Pharmacokinetics of Ganciclovir during Continuous Venovenous Haemodiafiltration in Critically Ill Patients

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ABSTRACT:

Ganciclovir is an antiviral agent that is frequently used in critically ill patients with cytomegalovirus (CMV) infections. Continuous venovenous haemodiafiltration (CVVHDF) is a common extracorporeal renal replacement therapy in intensive care patients. Aim of this study was to investigate the pharmacokinetics of ganciclovir in anuric patients undergoing CVVHDF.

Population pharmacokinetic analysis was performed in nine critically ill patients, with proven or suspected CMV infection undergoing CVVHDF. All patients received a single dose of ganciclovir at 5 mg/kg of bodyweight intravenously. Serum and ultradiafiltrate concentrations were assessed by high performance liquid chromatography and this data was used for pharmacokinetic analysis. Mean peak and trough prefilter ganciclovir concentrations were 11.8 ± 3.5 mg/L and 2.4 ± 0.7 mg/L. As pharmacokinetic parameters elimination half-life (24.2 ± 7.6 h), volume of distribution (81.2 ± 38.3 L), sieving coefficient (0.76 ± 0.1), total clearance (2.7 ± 1.2 L/h) and clearance of CVVHDF (1.5 ± 0.2 L/h) were determined. Based on population pharmacokinetic simulations with respect to a target area under the curve (AUC) of 50 mg·h/L and a trough level of 2 mg/L a ganciclovir dose of 2.5 mg/kg once daily seems to be adequate for anuric critically ill patients during CVVHDF.

Keywords: renal replacement therapy, renal failure, antiviral therapy, cytomegalovirus, cymevene, intensive care unit
Introduction

Ganciclovir is a pro-drug nucleoside analogue that shows antiviral activity against members of the herpes group and in particular against human cytomegalovirus (CMV).\[1\] It has proven therapeutic effect in treatment of several CMV related infections as retinitis, pneumonia, infections of the gastrointestinal tract, infections of the nervous system or prevention of the CMV disease in patients with AIDS or immunocompromised state following transplantation. \[1-3\] The risk of CMV infection is increased in critically ill patients due to requirement of mechanical ventilation, sepsis, immunodeficiency, transfusions and renal failure. \[4\]

Ganciclovir is mainly excreted by the kidneys and can be found almost unchanged in the urine with an elimination half-life of 2-4 hours. Elimination is significantly prolonged in patients with renal impairment and its clearance decreases linearly with diminishing creatinine clearance. \[5,6\] Therefore a dosage reduction is required in those patients. In patients with normal renal function a daily dosage of 10mg/kg body weight is recommended. Table 1 illustrates dosing recommendation for patients with impaired renal function adjusted by creatinine clearance as described in the summary of product characteristics.\[7\]

Up to date no specific therapeutic exposure values for ganciclovir have been established.\[8\] However, viremia suppression was reported with ganciclovir exposure (area under the curve, AUC) of 40-50 mg·h/L. \[9\] Therefore an AUC > 50 mg·h/L has been used as target exposure.\[10\] In order to ensure deep tissue penetration and avoid underdosing in patients with life-threatening CMV-infection we analysed both, AUC > 50 mg·h/L and trough levels of 2 mg/L. A specific exposure may reduce toxicity and maintains the therapeutic effect.

Continuous venovenous haemodiafiltration (CVVHDF) is a common form of extracorporeal renal replacement therapy in critically ill patients with renal failure. The elimination of any given drug by continuous renal replacement therapy (CRRT) is dependent on different factors such as specific properties of the membrane (pore-size, filter surface area, adsorption, filter material), characteristics of the CRRT technique used (blood flow rate, ultrafiltration rate) or properties of the drug (volume of distribution, molecular charge, molecular weight and protein-binding). \[11,12\] The low molecular weight of ganciclovir (255.2 daltons), high water solubility (3 mg/ml) and very low plasma protein binding (1-2%) are relevant factors in removal via CVVHDF.\[3,7\]

Pharmacokinetics (PK) of ganciclovir have been described in several studies.\[1,13,14\] However, there is a lack of pharmacokinetic data of ganciclovir administered during CVVHDF. Accordingly, there is no specific dosage recommendation for patients undergoing CVVHDF.

