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Disposition of valganciclovir during continuous renal replacement therapy in two lung transplant recipients

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***Objectives*: To determine whether valganciclovir 450 mg every 48 h for cytomegalovirus (CMV) prophylaxis provides appropriate ganciclovir exposure in solid organ transplant recipients during continuous renal replacement therapy (CRRT).**

***Patients and methods*: Ganciclovir pharmacokinetics was intensively studied in two lung transplant recipients under valganciclovir 450 mg every 48 h over one dosing interval. *In vitro* experiments using blank whole blood spiked with ganciclovir further investigated exchanges between plasma and erythrocytes.**

***Results*: Ganciclovir disposition was characterized by apparent total body clearance of 3.3 and 5.8 L/h, terminal half-life of 16.9 and 14.1 h, and apparent volume of distribution of 60.3 and 104.9 L in Patients 1 and 2, respectively. The observed sieving coefficient was 1.05 and 0.96, and the haemofiltration clearance was 3.3 and 3.1 L/h. *In vitro* experiments confirmed rapid efflux of ganciclovir from red blood cells into plasma, increasing the apparent efficacy of haemofiltration.**

***Conclusions*: A valganciclovir dosage of 450 mg every 48 h appears adequate for patients under CRRT requiring prophylaxis for CMV infection, providing concentration levels in the range reported for 900 mg once daily dosing outside renal failure.**

Keywords: haemofiltration, pharmacokinetics, renal failure, erythrocytes

Introduction

Valganciclovir is currently supplanting oral ganciclovir in various indications, such as the prophylaxis of cytomegalovirus (CMV) infection in solid organ transplant patients. The prodrug, valganciclovir, is characterized by better oral bioavailability. After administration, valganciclovir is hydrolysed to ganciclovir and extensively eliminated by the kidney, through both glomerular filtration and tubular secretion. Thus, in renal insufficiency, the dosage of valganciclovir has to be adjusted to the estimated glomerular filtration rate (GFR).[1] The manufacturer suggests a scheme for dosage adaptation as a function of GFR, but does not recommend the use of valganciclovir in patients requiring intermittent dialysis or continuous renal replacement therapy (CRRT). The high clearance of ganciclovir in healthy subjects ($\sim$14 L/h)[1] indicates that tubular secretion contributes to a similar extent as glomerular filtration (7 L/h). CRRT replaces only GFR and usually does not exceed half of a normal GFR. Thus, a rational dosage adjustment in CRRT patients would not exceed a quarter of the usual dose intensity, for example 450 mg every second day instead of 900 mg once daily. We aimed to confirm in two patients receiving CRRT through continuous veno-venous haemofiltration (CVVHF) that this dosing schedule provides adequate ganciclovir exposure in such a condition.

Patients and methods

This observational study was performed at the Lausanne University Hospital, Switzerland, with the approval of the local Ethics Committee, in two lung transplant recipients at risk for CMV infection.

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Patient 1

A 49-year-old, 92 kg male patient was admitted for double lung transplantation in the context of idiopathic pulmonary fibrosis. Valganciclovir prophylaxis was started on day 1 post-transplantation (900 mg once daily initially). On day 3, his condition deteriorated with cardiogenic and subsequent septic shock and multi-organ failure requiring initiation of CRRT. The CVVHF apparatus (Aquarius, Edwards Lifesciences S.A., St-Prex, Switzerland) was equipped with a 0.12 m^2 polyethersulfone fibre filter (Aquamax HF12, Edwards Lifesciences S.A.) connected through a double lumen venous catheter. On day 14, the treatment conditions were set to 300 mL/min blood flow, 3 L/h post-dilution flow (lactate-buffer electrolyte-glucose solution) and 150 mL/h patient's volume subtraction. The patient was anuric. He received his last valganciclovir 900 mg dose 48 h before switching to 450 mg dose every second day on the day of observation. Valganciclovir was given through a nasogastric tube after dissolution of the tablet in warm water. Concomitant drug therapy consisted of norepinephrine, midazolam, fentanyl, sufentanil, heparin, mycophenolate, tacrolimus, methylprednisolone, vancomycin, voriconazole, tazobactam/piperacillin, insulin, esomeprazole and neostigmine. CRRT was followed by intermittent chronic haemodialysis. The patient died 4 months later from septic shock.

