, S Young, D Naidoo, G Graham, M T Coroneo

Abstract

Background—Although intravitreal high dose ganciclovir has previously been found to provide excellent control of cytomegalovirus (CMV) retinitis, little was known about the vitreous concentrations of ganciclovir after a 2 mg intravitreal injection.

Methods—Eleven vitreous samples were taken from seven patients with CMV retinitis at 24 and 72 hours after a 2 mg intravitreal injection of ganciclovir and the concentration of ganciclovir was measured by high performance liquid chromatography.

Results—The mean concentration of ganciclovir at 24 hours was 143·8 mg/l (95% confidence interval 97·8–190) and at 72 hours was 23·4 mg/l (95% CI 0–49·7). The half life ranged from 11·9 to 26·3 (mean 18·8) hours in the four patients who had two samples taken. The mean half-life calculated from the mean concentrations at 24 and 72 hours was 18·3 hours, so the calculated mean concentration at 7 days was 0·6 mg/l.

Conclusions—This suggests that it takes about 7 days to eliminate the intravitreal ganciclovir, and that it is not likely to accumulate with weekly injections. The intravitreal concentrations achieved with high dose therapy remained above the ID₅₀ for CMV (0·25–1·22 mg/l) for up to 7 days.

(Br J Ophthalmol 1996; 80: 214–216)

Ganciclovir is the commonest treatment for cytomegalovirus (CMV) retinitis, but because it is only virostatic, maintenance therapy is required to prevent relapse of the infection. Most physicians administer the drug intravenously; however, up to 20% of infections do not resolve with induction therapy, and many patients relapse at a median time of about 8 weeks while on maintenance therapy. Some believe that systemic maintenance therapy is associated with eventual relapse in all patients.

Intravitreal therapy has the advantage of delivering the drug directly to the posterior segment of the eye, avoiding systemic side effects. Using high dose intravitreal ganciclovir (2 mg/0·1 ml) we successfully suppressed the retinitis in 35 eyes of 22 patients. We found that only two patients relapsed on maintenance therapy of weekly injections, at 25 and 42 weeks respectively.

Effective and ongoing control of CMV retinitis by high dose intravitreal ganciclovir injections may reduce the incidence of blinding complications. However, there is a paucity of data about the intraocular pharmacokinetics of ganciclovir. Only one other study estimated the half life to be 13·5 hours from just two vitreous samples after intravitreal ganciclovir injection of 200 μg/0·1 ml. In this study, we demonstrated that high dose therapy provides at least 7 days of virostatic levels of ganciclovir in the human eye.

Methods

Eleven samples of vitreous humour were taken from seven male patients after informed consent, 24 and 72 hours after an intravitreal ganciclovir (2 mg/0·1 ml) injection for CMV retinitis. The eye was anaesthetised by peribulbar block and decompressed with a mercury bag (30 mm Hg) for 15 minutes. Using a 23 gauge needle via the temporal pars plana, 0·1–0·2 ml of liquid vitreous was aspirated. The samples were then stored frozen at −8°C until analysed by high performance liquid chromatography (HPLC).

HPLC analysis was performed after equal volumes (100 μl) of vitreous fluid and 0·8 M perchloric acid were mixed, vortexed, and centrifuged at 10 000 g for 2 minutes. A 10 μl aliquot of the supernatant was then injected into a 4·6 mm octadecyl silica column (UltraspHERE), using an ultraviolet detector set at 254 nm, and a peak integrator. The elution buffer used was 20 mM ammonia acetate and 1·2% acetic acid at a flow rate of 1·5 ml/min.

Ganciclovir is a potent antiviral agent for the treatment of CMV retinitis, and it is effective in suppressing the infection in most patients. However, maintenance therapy is often required to prevent relapse of the infection.

Figure 1 Intravitreal concentration at 24 and 72 hours after intravitreal injection of 2 mg ganciclovir for four patients, and the mean of 11 concentrations from seven patients (bold line).
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**Table 1**  Intravitreal concentration of ganciclovir (mg/l) after an intravitreal injection of 2 mg/0.1 ml 24 or 72 hours earlier in seven patients receiving treatment for cytomegalovirus retinitis

<table>
<thead>
<tr>
<th>Concentration at</th>
<th>t1/2 (hours)</th>
<th>Estimated concentration at 7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours</td>
<td>72 hours</td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>212-0</td>
<td>59-8</td>
</tr>
</tbody>
</table>

*Calculated from mean concentrations at 24 and 72 hours.

The ganciclovir peak eluted at 9 minutes. Quantitation of ganciclovir levels was done by peak area comparison using a set of five prepared calibrators covering the range measured.

The logarithm of the concentrations of ganciclovir in the vitreous humour was plotted against time (Fig 1), and the slope (k) determined by linear regression. The half life of loss of ganciclovir (t1/2) is given by the relation t1/2 = 0-693/k.

**Results**

The concentrations obtained from the 11 samples are shown in Figure 1 and Table 1. The mean concentration of ganciclovir at 24 hours was 143.8 mg/l (95% confidence interval 97.5-190) and at 72 hours 23.4 mg/l (95% CI 0-49-7). The half life ranged from 11.9 to 26.3 (mean 18.8) hours in the four patients who had two samples taken. The mean half life calculated from the mean concentrations at 24 and 72 hours was 18.3 hours, so the calculated mean concentration at 7 days was 0.6 mg/l.

**Discussion**

This study provides preliminary data on the kinetics of loss of ganciclovir from the vitreous humour in humans. The estimated half life suggests that it takes about 7 days to eliminate ganciclovir after a 2 mg injection, and that ganciclovir is not likely to accumulate with weekly injections. The intravitreal concentration achieved with high dose therapy remained above the inhibitory dose that will inhibit 50% of activity (ID50) for CMV (0.25-1.22 mg/l), Table 2 for up to 7 days. This may account for our observation that rapid resolution of CMV retinitis occurs with twice weekly induction therapy, and there is little relapse with weekly injections.

Although the numbers in our analysis are small, once we established that weekly high dose intravitreal ganciclovir injections were not likely to accumulate in the vitreous, ethically we could not justify pursuing further samples. Apart from the slight discomfort involved during the procedure, multiple vitreous sampling may slightly increase the risk of retinal detachment in patients with CMV retinitis.

High dose intravitreal ganciclovir therapy may also be a useful treatment for retinchoroiditis caused by other herpesviruses — for example, the acute retinal necrosis syndrome. Table 2 shows the antiviral activity of ganciclovir for all the herpesvirus family. As for CMV, high dose intravitreal ganciclovir would provide up to 7 days of intraocular antiviral activity.

**Table 2**  Antiviral activity of ganciclovir against the herpesvirus family (from Diaz-Lloreta et al13)

<table>
<thead>
<tr>
<th>Virus</th>
<th>IC50 (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex 1</td>
<td>0.05-0.18</td>
</tr>
<tr>
<td>Herpes simplex 2</td>
<td>0.08-0.46</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>0.25-1.22</td>
</tr>
<tr>
<td>Varicella zoster</td>
<td>0.38-1.43</td>
</tr>
<tr>
<td>Epstein-Barr</td>
<td>0.013</td>
</tr>
</tbody>
</table>

IC50 = inhibitory concentration that will inhibit 50% of activity.

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