

New algorithm for valganciclovir dosing in pediatric solid organ transplant recipients

Åsberg A, Bjerre A, Neely M. New algorithm for valganciclovir dosing in pediatric solid organ transplant recipients.

Abstract: CMV infections are common after SOT. v-GCV is increasingly used in children. The aim of this study was to evaluate presently used dosing algorithms. Data from 104 pediatric SOT recipients (kidney, liver, and heart) aged 0.3–16.9 yr and receiving v-GCV once a day were used for model development and validation with the Pmetrics package for R. Monte Carlo simulations were performed to compare the probability of a GCV AUC 40–60 mg*h/L with the different algorithms across a range of ages, weights, and GFRs. GCV pharmacokinetics was well described by the non-parametric model. Clearance was dependent on GFR and Cockcroft-Gault estimates improved the model fit over Schwartz. Simulations showed that our new algorithm, where v-GCV dose is: $\text{Weight [kg]} \cdot (0.07 \cdot \text{GFR [mL/min]} + k)$, where $k = 5$ for $\text{GFR} \leq 30$ mL/min, $k = 10$ for $\text{GFR} > 30$ mL/min and $\text{weight} > 30$ kg and $k = 15$ for $\text{GFR} > 30$ mL/min and $\text{weight} \leq 30$ kg, outperformed the other algorithms. Thirty-three percent of all patients achieve an exposure above and 21% within the therapeutic window. We propose a simple algorithm for initial v-GCV dosing that standardizes plasma drug exposure better than current algorithms. Subsequent TDM is strongly suggested to achieve individual drug levels within the therapeutic window.

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CMV infection is a common complication after SOT, and it is associated with morbidity, impaired long-term outcomes and occasional mortality (1, 2). Intravenous GCV is the gold standard for prevention and treatment of CMV infections (2, 3). v-GCV is a prodrug of GCV with a high oral bioavailability of about 60%, and it is rapidly converted to GCV following oral administration (4). The clinical effect of v-GCV is hence comparable to that of GCV as long as the same plasma concentrations of GCV are achieved.

Abbreviations: AIC, Akaike Information Criterion; AUC_{0-t} , area under the plasma concentration vs. time curve within one dose interval; BSA, body surface area; CMV, cytomegalovirus; GCV, ganciclovir; IQR, inter quartile range; LLoQ, lower level of quantification; PE, predictive error; SCH, Seattle Children's Hospital; SOT, solid organ transplantation; TDM, therapeutic drug monitoring; v-GCV, valganciclovir.

Data on the clinical efficacy of v-GCV are limited in the pediatric population. v-GCV is non-inferior to GCV, both as primary prophylaxis and treatment of active CMV disease in adult SOT patients (5–7). International treatment guidelines advocate that v-GCV is comparable to intravenous GCV for most patients, with an extra focus on situations that may limit its oral bioavailability, such as gastrointestinal CMV disease for example, or where data are scarce regarding its bioavailability, such as in the pediatric population (3). Measuring GCV concentrations would add confidence that a v-GCV dose is acceptable for a specific patient. However, GCV TDM is not commonly performed after v-GCV administration, and treating physicians tend to trust dosing algorithms combined with monitoring of viral loads for anti-CMV treatment strategies in SOT. However, when TDM is used, the therapeutic window for GCV is an area under the plasma concentration vs. time curve (AUC)

between 40 and 60 mg*h/L, AUC_{0-24} for prophylaxis and AUC_{0-12} for treatment of active disease (8).

GCV is a small molecule (255.23 Da) with low plasma protein binding (3%) and it is eliminated via the renal route (1). v-GCV doses therefore need to be adjusted according to patients' renal function and the currently most widely applied algorithm for pediatric patients is the Pescovitz algorithm (9):

$$\text{Dose} = 7 * \text{BSA}(\text{m}^2) * \text{CL}_{\text{creat}}(\text{mL}/\text{min}/1.73 \text{m}^2),$$

where CL_{creat} is determined by the Schwartz formula (10).

Recently, however, Villeneuve et al. (11) suggested an alternative dosing strategy (SCH algorithm) in an attempt to better standardize plasma GCV exposure in patients between 0.5 to 3 yr of age. This strategy is based on a dose of 14–16 mg/kg and adjustment for renal function in accordance with the package insert for adults.