Patient 2

A 54-year-old, 46 kg Asian male patient was admitted for a second double lung transplantation because of bronchiolitis obliterans, *Mycobacterium*, *Pseudomonas* and *Aspergillus* infections of the first allograft. During the intervention, haemorrhagic shock led to acute renal failure and the initiation of CRRT (same supplies as Patient 1). Valganciclovir prophylaxis was started on day 8 post-transplantation (450 mg every 48 h; the valganciclovir tablet being crushed and dissolved in cold water before administration through nasogastric tube). On day 19, the CVVHF conditions were set to 250 mL/min blood flow, 1 L/h pre-dilution flow, 3 L/h post-dilution flow and 180 mL/h patient's volume subtraction. The patient was anuric. Concomitant drug therapy consisted of norepinephrine, propafenone, sufentanil, propofol, lorazepam, heparin, mycophenolate, cyclosporine, methylprednisolone, vancomycin, tazobactam/piperacillin, ethambutol, azithromycin, caspofungin, lamivudine, colistimethane, nystatin, insulin and esomeprazole. He died 2 months later from cardiac arrest.

Sample collection and assay

Blood samples were collected from both arterial and venous lines, along with filtrate samples from the output line, at 0 (before drug administration), 1, 2, 3, 4, 6, 12, 24, 36 and 48 h after administration of valganciclovir 450 mg. Blood samples were centrifuged, and plasma and filtrate samples stored at −20°C until analysis.

Ganciclovir concentration in plasma was measured using a validated high-performance liquid chromatography method after protein precipitation, on a reversed-phase C18 column, using a mobile-phase gradient of sodium heptanosulfonate 0.4% buffer (pH 2.6) and acetonitrile, and spectrofluorimetric detection.[2] The lower limit of detection was 0.1 mg/L, the inter-day coefficient of variation was <3.5% and the range of inter-day deviations was comprised within −0.4% to −1.4%. Filtrate samples were analysed using calibration and quality controls prepared with blank filtrate.

In vitro experiments

A spiking experiment was performed after examination of study results to investigate the importance and kinetics of ganciclovir exchanges between plasma and erythrocytes. Ganciclovir permeation across the red blood cell membrane was assessed at 37°C in two phases: influx and efflux study. A citrated blood sample from a healthy donor was spiked with ganciclovir dissolved in 0.9% NaCl to yield a concentration of 5 mg/L. For the influx study, 4 mL aliquots were drawn at 0, 5, 10, 20, 30, 45 min, 1, 1.5, 2, 2.5, 3 and 4 h and centrifuged at 1850 **g** for 4 min at +4°C. Plasma and blood cells were separately stored frozen at −20°C prior to analysis. After the 4 h of incubation period, the remaining plasma was separated by centrifugation, removed and replaced by a volume of blank plasma of the same donor adjusted to reach the same haematocrit. In the subsequent efflux study, samples were drawn at 0, 5, 10, 20, 30, 45 min, 1, 1.5 and 2 h and processed as described earlier. To exclude the occurrence of degradation, ganciclovir concentrations were measured in one control blood sample spiked with ganciclovir at 5 mg/L, left in parallel for 6 h at 37°C. For ganciclovir determination in erythrocytes, haemolysed samples were analysed using matrix-matched calibration and quality control prepared with haemolysed red blood cells.

Pharmacokinetic analysis

Ganciclovir concentration–time data in plasma and filtrate were analysed using non-compartmental methods. The area under the curve during one dosing interval (AUC_{0-48}) was estimated by trapezoidal and log-trapezoidal methods, and the apparent total body clearance (CL_{TOT}/F) was calculated as the dose divided by AUC_{0-48}. This analysis was completed by curve fitting with a two-exponential model, enabling the estimation of an initial (λ_1) and a terminal rate constant (λ_Z). The elimination half-life ($t_{1/2}$) was derived as $\log_e(2)/\lambda_Z$ and the apparent terminal volume of distribution (V_Z/F) as CL_{TOT}/λ_Z. Two approaches were used to determine the clearance of ganciclovir through the CRRT apparatus. The first is based on the amount of drug removed from blood, calculated from ganciclovir plasma pre-filter (C_A) and post-filter (C_V) concentrations and defined as 'haemofiltration clearance' (CL_{CRRT}). The second compares simultaneous filtrate and 'arterial' plasma concentration. Their ratio is taken as sieving coefficient (S_C) and the filtration clearance (CL_F) is estimated by the product of S_C and total filtrate flow, reflecting the rate of drug appearance in the filtration fluid, divided by the circulating concentration. The recovery (R) in the filtrate is calculated as the ratio of CL_{CRRT} over CL_F. S_C, CL_{CRRT} and CL_F are calculated for each sampling time and averaged using the geometric mean.[3]