The aims of this study were (i) to investigate the pharmacokinetics of ganciclovir during...
CVVHDF in critically ill patients with suspected or proven CMV infection; (ii) to find potential predictive factors for dose individualization; and (iii) to establish a pharmacokinetic model of ganciclovir in order to evaluate different body weight-based dosage regimens (5 mg/kg/24h, 2.5 mg/kg/24h, 1.5mg/kg/12h) and individualized dosing via target-AUC to prevent under- or overexposure in patients with renal replacement therapy.

Materials and methods

Patient eligibility

This was a prospective open-label study. All patients at the age of 18 years and older, who were treated at an intensive care unit (ICU) and were prescribed ganciclovir as part of their required medical care due to suspected or proven CMV infection and who underwent CVVHDF for treatment of severe renal disease were eligible for this study. Exclusion criteria included age less than 18 years and other extracorporeal therapy than CVVHDF. The study protocol was approved by the local ethics committee.

Medication

All patients received 5 mg/kg ganciclovir in a 30 min infusion via a central venous line, different from the one used for CVVHDF.

Sampling and storage

Blood samples were drawn from the prefilter (arterial) and postfilter (venous) line of the extracorporeal circuit at 0, 30, 60, 90, 180, 360, 480 and 1440 minutes after finishing the infusion. Regarding tolerability and occurrence of haematological side effects, red blood cells (RBC), haemoglobin (HB), platelets (PLT) and white blood cells (WBC) were quantified on a daily basis during the treatment phase. Ultradiafiltrate samples were taken from the outlet of the ultradiafiltrate compartment of the haemodiafilter at corresponding times.

All samples were centrifuged immediately and stored at -70°C until assayed.

Continuous venovenous haemodiafiltration

CVVHDF was performed using an AN 69 HF hollow fiber haemofilter (Prisma M100 Pre Set, Hospal Industrie, Meyzieu, France) with a membrane surface area of 0.9 m². Dialyzers and lines
were steam sterilized. The standard blood flow rate was 9 L/h, pre-dilution volume was infused at a rate of 1 L/h and dialysate rate was 1 L/h, as described previously. [15, 16] Net fluid balance was modified according to clinical requirements. No filter change occurred during study period.

Sample assay
The concentration of ganciclovir in serum and ultrafiltrate was measured by a high performance liquid chromatography (HPLC) using a Dionex “UltiMate 3000” system (Dionex Corp., Sunnyvale, CA). Briefly, after the addition of 200 µl of methanol to 100 µl of serum or ultrafiltrate, the samples were centrifuged (5000g for 5 min at 4°C), and 100 µl of the sample was injected onto a Hypersil BDS-C18 column (5 µm, 250 × 4.6 mm I.D., Thermo Fisher Scientific, Inc, Waltham, MA), preceded by a Hypersil BDS-C18 precolumn (5 µm, 10 × 4.6 mm I.D.) at a flow rate of 1 ml/min. Ganciclovir was monitored fluorimetrically at 278 nm (excitation) and 380 nm (emission). Mobile phase A consisted of potassium phosphate (50 mM, pH 3.0 with phosphoric acid) and heptanesulfonic acid (5 mM) and the mobile phase B consisted of methanol. Mobile phase was filtered through a 0.45 µM filter (HVLP04700, Millipore, Vienna, Austria). The gradient ranged from 3 % B (0 min) to 14 % at 30 min, kept constant at 14 % until 36 min, and finally decreased linearly to 3 % again at 37 min. The columns were allowed to re-equilibrate for 13 min between runs. Linear calibration curves were performed from the peak areas of ganciclovir to the external standard by spiking drug-free human serum and ultrafiltrate with standard solutions of ganciclovir (final concentrations ranging from 0.005 µg to 10 µg/ml). For this method the lower limit of quantification for ganciclovir was determined to be 5 ng/ml for ganciclovir in serum and ultrafiltrate. Intra-day values for ganciclovir ranged from 4.1 to 8.0 %, inter-day values from 4.9 to 9.3 % using ganciclovir concentrations of 0.01, 0.1, and 1 µg/ml.