The aim of the present analysis was to develop a non-parametric population model for v-GCV in pediatric SOT recipients to evaluate the two above mentioned dosing algorithms and if necessary develop a new algorithm.

Material and methods

Patients

The development of this population model is based on previously published pediatric data (9), with a total of 25 renal and 18 liver transplant recipients between 0.5 to 16 yr of age (median age nine yr). Demographic data of the 26 male and 17 female patients are shown in Table 1. All patients received both v-GCV (powder for oral solution) and intravenous GCV. The doses were based on adult dose recommendations adapted to children by BSA scaling; 520 mg/m² of v-GCV and 260 mg/m² for intravenous GCV (administered as a one h infusion), both adjusted for estimated renal function by the Schwartz formula (10). Patients received four doses: Intravenous GCV on days 1 and 2 and v-GCV on days 3 and 4. Blood samples for determination of GCV concentrations on day 2 were drawn pre-dose (–2 to 0 h), immediately at the end of the infusion (one h) and between 2–3, 5–7, and 10–12 h post-dose. On days 3 and 4, samples were drawn pre-dose and between 0.25–0.75, 1–3, 5–7, and 10–12 h post-dose. In renal transplant recipients a sample between 22 and 24 h after the day 4 dose was also collected. Serum creatinine was measured daily.

The population model was validated on an external data set previously presented (9). The demographics of these 61 validation pediatric patients were comparable to the population used for model development, as shown in Table 1. They received once daily v-GCV (either powder for oral solution or tablets or a combination of both) as primary prophylaxis for up to 100 days after transplantation. In addition to kidney and liver transplants, these data also include heart and one combined kidney–liver transplants.

Table 1. Median (range) demographic data of patients used for development and validation of the non-parametric population model

	Patients used for development of population model (n = 43) (22)	Patients used for model validation (n = 61) (12)	The combined data set (n = 104) (12, 22)
M:F	26:17	33:28	59:45
Age (yr)	10.0 (0.5–16)	7.8 (0.3–16.9)	9.9 (0.3–16.9)
Organ transplanted			
Kidney	25	31	56
Liver	18	17	35
Heart		12	12
Kidney and liver		1	1
Body weight (kg)	26.0 (6.1–81.6)	23.5 (5.8–89.4)	25.9 (5.8–89.4)
Height (cm)	129 (59–185)	126 (62–173)	127 (59–185)
BSA (m ²)	0.97 (0.31–2.04)	1.00 (0.32–2.07)	0.98 (0.31–2.07)
Cockcroft-Gault GFR (mL/min)	80 (29–165)	69 (16–142)	73 (16–165)
Schwartz GFR (mL/min/1.73 m ²)	113 (48–212)	107 (46–196)	112 (46–212)

The dose of v-GCV was administered according to the Pescovitz algorithm (Dose [mg] = 7*BSA [m²]*GFR_{Schwartz} [mL/min/1.73 m²]). Blood samples for determination of plasma GCV concentrations were obtained between 3 to 14 days post-transplant at the following time points; pre-dose and 1–2, 3–7, and 7–12 h post-dose. Additional single samples were up to the discretion of the treating physician. These clinical trials were performed in accordance with the Helsinki declaration and local Ethics Committee approvals.

Furthermore, four SOT patients treated with v-GCV at our transplant center served as a “standard of care” validation population. Their demographic data are summarized in Table 2.

GCV analysis

Plasma concentrations of GCV in the two published populations were analyzed with validated specific LC-MS/MS assays as previously presented (9, 12), while samples from the four patients from our center were analyzed with a validated specific LC-UV assay (13). Assay characteristics in short; LC-MS/MS: LLoQ is 0.04 µg/L, overall accuracy between 99% and 105% and inter-assay variability between 0.7% and 12%, LC-UV: LLoQ is 0.1 µg/L, overall accuracy between 90% and 117% and inter-assay variability between 10% and 20%. The standard deviations (s.d., i.e., assay error) for measured (observed) GCV are derived from the analytical validation data (13), resulting in the following error polynomial: s.d. = –0.0045291 + 0.12022645*[obs], where [obs] is the observed concentration of GCV.

