Pharmacokinetic assessment of oral ganciclovir in lung transplant recipients with cystic fibrosis

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Oral ganciclovir has been used as prophylaxis and therapy against cytomegalovirus in patients with HIV infection and following organ transplantation. Oral ganciclovir has clear practical advantages over intravenous ganciclovir but has a relatively low bioavailability and this may be problematic in at-risk patients with malabsorption. The bioavailability and therefore therapeutic potential of oral ganciclovir in cystic fibrosis (CF) patients post-lung transplant (LT) might be expected to be inadequate given the high incidence of malabsorption in these patients. An 8 h pharmacokinetic study was performed in 12 CF patients 160 ± 122 days post-transplant who had been taking 1 g oral ganciclovir tds for 3 days with food (plus normal enzyme supplements). Mean (range) serum creatinine was 150 µmol/L (70–280). Blood was sampled at 0.5, 1, 2, 3, 4, 6 and 8 h post-final dose. Plasma was stored at –20°C and later analysed by high-performance liquid chromatography. Mean peak concentration (Cmax) was 4.8 mg/L (0.96–12.8), mean minimum concentration (Cmin) was 3.6 mg/L (0.78–11.7) and mean area under the curve (AUC) was 35.4 mg.8 h/L (8–99). Cmax, Cmin and AUC correlated significantly with one another (P < 0.001) as well as with serum creatinine and creatinine clearance (P < 0.01). When corrected for alterations in renal function, plasma oral ganciclovir levels are as predicted for other transplant populations. Three days of oral ganciclovir results in therapeutically useful plasma drug levels in the CF LT population, despite a background of general malabsorption. Cmax, Cmin and AUC are highly correlated, allowing for the possibility of steady-state drug monitoring to confirm that the recommended dosing algorithm produces appropriate plasma levels.

Introduction

Cytomegalovirus (CMV) is a major cause of morbidity and mortality in recipients of organ transplants and a particular problem for lung transplant recipients.1 In lung transplant recipients, ganciclovir is an effective antiviral agent which is commonly administered intravenously for prolonged periods to treat and prevent CMV disease.1–3 Recently, oral ganciclovir has been used as prophylaxis and therapy against CMV in human immunodeficiency virus (HIV)-infected patients and, to a lesser degree, in solid organ transplant recipients.4,5 Oral ganciclovir has clear practical advantages of administration in comparison with intravenous ganciclovir with regard to expense, convenience and morbidity risk. Therapy with long-term intravenous ganciclovir is associated with specific problems of maintenance of intravenous access, the necessity for cytotoxic precautions for discarded dosing sets and the avoidance of line sepsis. However, oral ganciclovir has been noted to have a low bioavailability of 6–9%.4–6 This is an important consideration since the therapeutic success of this agent, with the additional need to avoid development of ganciclovir resistance, depends largely on achieving adequate plasma levels for the majority of the oral dosing interval.7,8 It has been noted that to achieve the desired minimum 50% viral inhibition, plasma levels need to exceed 1.0 mg/L.7 The site of oral ganciclovir absorption in the human gut

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has not been determined, although pharmacokinetic studies have shown that food increases absorption. Experience in the HIV population also suggests that alterations in gut motility can affect plasma levels.

Respiratory failure associated with cystic fibrosis (CF) is the most common indication for bilateral lung transplantation. Lung transplant recipients with CF may represent a group where the bioavailability and subsequent serum profile of oral ganciclovir may be inadequate. To be effective, the drug needs to achieve reproducible therapeutic levels over a significant portion of the dosing interval, without inappropriately elevated levels that predispose to dose-related toxicity. Gastro-oesophageal reflux, delayed gastric emptying, peptic ulcer disease, pancreatic insufficiency with malabsorption and the distal intestinal obstructive syndrome are common in the CF patient group. Liver metabolism, entero-hepatic shunting and renal clearance of drugs are also known to be abnormal in these patients.

For example, these disorders have been shown to have a major impact on cyclosporin kinetics in CF transplant recipients. Despite this, difficulties with venous access, a high incidence of CMV sero-mismatching and persistent CMV disease may persuade the clinician to use oral ganciclovir preferentially in this very population.

There is currently no information available on oral ganciclovir pharmacokinetics in CF patients. Therefore, the aim of the present study was to assess the pharmacokinetics of oral ganciclovir in CF patients who have undergone lung transplantation, specifically, to determine whether therapeutic levels can be achieved. Therapeutic oral ganciclovir levels in this medically complicated patient group would lead us to postulate that similar or higher drug levels are likely to be attained in less complicated lung transplant recipients.

### Materials and methods

#### Study population

Twelve lung transplant recipients with an underlying diagnosis of CF (mean age 30.7 years, range 21–41 years, seven male, five female) were recruited for an 8 h open-label pharmacokinetic study of oral ganciclovir. Patients were studied a mean (s.d.) of 160 (122) days post-transplant. The study population demographics are shown in Table I. Patients were all clinically and biochemically stable without alterations to medications in the previous 2 weeks. All subjects had previously been on tri-weekly intravenous ganciclovir but were not eligible for inclusion unless they had discontinued ganciclovir therapy for at least 2 weeks.