Pharmacokinetic analysis
Pharmacokinetic analysis was performed in all patients after receiving a single dose of 5 mg/kg ganciclovir. The serum concentration-time curves of ganciclovir in plasma were adjusted to the data sets via nonlinear iterative least-square regression analysis. Curve modelling was performed using the two-compartment PK model with the program WinNonlin (vers. 5.1), Scientific Consulting, USA). The following parameters were calculated: area under the concentration curve from 0 to 24 h (AUC0-24) using the linear trapezoidal rule, total clearance (Cltot), volume of distribution (V), distribution half-life (t1/2a), elimination half-life (t1/2β), The sieving coefficient (S) was calculated as S = CUDF/CA. The clearance of haemodiafiltration (ClCVVHDF) was
determined according to the formula $\text{Cl}_{\text{CVVHDF}} = \frac{C_{\text{UDF}}}{C_A} \cdot (Q_{\text{UF}} + Q_D) = (Q_{\text{UF}} + Q_D) \cdot S$, where $C_{\text{UDF}}$ is the concentration of ganciclovir in the ultrafiltrate, $C_A$ and $C_V$ are the concentrations of ganciclovir in the prefilter (arterial) and postfilter (venous) line of the extracorporeal circuit, respectively, and $Q_{\text{UF}}$ and $Q_D$ are the ultrafiltration rate and the dialysis rate, respectively. Total removal ($\text{Re}_{\text{tot}}$) of the drug was calculated as $\text{Re}_{\text{tot}} = \frac{(C_{\text{max}} - C_{\text{min}})}{C_{\text{max}}} \cdot 100$ where $C_{\text{max}}$ refers to arterial peak serum concentration at the end of the first ganciclovir infusion and $C_{\text{min}}$ to the arterial trough serum concentration prior to the second infusion of ganciclovir, respectively.

Removal of ganciclovir via haemodiafiltration ($\text{Re}_{\text{CVVHDF}}$) was calculated as $\text{Re}_{\text{CVVHDF}} = \frac{\text{Cl}_{\text{CVVHDF}}}{\text{Cl}_{\text{tot}} \cdot 100}$.

Population pharmacokinetic model

Population pharmacokinetic analysis of the arterial concentration-time data of single-dose ganciclovir was performed using the nonlinear mixed-effects modelling software NONMEM®, Version 7.2 (ICON Development Solutions, Ellicott City, MD, USA). A two-compartmental model with linear elimination was best to describe the structural model of the i.v. concentration-time data of ganciclovir. Following PK parameters were estimated from the model: total clearance ($\text{Cl}_{\text{tot}}$), volume of the first compartment ($V_1$), volume of the second compartment ($V_2$) and intercompartmental clearance ($Q$). Interindividual variability was estimated for all PK parameters using an exponential error model. The residual error was described with a proportional error model. Covariates were not included in the model due to the small number of patients. Typical and individual PK parameters were estimated using the “FOCE” method in NONMEM®. Model evaluation was performed using objective function value, goodness-of-fit plots, standard errors and visual predictive check.

Model-based simulations

With the final PK model three different simulation scenarios were performed with the study population: (i) simulating ganciclovir courses 2-7 based on the dose resulting in a target-AUC of 50 mg·h/L. Therefore, the estimated individual clearance of each patient from the final PK model was multiplied with the target-AUC resulting in the next-course dose (Individualized dose = $\text{AUC}_{\text{target}} \cdot \text{Cl}_{\text{tot}}$). (ii) Simulating course 2-7 with a ganciclovir dose of 5 mg/kg and (iii) with 2.5 mg/kg for each patient. Simulations were performed separately for each patient fixing the individual estimated PK parameters from the final PK model for the simulation of each patients’ courses. Residual and inter-individual variability were fixed to zero.
Monte Carlo simulation

In addition, ganciclovir plasma levels were simulated in four populations of 1000 patients using a Monte Carlo approach. The simulated datasets comprised seven ganciclovir administrations. A weight between 40-140 kg was randomly assigned to every simulated patient. Each population was characterized by a different dosing regimen (5 mg/kg/24h, 2.5 mg/kg/24h, 1.5 mg/kg/12 h and target-AUC adjusted dosing every 24 h, respectively).

Statistical analysis of PK parameters

Correlation of body weight with total clearance and other PK values was performed by Spearman’s correlation and expressed via Spearman’s correlation coefficient. Two-sided p-values <0.05 were considered as statistically significant.