Population pharmacokinetic modeling and validation

The non-parametric pharmacokinetic modeling was performed in Pmetrics (version 0.40, Laboratory for Applied Pharmacokinetics, Los Angeles, CA, USA) (14) using the algebraic model solver. We chose to use a non-parametric approach because for certain advantages over parametric

Table 2. Clinical data on the four patients treated with valganciclovir in a clinical setting at our transplant center and their model calculated $AUC_{0-\tau}$.

Patient	Age (yr)	Sex	Weight (kg)	Height (cm)	P-creat (μM)	Tx organ	Indication for valganciclovir	Dose administered	Dose (Pescovitz-algorithm)	Dose (SCH algorithm)	Dose (NEW algorithm)	Model calculated $AUC_{0-\tau}$ (mg*h/L)
1	4.25	F	19	102	26	Kidney	CMV disease	150 mg BID	900 mg BID (988 mg)	225 mg BID	504 mg BID	17.1
2	8.5	F	23	117	38	Kidney	Primary proph.	450 mg QD	900 mg QD (914 mg)	450 mg QD	479 mg QD	55.2
3	15	F	55	162	55	Heart	Primary proph.	450 mg BID	900 mg QD (1591 mg)	900 mg QD	1053 mg QD	26.5
4	8.0	M	24	130	41	Heart	Primary proph.	450 mg BID	900 mg QD (1014 mg)	450 mg QD	520 mg QD	58.8

P-creat, plasma creatinine; Tx, transplant; BID, twice daily; QD, once daily. For the “Dose according to the Pescovitz-algorithm” the figure within Parenthesis are the actually calculated doses if not limited by the maximum dose of 900 mg and for the NEW algorithm, the actual calculated start doses are given.

methods (14): (i) to better detect outlier patients if present; (ii) to detect any unexpected subpopulations; (iii) and to build a model that could be used for multiple-model adaptive control as implemented in the BestDose clinical dose optimization software package produced by LAPK (Laboratory for Applied Pharmacokinetics; www.lapk.org). We intend to use this tool prospectively for v-GCV TDM.

To be consistent with a previous population model of GCV in pediatric patients (9), the structural model was set to three compartments with first-order v-GCV absorption from the dosing compartment into the central compartment (including conversion to GCV) after a delay or lag time, and distribution to and from a peripheral tissue compartment. As intravenous data were available, the model was parameterized with central clearance (CL), inter-compartment clearance (Q), central and peripheral volumes of distribution (V, Vp), and an absolute bioavailability (FA) term was also introduced. The data used in the present analysis come from oral administration of both v-GCV tablets as well as oral solution. This was however not differentiated in the model since the two formulations previously have been shown to be bioequivalent (15).

Both the additive lamda and multiplicative gamma error models in Pmetrics were tested during the model development, using the assay error polynomial as presented above. As many multiples of 80 021 grid points as possible were applied (limited by hardware storage capacity), with uniform initial distribution, and the analyses were run on a MacBook Pro (2.66 GHz Intel Core 2 Duo processor, 8 GB 1067 MHz DDR3 memory and running OS X, version 10.8.2; Apple Inc, Cupertino, CA, USA).

All pharmacokinetic disposition parameters were allometrically scaled to body size using total body weight and coefficients of 3/4 for clearances and 1 for volumes (16). Covariates were scaled to the median population values and continuous covariates were extrapolated between observations. Covariates were included stepwise, followed by a reduction of the resulting model by taking one covariate out of the model. Both the old and new Schwartz formulas’ as well as the Cockcroft-Gault formulae for estimation of GFR were tested (10, 17, 18). The estimated GFRs, individually converted to the unit of mL/min for the Schwartz formulas, were included in the model to the power of a parameter (GFRcl) that was estimated in the model.

Model selection was based on comparison of the AIC, the fit of both the population and individual predicted vs. observed plots and biological plausibility.

The model was evaluated for its predictive accuracy on the external validation data set of 61 new patients receiving v-GCV for primary prophylaxis after transplantation. From the Bayesian prior model parameter joint density, Pmetrics

calculated the Bayesian posterior joint density for each subject in the external validation set. The median marginal parameter values of each posterior density were used to calculate the predicted GCV concentrations, given individual v-GCV dosing and patient covariates. The following statistics were computed: PE (predicted minus observed concentrations), bias (mean weighted PE), imprecision (bias-adjusted mean weighted squared PE), and the R^2 and slope of the individual predicted vs. observed plots. These statistics in the external validation set were compared to the same statistics in the model development subjects. Analyses in the external data set were performed with only single kidney and single liver transplant recipients as well as in all 61 patients, including heart and one combined kidney-liver transplant, all together.