Results and discussion

The concentration–time profiles of ganciclovir in Patients 1 and 2 receiving valganciclovir 450 mg every 48 h are shown in Figure 1 and the resulting pharmacokinetic parameters are given in Table 1. For Patient 2, samples were collected over 24 h instead of 48 h because CRRT was interrupted after 24 h due to filter failure. C_{max}, C_{min} and AUC_{0-48} determined for Patient 1 may be influenced by his prolonged dosage of 900 mg once a day, with a change to 900 mg every second day, two days before investigation. This may have affected AUC_{0-48} and CL_{TOT}/F but not CL_{CRRT}, S_C and CL_F.

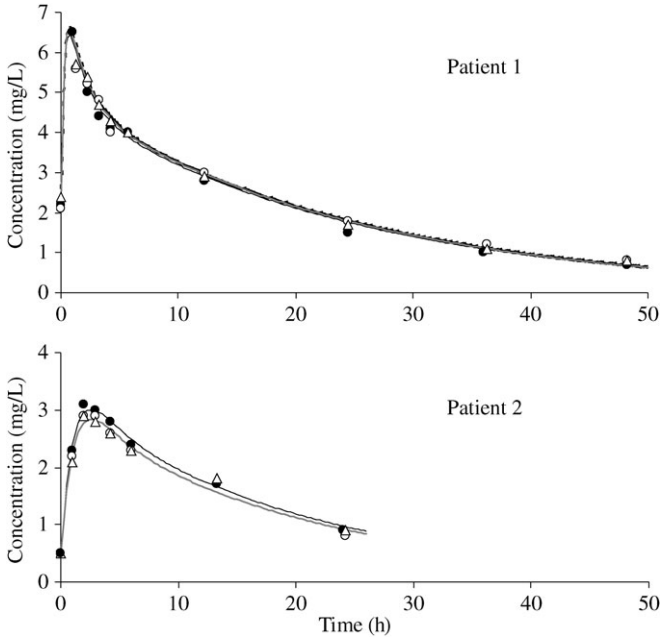

Figure 1. Concentration–time points and fitted bi-exponential curves of ganciclovir in 'arterial' and 'venous' lines and in filtrate in Patients 1 (lower panel) and 2 (upper panel) (filled circles and solid black line: 'arterial' concentrations; open circles and dotted black line: 'venous' concentrations; triangles and solid grey line: filtrate concentrations).

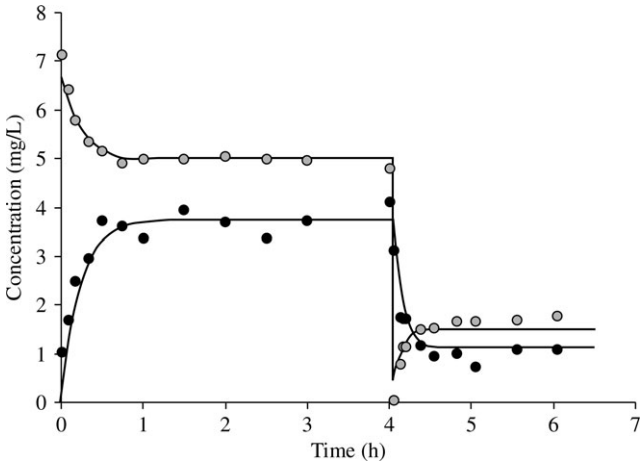

Figure 2. Concentration–time points and fitted exponential curves obtained from the *in vitro* ganciclovir permeation experiment. A 90 mL citrated blood volume obtained from a healthy donor was spiked with an amount of 500 μg ganciclovir (dissolved in 10 mL 0.9% NaCl) on time 0. During 4 h ('influx' phase), the blood pool was regularly sampled and ganciclovir concentration was followed up in the plasma (open circles and grey line) and in the red blood cells (filled circles and black line). On time 4 h, all the remaining plasma was separated by centrifugation and replaced with an identical volume of blank plasma from the same donor. Ganciclovir concentration was again followed up in the plasma and in the erythrocytes during the next 2 h ('efflux' phase). The profile was fitted according to a two-compartmental model with passive bidirectional diffusion (see text).