Results

Patients

Nine intensive care patients with acute renal failure and proven or suspected CMV infection were included in this study. Detailed patients’ characteristics are listed in table S1. All patients were anuric and had no additional diuresis. Mean age (mean ± SD) was 56 ± 9 years and mean body weight was 86 ± 25 kg. All patients were mechanically ventilated and mean SAPS II score (severity of disease classification system) was 62 ± 13. None of these patients received imipenem, mycophenolate, probenecid, tenofovir or zidovudine, which are known to possibly enhance toxic effects of ganciclovir. [5, 17] None of these patients had a known hypersensitivity or intolerance to the substance ganciclovir.

Ganciclovir serum levels

Ganciclovir was administered to all patients in a dosage of 5 mg/kg per day. The mean concentration time course of ganciclovir (levels drawn from the prefilter and postfilter line of the extracorporeal circuit and from the ultradiafiltrate) is illustrated in Figure 1. The mean peak plasma concentration after infusion was 11.8 ± 3.5 mg/L at the prefilter port and 10.9 ± 3 mg/L at the postfilter port. Mean trough plasma concentration was 2.4 ± 0.7 mg/L at the prefilter port.
and 2.1 ± 0.7 mg/L at the postfilter port. Detailed pharmacokinetics of ganciclovir are summarized in table 2.

Tolerability

All patients tolerated the ganciclovir infusion (5 mg/kg/24h) without any adverse reaction. Quantification of haematological parameters was assessed on a daily basis. RBC, HB, PLT and WBC levels are shown in table S2. In none of the patients a decline of haematological parameters during therapy with ganciclovir was observed.

Population pharmacokinetic model

The PK model developed with NONMEM\textsuperscript{®} could adequately describe the concentration-time data of ganciclovir (model evaluation data not shown). The estimated population PK parameters $\text{Cl}_{\text{tot}}$, $V_1$, $V_2$, $Q$ are illustrated in table 3. The individual PK parameters AUC, $\text{Cl}_{\text{tot}}$, and $V_D$ estimated with NONMEM\textsuperscript{®} were comparable to those calculated with WinNonlin\textsuperscript{®} as shown in table S3.

A full covariate analysis was not performed due to the small number of patients. Because of inconsistent results in the literature about body weight (BW) as a covariate on $\text{Cl}_{\text{tot}}$, body weight was tested as covariate on $\text{Cl}_{\text{tot}}$.\textsuperscript{[10, 18]} A significant correlation (P<0.005) between BW and $\text{Cl}_{\text{tot}}$ was found using following relation (with TV$\text{Cl}_{\text{tot}}$ as the typical $\text{Cl}_{\text{tot}}$ and 86 as the mean of patients’ body weight): $\text{Cl}_{\text{tot}} = TV\text{Cl}_{\text{tot}} \cdot (\text{BW}/86)^{1.68}$. But due to the small number of patients and the associated uncertainty of this covariate for further simulations, we decided not to include BW into the model.

Model-based simulations

Simulations of arterial ganciclovir concentrations on additional six days of dosing in the underlying nine patients showed that nearly every patient exceeded the anticipated trough-level of 2 mg/L with bodyweight-adjusted dosing (see Figure 2 A/B), independent of the applied ganciclovir dose (5 or 2.5 mg/kg/24h, respectively). In addition, AUC values > 50 mg·h/L were achieved after each administration in all nine patients receiving a ganciclovir dose of 5 and 2.5 mg/kg/24h with a mean AUC for the seven courses of 157.3 mg·h/L and 91.4 mg·h/L, respectively.

With the PK-adjusted dosing approach using a target-AUC of 50 mg·h/L all nine patients reached the target-AUC and its interindividual variability could be reduced (see Figure 3), but
trough-concentrations systematically fell below the minimum value of 2 mg/L (see Figure 2 C).

Only 15.9% of all ganciclovir administrations resulted in a trough-concentration > 2 mg/L.

Monte Carlo simulation

The results of the dosing scenarios in the study population could be confirmed in simulations of
1000 new patients. Mean arterial ganciclovir concentrations of all patients exceeded the trough-
level of 2 mg/L after the second ganciclovir infusion, independent of a 5 mg/kg/24h or
2.5 mg/kg/24h or a 1.5 mg/kg/12h ganciclovir dose (see Figure 4 A/B/C). AUC values for the
majority of the simulated patients, who received 5 mg/kg or 2.5 mg/kg of ganciclovir, passed the
anticipated target-AUC of 50 mg·h/L, as illustrated in table S4. Thirty-seven percent of the
patients receiving the lower dose of 1.5 mg/kg/12h fell at least once during a course of seven
ganciclovir administrations below the target-AUC of 50 mg·h/L.