#### Study medication

Oral ganciclovir (Cymevene Oral, 250 mg capsules, Roche Products, Sydney, Australia) was self-administered at a dose of 1 g tds for 3 days. Patient 12 was inadvertently dosed at 500 mg instead of 1 g during the entire period of drug administration. The first dose was taken at 1600 h on day 1 and subsequent doses at 0800, 1600 and 2400 h. The subjects were advised to take the ganciclovir with food and their usual pancreatic enzyme supplementation. The final dose was administered at 0800 on day 4, the pharmacokinetic study day. Subjects were instructed to fast from 2400 h the night before, and were given a light breakfast with administration of the final dose of oral ganciclovir. Subjects were instructed to take their normal medications before 0600 h (i.e. at least 2 h before their final dose of ganciclovir). Times of study medication administration were accurately recorded.

### Table I. Study population demographics

<table>
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<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Sex</th>
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<th>Weight (kg)</th>
<th>Immunosuppression</th>
<th>Gut medication</th>
<th>Serum creatinine (μmol/L)</th>
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*Aza, azathioprine; CsA, cyclosporin; Tac, tacrolimus; P, prednisolone.

*H2, H2 receptor blocking drug; PPI, proton pump inhibitor.*
The study was approved by the Alfred Hospital Ethics Committee and written informed consent was obtained from each patient.

Ganciclovir levels

An intravenous catheter was placed in the antecubital fossa at least 30 min before the first (pre-dose) sample was collected. Blood samples were taken from the catheter pre-dose and 0.5, 1, 2, 3, 4, 6 and 8 h post-dose. Each sample was immediately centrifuged to separate plasma which was then transferred to a plain polypropylene tube and stored at –20°C until assayed for ganciclovir.

Ganciclovir was measured using high performance liquid chromatography (HPLC) according to the method of Page et al. Minor modifications include the use of a Varian Star HPLC (Los Angeles, CA, USA) with a model 9010 solvent delivery system, a 9100 Autosampler, 9065 Polychrom Diode Array detector and a 150 × 4.6 mm Alltech Alltima C18.5 micron HPLC column (Deerfield, IL, USA) fitted with a 7.7 × 4.6 mm guard column cartridge of the same material as the analytical column. The ganciclovir standard was provided by Roche Laboratories, Sydney, Australia. This provided excellent linearity in the 0.05–20.0 mg/L range.

Pharmacokinetic analysis

The following parameters were determined by non-compartmental pharmacokinetic analyses of the plasma drug concentration–time profiles: $C_{\text{max}}$, maximum plasma concentration (where the $C_{\text{max}}$ value occurred at more than one time-point, the first occurrence was taken as $C_{\text{max}}$); $C_{\text{min}}$, minimum plasma concentration; AUC, area under the plasma concentration–time curve from time zero to that of the last measured plasma concentration at 8 h, determined by log/linear trapezoidal rule integration. Serum creatinine (Cr) was measured by the Jaffe method on a Hitachi 747 (Tokyo, Japan) analyser. Creatinine clearance (CrCl) for males was estimated according to the formula:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times 0.011 \times \text{Cr (\mumol/L)}}$$

Females = 0.85 × male value.

Since ganciclovir follows first-order kinetics, the minimum concentrations at steady state were linearly related to dose and dosage rate. Therefore, the ratio between the measured and desired ganciclovir concentrations ($C$) can be used to correct dosage rate (mg oral ganciclovir/day) according to the equation:

$$\text{dosage rate (corrected)} = \frac{\text{dosage rate (used) \times C}_{\text{ganciclovir (desired)}}}{C_{\text{ganciclovir (measured)}}}$$

Statistics

Data are presented as means plus or minus standard deviations. Statistical analysis was performed by calculating correlation coefficients according to Spearman and by linear regression analysis.

Results

The study subjects were receiving 9 ± 4 medications as part of their routine post-transplant management. All had pancreatic insufficiency as part of their CF. Two patients were receiving H2 blockers, and three were receiving proton pump inhibitors, for peptic ulcer disease and reflux oesophagitis. Two patients were receiving pro-motility agents for gastric stasis and reflux oesophagitis. Ten patients were taking trimethoprim–sulphamethoxazole as Pneumocystis carinii prophylaxis.

The body heights and weights of the 12 study subjects are summarized in Table I. Mean body mass index (BMI) was 20.8 ± 1.7 kg/m² (range 18.9–24.0) for the group. Mean Cr concentration pre-study was 150 ± 70 μmol/L (range 70–280) and CrCl averaged 59 ± 27 mL/min (range 21–107). The other notable baseline abnormality, consistent with CF-related background intrahepatic cholestasis, was an elevated alkaline phosphatase of 251 ± 120 U/L (range 47–1100). These measurements and other baseline biochemistry and haematology screening values were not significantly different following the study. No adverse events were noted during or after the study at the 2 week follow-up visit.