Valganciclovir has proved successful for the prophylaxis of CMV in solid organ transplant recipients without renal impairment at 900 mg once daily.[4] The AUC calculated for Patient 2 is in the range reported with 900 mg once daily (42–63 mg·h/L)[4–7] and Patient 1 shows an even higher exposure. CL_{TOT}/F obtained in both patients is much lower than CL_{TOT}/F reported in the absence of renal impairment (10.2–15.5 L/h)[4–7] and corresponds to values reported for patients with fairly reduced GFR.[1] Accordingly, $t_{1/2}$ is longer than in patients without renal impairment (~5 h in liver recipients[5] and 3.5 h in healthy subjects[1]) and is in the range reported for patients under CRRT receiving intravenous ganciclovir.[8–10] V_z/F determined in these two patients are in the range reported for healthy subjects and patients with and without renal impairment.[1] These results are in accordance with the almost exclusive renal elimination of ganciclovir, including a large component of tubular secretion, which is not replaced by CRRT. In addition, the dose preparation and nasogastric tube administration seem not to grossly impair drug absorption.

In Patient 1, CL_{CRRT} based on plasma disappearance rate and CL_F estimated from appearance in filtrate-dialysate accounted for ~70% to 100% of the apparent total clearance. Accordingly, the average recovery of ganciclovir was 104% and the sieving coefficient was 1.05. In Patient 2, CL_{CRRT} and CL_F accounted for ~50% to 60% of the apparent total clearance and indicated the average recovery of 87% and the sieving coefficient of 0.96. These results are in accordance with sieving coefficients and percentage of total clearance achieved by CRRT previously reported for ganciclovir (0.75 to 0.95 and 40% to 115%, respectively).[8–10]

The profile (concentration versus time) of ganciclovir influx and efflux through red blood cell membranes is shown in Figure 2. In the first phase (influx study), ganciclovir enters erythrocytes to reach an equilibrium between cells and plasma (erythrocytes/plasma ratio = 0.77). In the second phase (efflux study), ganciclovir leaves the erythrocytes following the concentration gradient between cells and plasma for attaining the same ratio. Of note, ganciclovir concentrations in plasma and red

Table 1. Pharmacokinetic parameters

Patient	Dose (mg)	C_{max} (mg/L)	C_{min} (mg/L)	AUC_{0-48} (mg·h/L)	λ_1 (h^{-1})	λ_Z (h^{-1})	$t_{1/2}$ (h)	CL_{TOT}/F (L/h)	V_Z/F (L)	CL_{CRRT} (L/h)	S_C	CL_F (L/h)	R (%)
1	450[a]	6.5	0.7	98.0	0.62	0.041	16.9	3.3	80.7	2.4	1.05	3.3	104
2	450[a]	3.1	0.2[b]	55.4	0.65	0.049	14.1	5.8	118.6	3.5	0.96	3.1	87

[a]Corresponding to 324.1 mg of ganciclovir.
[b]Value extrapolated from λ_Z.

blood cell control samples remained stable for 4 and 6 h at 37°C and without any change of pH. Ganciclovir was previously reported to enter erythrocytes through nucleobase and nucleoside transporters.[11] In our experiment, we show that ganciclovir also leaves red blood cells in accordance with the concentration gradient. This phenomenon could play a role during blood filtration by CRRT as the plasma/erythrocytes equilibrium is modified while ganciclovir is removed from plasma. Such exchanges occur in the haemofiltration filter and during post-dilution, providing an explanation for sieving coefficients and recovery fraction greater than the unity, as observed in Patient 1. Thus, drug transport by red blood cells may increase CRRT efficacy for substances with significant distribution in the erythrocytes, a compartment often neglected in pharmacokinetics.[12]

In conclusion, a 450 mg valganciclovir dose administered every 48 h achieves, in transplant recipients under CRRT, exposure levels similar to those observed under the usual dosage (900 mg once daily) recommended in the absence of renal failure.

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Transparency declarations

None to declare.

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