As with the study population, AUC-adjusted dosing resulted in target-AUC values for most of
the simulated patients (data not shown), but often the trough-concentrations were under the
threshold of 2 mg/L. Trough levels were extremely low, almost reaching zero in the third course
(see Figure 4D).

Statistical analysis of PK values

Body weight correlated significantly with total clearance (r = 0.92, p < 0.005) and volume of
distribution (r = 0.75, p < 0.05). Furthermore body weight correlated with minimal drug serum
concentration (C_{min} / C_{24}) (r = 0.68, p < 0.05) but not with drug exposure by means of AUC (p =
n.s.).

Discussion

Ganciclovir is an effective antiviral substance used for first-line treatment in CMV infections,
which has a predominantly renal elimination. [1, 3, 5, 19] Although ganciclovir is often used in
clinical routine, pharmacokinetic data in critically ill patients undergoing CRRT are rare and
inconsistent. Up to date, only two case reports of pharmacokinetic properties of ganciclovir in
patients receiving CVVHDF are published. [20, 21] Table 4 summarizes available
pharmacokinetic data on ganciclovir in patients undergoing CRRT. This is the first study
investigating pharmacokinetics of ganciclovir in critically patients undergoing CVVHDF with modern high-flux membranes. Basic pharmacokinetic parameters were described by a two-compartment model. Furthermore we performed three different dosing-scenarios simulating seven ganciclovir courses (of 5 mg/kg, 2.5 mg/kg and target-AUC of 50 mg h/L). Individualized dosing based on target-AUC was calculated (AUC_target multiplied by CLtot) as Caldes et al. reported.[10]

Actual dosing recommendations [7] refer to the renal function, adjusted by creatinine clearance calculated using the Cockcroft-Gault formula, [22] but do not give guidance for anuric patients during CVVHDF at the intensive care unit. Extracorporeal elimination of a substance is influenced by several factors, like CRRT calibration (blood flow rate, ultrafiltration rate) and properties of the membrane (pore-size, filter surface area, adsorption, filter material). [11, 12] Present-day synthetic dialyzer membranes - like AN 69 acrylonitrile as used in this study - have an increased drug removal in comparison to conventional (e.g. cuprophane) membranes. [23] Furthermore, clearance of a substance may vary even between membranes of the same class. [24, 25] In addition, pharmacokinetics in critically ill patients with severe sepsis or septic shock differ significantly from pharmacokinetics of healthy volunteers due to profound changes in the organism, as capillary leakage, compromised tissue perfusion, changes in protein binding, pH or an increase of total body water. [26, 27]

No distinct dosing recommendations for ganciclovir in renal-replacement patients have been described so far. A prior study used AUC levels of at least 50 mg h/L as a target exposure in solid-organ transplant patients. [8-10] However, there are no data for any dosing recommendations ensuring effective drug levels during therapy. IC_{50}, the concentration of the drug that is required for 50% inhibition has been reported, dependent on the strain, ranging from 0.3 – 2.8 mg/L. [3, 8, 28] It is known that appropriate dosing of ganciclovir is important to avoid clinical inefficacy and possible development of resistance.[29] However, the therapeutic range of the drug, especially the relationship between exposure, serum concentration and clinical efficacy, has not been clearly defined. [8] Significantly diminished tissue concentrations of antimicrobial drugs in comparison to their blood serum levels have been reported in several studies. [30, 31] We aimed at AUC values of at least 50 mg h/L and a trough concentration of at least 2mg/L in the present study to avoid underdosing in these patients with life-threatening CMV-infection.