The ganciclovir concentrations and pharmacokinetic profiles achieved are shown in Table II. Individual patient data are shown in Figure 1. The mean (range) $C_{\text{max}}$ was 4.8 mg/L (0.96–12.81). The mean $C_{\text{min}}$ was 3.6 mg/L (0.78–11.7). The mean AUC was 35.4 mg/L (8–99). $C_{\text{max}}$,
C\textsubscript{min} and AUC correlate significantly with one another ($P < 0.001$, $r^2 = 0.85$, see Figure 1). $C_{\text{max}}$, $C_{\text{min}}$ and AUC correlate significantly with Cr and CrCl. $C_{\text{min}}$ is plotted against CrCl in Figure 2 ($P < 0.01$, $r^2 = 0.51$).

Using the formula as outlined in Materials and methods, oral ganciclovir dosage/day can be ‘corrected’ to reveal a theoretical dosage/day that would provide a therapeutic serum level (i.e. a $C_{\text{min}}$ level $>1.0$ mg/L) for that individual—based on their achieved levels in the current study.$^7,16$ The calculated individual corrected dosages are shown in Table II. When corrected oral ganciclovir dosage/day is plotted against CrCl in Figure 3, the line of best fit is similar to the manufacturer’s suggested daily dosing algorithm for variations in CrCl and the variation upon this suggested in the recent renal transplant study by Pescovitz.$^14$

**Discussion**

This study demonstrates that oral ganciclovir has predictable pharmacokinetics in the CF population following lung transplantation. As has been shown previously for the HIV and the general transplant population, serum levels can be anticipated by dosing according to CrCl.$^7$ There is a tight correlation between $C_{\text{max}}$, $C_{\text{min}}$ and AUC.

The adequacy of plasma ganciclovir levels, despite a background of blockade of acid production, therapy for pancreatic insufficiency and altered gut motility in the CF study population, suggests that ganciclovir absorption may be independent of these factors.

The CF patients studied represent a sub-section of the lung transplant population. Their medication profile and renal function will reflect that of other lung transplant recipients.$^17$ Based on the current study and the previous transplant literature, oral ganciclovir is likely to achieve

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**Table II. Ganciclovir levels and pharmacokinetic results**

<table>
<thead>
<tr>
<th>Subject</th>
<th>$C_{\text{min}}$ (mg/L)</th>
<th>$C_{\text{max}}$ (mg/L)</th>
<th>AUC (mg.8h/L)</th>
<th>Corrected daily dosage (g/day)</th>
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**Figure 2.** Correlation between creatinine clearance and oral ganciclovir dosage/day ‘corrected’ to reveal a theoretical dosage/day that would provide a therapeutic serum level (i.e. a $C_{\text{min}}$ level $>1.0$ mg/L) for that individual. The current study is compared with other suggested dosing schedules. (______, line of best fit for test subjects; _ _, suggested dosing as per manufacturer; ……., suggested dosing as per Pescovitz$^{15}$ ($P < 0.01$, $r^2 = 0.51$).

**Figure 3.** Regression plot of minimum plasma ganciclovir concentration after oral dosing and creatinine clearance.
suitable serum levels in the majority of lung transplant recipients. This has important implications: oral ganciclovir does not require the venous access for prolonged periods that is associated with serious morbidity, and even mortality, in recipients receiving intravenous ganciclovir. Oral ganciclovir can be administered to achieve adequate levels each day (rather than the drop off between doses associated with three-times-weekly dosing) and is practical to administer beyond the current standard 3 month post-transplant period. This may be important given the potential for CMV infection to have indirect, late effects including an association with chronic allograft rejection.

Additionally, it is notable that only three of 12 study subjects had a CrCl greater than 70 mL/min. This would allow once-daily oral dosing in many lung transplant recipients. Much of the oral ganciclovir literature to date has focused on the HIV and only recently have studies been published, predominantly in the renal transplant literature, regarding the efficacy and safety of oral ganciclovir using a dosing algorithm based on renal function. The measurement of steady-state ganciclovir levels to ensure correct dosage is potentially useful. The correlation between $C_{\text{max}}$, $C_{\text{min}}$ and AUC is consistent with ganciclovir’s first-order kinetics and suggests that a full pharmacokinetic profile is not necessary. This means a trough level could be used to optimize dosing, thereby improving efficacy, avoiding drug toxicity and theoretically decreasing resistance. Viral resistance has been reported to occur in 5–10% of HIV patients treated long-term with oral ganciclovir, although the incidence in solid organ transplant recipients seems considerably less than this. It has been suggested that an inadequate therapeutic response with oral ganciclovir can lead to the selection of resistant strains of CMV. Monitoring of serum ganciclovir levels has not been reported in this setting but warrants further consideration.

In conclusion, oral ganciclovir achieves predictable pharmacokinetics in the complex situation of lung transplantation for CF. The achievement of adequate levels in this scenario suggests that, with appropriate dosing according to renal function, oral ganciclovir should be able to replace intravenous ganciclovir as a prophylactic anti-viral agent in many circumstances. The measurement of ganciclovir levels could theoretically be successfully extended to the clinical arena to optimize dosing. Randomized clinical trials need to be performed to look at these clinical and financial issues specifically in a lung transplant setting where the potential burden of CMV disease remains high for prolonged periods post-transplantation.

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References


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