Consistent with previous reports serum concentrations in our study were elevated in comparison to those of patients with normal renal function. [1, 3, 21, 32] Gando et al. reported elevated blood serum concentrations at the same dosage as we used (peak level of 11.8 mg/l in our study
versus 20.3 mg/L in the case report of Gando et al. [21] However, this could be attributed to a different type of membrane (cellulose triacetate) they have been using. McGloughlin et al. observed significantly lower drug levels (peak serum concentration of 5.7 mg/L; trough concentration was not reported) at a dosage of 2.5 mg/kg/24h; however considerably higher flow rates were used. [20] Sieving coefficient was in the range described in other studies. [1, 3, 10, 13, 33] Volume of distribution was elevated in comparison to non-critically ill patients, most likely due to additional fluid load. [20, 34] The extracorporeal clearance reached approximately 55% of the total clearance in our study and was comparable to prior reports. [21, 34] Estimated population pharmacokinetic parameters were comparable to those reported by Caldes et al. [10] However, patients of our study had a lower total clearance. All study patients reached an AUC above the target of 50 mg·h/L in the simulated ganciclovir courses. Nearly all patients with body weight-adjusted dosing exceeded the target trough level. Interindividual variability of the AUC could be reduced in the individualized dosing approach using target-AUC. However, trough concentrations systematically fell below the anticipated value of 2 mg/L in this cohort. These findings were confirmed in a Monte Carlo simulation of 1000 new patients. Solely the lowest simulated dosage of 1.5 mg/kg/12h did not result in adequate exposure by means of AUC. Based on these findings, bodyweight-based dosing seems to be superior over AUC-adjusted dosing, as long as no clear clinical relevant AUC value is defined. With a ganciclovir dose of 2.5 and 5 mg/kg/24h AUC values above 50 mg·h/L and trough concentrations above 2 mg/L could be achieved in the simulations of additional courses for most of the nine patients, whereas in the Monte Carlo simulations AUC-based dosing lead to extremely low ganciclovir trough-levels (close to zero) in some patients (see Fig. 4D). Therefore, with respect to a target-AUC of 50 mg·h/L and a ganciclovir trough-level of 2 mg/L the majority of patients would be sufficiently dosed with 2.5 mg/kg/24h.

Caldes et al., who also focused on target-AUC, indicated that pharmacokinetic parameters, especially total clearance (Cl\text{tot}), were not related to body weight and therefore variability in renal function is more relevant than differences in body weight. [10] In contrast to his assumption, we observed a significant correlation between bodyweight, total clearance and volume of distribution in our anuric patients. However, it has to be mentioned that Caldes et al. estimated clearance based on a mean population body weight of 66.2 kg, whereas in the present Monte Carlo simulations patients with a weight between 40 and 140 kg were randomly generated. Furthermore, as sieving coefficient (which was the same for everyone) is related to drug clearance, among patients undergoing CVVHDF, it may be assumed that Cl\text{tot} and Cl\text{CVVHDF} are
closely correlated and therefore weight based dosing is not needed. However, we did not detect a
significant correlation between Cl_{tot} and Cl_{CVVHDF} (see Fig. S1), which may be due to the large
variability of Cl_{tot} in our dataset. As at steady state, the product of rate constant k_{ss} and the
volume of distribution may be defined as the total body clearance (Cl_{tot} = k_{ss} \cdot V_{d,ss})[35], large
differences in volume of distribution, mostly due to excessive fluid resuscitation (positive net
fluid balance up to 20 litres or more) in patients with severe septic shock, may be a possible
explanation for interindividual differences in Cl_{tot}[36] Indeed patient #6 with a body weight 120
kg has about 3.7-fold-higher Cl_{tot} and also 3.3-fold higher V_{d} values than patient #4 (4.19l and
167.41 vs.1.6 l and 50.3l) strongly supporting the effect of V_{d} on Cl_{tot}.

Adverse events of ganciclovir due to toxicity are primarily of haematological nature including
anaemia, thrombocytopenia or leukopenia. [3] Recently it was reported that ganciclovir
associated cell toxicity is not solely dose-dependent but also duration-dependent. [37] We did
not observe any new haematological adverse events during treatment with ganciclovir in our
patients as illustrated in table S2. Higher serum levels and exposure may be accepted especially
in critically ill patients suffering from life threatening infections in order to penetrate deeply into
tissue and therefore possibly shorten treatment duration.

Limitations of this study are the small number of patients and thus the lack of reliable covariates
in the underlying pharmacokinetic model, e.g. covariates on clearance. However, this is a
common number of patients in pharmacokinetic studies in critically ill patients with CRRT [15,
16, 24]. Furthermore, we used one type of filter (AN 69 HF hollow fiber haemofilter) and
CVVHDF calibration (blood flow rate, ultrafiltration rate). Since this is a frequently used
modern filter-type with a commonly used blood flow rate, other filter-types or flow rate
conditions were not tested.

In conclusion, body weight dosing of ganciclovir was feasible in critically ill patients
undergoing. Larger studies should be performed to confirm the optimal dosage, especially the
impact of individualized dosing regimens. Based on our population pharmacokinetic simulations,
with respect to a target area under the curve of 50 mg·h/L and a trough level of 2 mg/L a daily
ganciclovir dose of 2.5 mg/kg seems to be adequate for anuric patients during CVVHDF.
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References:

Legends to the figures:

Fig. 1: Serum ganciclovir levels drawn from the prefilter and postfilter line of the extracorporeal circuit and from the ultradiafiltrate in anuric patients undergoing CVVHDF. Data are expressed as mean ± SD (n = 9).

Fig. 2: Mean +/- standard deviation of the simulated concentration-time-curves from the study population (n=9) receiving a ganciclovir dose of (A) 2.5 mg/kg/24h, (B) 5 mg/kg/24h and (C) AUC-adjusted dose resulting in a target AUC of 50 mg·h/L. The black dashed horizontal line represents the trough-level of 2 mg/L.

Fig. 3: Boxplots of ganciclovir AUCs [mg·h/L] obtained with the AUC-adjusted simulated dosing of the study population. The grey dashed horizontal line represents the target-AUC of 50 mg·h/L. The median is indicated by the horizontal line, the bottom and top edges of the box represent the 25th and 75th percentiles of the AUC and the whiskers the 2.5th and 97.5th percentile.

Fig. 4: Mean +/- standard deviation of the simulated concentration-time-curves from the simulated populations (n=1000) receiving a ganciclovir dose of (A) 2.5 mg/kg/24h, (B) 5 mg/kg/24h, (C) 1.5 mg/kg/12h and (D) AUC-adjusted dose resulting in a target AUC of 50 mg·h/L. The black dashed horizontal line represents the trough-level of 2 mg/L.
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Tab. 1: Manufacturers dosage recommendation for patients with impaired renal function.
Tab. 2: Pharmacokinetics of ganciclovir at a dosage of 5 mg/kg bodyweight

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<td>69.32</td>
<td>63.11</td>
<td>0.60</td>
<td>25.19</td>
<td>0.61</td>
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<td>1.82</td>
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<td>73.39</td>
<td>64.99</td>
<td>0.51</td>
<td>25.68</td>
<td>0.91</td>
<td>10.57</td>
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<td>575</td>
<td>87.96</td>
<td>4.51</td>
<td>1.76</td>
<td>88.26</td>
<td>39.02</td>
<td>94.88</td>
<td>0.54</td>
<td>19.84</td>
<td>0.88</td>
<td>16.01</td>
</tr>
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<td>200</td>
<td>75.48</td>
<td>1.16</td>
<td>1.34</td>
<td>65.38</td>
<td>115.52</td>
<td>50.31</td>
<td>0.82</td>
<td>30.13</td>
<td>0.67</td>
<td>8.06</td>
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<td>5</td>
<td>375</td>
<td>117.40</td>
<td>1.63</td>
<td>1.72</td>
<td>80.92</td>
<td>105.52</td>
<td>57.48</td>
<td>0.55</td>
<td>24.52</td>
<td>0.86</td>
<td>17.03</td>
</tr>
<tr>
<td>6</td>
<td>600</td>
<td>67.83</td>
<td>4.19</td>
<td>1.38</td>
<td>82.17</td>
<td>32.94</td>
<td>167.40</td>
<td>0.85</td>
<td>27.69</td>
<td>0.69</td>
<td>10.09</td>
</tr>
<tr>
<td>7</td>
<td>500</td>
<td>87.18</td>
<td>3.20</td>
<td>1.26</td>
<td>84.96</td>
<td>39.38</td>
<td>100.40</td>
<td>0.57</td>
<td>21.72</td>
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<tr>
<td>8</td>
<td>375</td>
<td>86.64</td>
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<td>1.60</td>
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<td>89.89</td>
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<tr>
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<td>91.24</td>
<td>45.23</td>
<td>41.79</td>
<td>0.44</td>
<td>7.89</td>
<td>0.83</td>
<td>12.79</td>
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Mean ± SD

<table>
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<tr>
<th></th>
<th>92.01 ± 15.38</th>
<th>2.71 ± 1.22</th>
<th>1.53 ± 0.22</th>
<th>77.9 ± 9.74</th>
<th>67.8 ± 10.74</th>
<th>81.22 ± 11.66</th>
<th>0.73 ± 0.38</th>
<th>24.21 ± 1.69</th>
<th>0.76 ± 0.11</th>
<th>7.69 ± 0.38</th>
<th>12.79 ± 1.77</th>
<th>2.36 ± 0.66</th>
</tr>
</thead>
</table>

AUC$_{0-24h}$, area under the curve from 0 to 24 hours; $C_{I\text{ass}}$, total clearance; $C_{I\text{ass}}$, CVVHDF clearance; $R_{\text{e tot}}$, total removal; $R_{\text{CVVHDF}}$, removal via CVVHDF; $V_{D}$, volume of distribution; $t_{1/2\alpha}$, distribution half-life; $t_{1/2\beta}$, elimination half-life; $S$, sieving coefficient; $C_{0}/C_{\text{max}}$, prefilter peak serum concentration directly after drug administration; $C_{0.5}$, prefilter serum concentration 30 minutes after drug administration; $C_{24}/C_{\text{min}}$, prefilter trough serum concentration after 24 hours.
Tab. 3: Ganciclovir population pharmacokinetic parameter estimates from population analysis with NONMEM®

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Relative standard error [%]</th>
<th>IIV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Cl_{tot}$ [L/h]</td>
<td>2.2</td>
<td>20</td>
<td>61.5</td>
</tr>
<tr>
<td>$V_1$ [L]</td>
<td>32.4</td>
<td>11</td>
<td>33.6</td>
</tr>
<tr>
<td>$Q$ [L/h]</td>
<td>16.8</td>
<td>16</td>
<td>34.7</td>
</tr>
<tr>
<td>$V_2$ [L]</td>
<td>33.5</td>
<td>18</td>
<td>60.6</td>
</tr>
<tr>
<td>Residual error</td>
<td>0.0722</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

$Cl_{tot}$, total clearance; $V_1$, volume of the first compartment; $V_2$, volume of the second compartment; $Q$, intercompartmental clearance; IIV, interindividual variability.
### Tab. 4: Pharmacokinetic characteristics of ganciclovir in different studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal, Year of Publication</th>
<th>Nr. of Patients</th>
<th>RRT</th>
<th>Dosage (mg/kg/48h or 24h)</th>
<th>C_{max} (mg/L)</th>
<th>C_{min} (mg/L)</th>
<th>S</th>
<th>t_{1/2 β} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bastien et al.</td>
<td>Intens Care Med, 1993</td>
<td>3</td>
<td>CVVHD</td>
<td>5</td>
<td>16.1</td>
<td>5.5</td>
<td>0.75 - 0.95</td>
<td>18.6</td>
</tr>
<tr>
<td>Boulieu et al.</td>
<td>Ther Drug Monit, 1993</td>
<td>3</td>
<td>CVVHD</td>
<td>5</td>
<td>15.9 - 18.6</td>
<td>4.6 - 5.4</td>
<td>0.84</td>
<td>18.9</td>
</tr>
<tr>
<td>Gando et al.</td>
<td>Crit Care Med, 1998</td>
<td>1</td>
<td>CVVHDF</td>
<td>5</td>
<td>20.3</td>
<td>8</td>
<td>n.a.</td>
<td>12.6</td>
</tr>
<tr>
<td>McGloughlin et al.</td>
<td>Int J Antimicrob Agents, 2011</td>
<td>1</td>
<td>CVVHDF</td>
<td>2.5</td>
<td>5.7</td>
<td>n.a.</td>
<td>n.a.</td>
<td>14</td>
</tr>
<tr>
<td>Horvatits et al.</td>
<td>this study</td>
<td>9</td>
<td>CVVHDF</td>
<td>5</td>
<td>11.8</td>
<td>2.4</td>
<td>0.76</td>
<td>24.2</td>
</tr>
</tbody>
</table>

RRT, renal replacement therapy; C_{max}, peak serum concentration; C_{min}, trough serum concentration; S, sieving coefficient; t_{1/2 β}, elimination half-life; CVVHD, continuous venovenous haemodialysis; CVVHDF, continuous venovenous haemodiafiltration; HD, haemodialysis
Fig. 2

Graphs showing the concentration of Ganciclovir over time.

A: Time [h] vs. Ganciclovir concentration [mg/L]
B: Time [h] vs. Ganciclovir concentration [mg/L]
C: Time [h] vs. Ganciclovir concentration [mg/L]