For prediction of concentrations in the four patients monitored during standard clinical conditions, the two data sets previously mentioned were combined, and new population parameter estimates were established. The new model, now including data from 104 patients, was used as a prior and data from the four patients from our clinic were included in the analysis. Steady-state samples from three of these patients had been obtained before the morning dose (zero h), and 0.5, 1, 1.5, 2, 4, 6, 9, and 12 h after the dose. Patient one, however, only donated two blood samples at trough and two h after the morning dose. At the time of sampling, the hospital protocol for prophylaxis in heart transplants was to split the daily dose into twice daily administrations.

Current v-GCV dose algorithm evaluation

To evaluate the current Pescovitz and SCH dosing algorithms, a Monte Carlo simulation of patients spanning 0.5–16 yr, having poor and good renal function was performed. Based on WHO weight and height curves the 5% and 95% quintiles for the following ages were used: 0.5, 3, 6, 12, and 16 yr (19). Three GFRs were applied to the 10 age/size combinations, representing poor, moderate, and normal renal function: 25, 75, and 125 mL/min/1.73 m², respectively. Each of these 30 fictive patients served as a simulation template for 1000 GCV time-concentration profiles calculated from parameters sampled from the model population joint density, including the full covariance matrix. Simulated GCV concentrations were corrupted by noise using the same error polynomial as in the population model. Simulated parameter values were restricted to be physiologically plausible by applying the same boundaries as in the model. Four or seven doses of v-GCV, depending on the fictive patient’s renal function were administered and the steady-state AUC_{0-24} was calculated from 144 to 168 h after the first dose administered. For each simulated

population, the probability of the AUC_{0-24} lying between 40 and 60 mg*h/L was calculated as the number of simulated profiles within that range divided by the total number in that population, that is, 1000.

v-GCV dose algorithm development

A new simple algorithm was developed in order to reflect our non-parametric population model, including the effects of GFR and body weight on GCV clearance. Our proposed algorithm was first scaled to attain an average percent target achievement of 50% using the center of the therapeutic window as a target (50 mg*h/L), when using patients with body weights from 10 to 100 kg and GFRs from 10 to 160 mL/min as simulation templates for 1000 profiles drawn from the population model joint density, including the full covariance matrix. The new algorithm was then tested with a simulation of patients with age ranges from 0.5 to 16 yr and GFRs from 25 to 125 mL/min/1.73 m² as performed for the current available algorithms and which is described in detail in the previous section.

Results

Population model development

Model parameter values are shown in Table 3. The model with a lambda error model was initiated with 16 × 80 021 grid points and it converged after 8008 cycles to 42 support points. The final cycle AIC was 157. Using a gamma model reduced the AIC to 90.1 but the predicted vs. observed plots were somewhat inferior and it was not possible to predict concentrations in three of the patients in the external validation data set when using the gamma model. The lambda model was hence chosen, and the population bias was 0.175 and imprecision was 0.050. Fig. 1 shows the population and individual predicted vs. observed plots and associated R²-value of 0.78 and 0.98, respectively. The final cycle lambda was 0.0611. Since this was high relative to the first term of the assay error polynomial, it

Table 3. Parameter values (median and IQR) for the final model with the population of 43 patients used for development of the model and for the model using combined data of the 43 patients used for model development and the 61 external validation patients (total n = 104)

Parameter	Developed model (n = 43)		Model with combined data (n = 104)	
	Median	IQR	Median	IQR
Clearance (CL) [L/h]	4.8	3.6	5.0	4.9
Intercompartment clearance (Q) [L/h]	3.3	6.1	5.0	7.3
Central volume of distribution (V) [L]	9.8	14.5	9.8	12.8
Peripheral volume of distribution (Vp) [L]	12.7	20.1	16.2	21.7
Bioavailability (FA)	0.57	0.22	0.59	0.27
Lag time (Tlag) [h]	0.34	0.27	0.38	0.58
Absorption rate constant (Ka) [h ⁻¹]	0.72	1.03	0.84	1.17

may reflect some uncertainty about exact sample or dose times.

Allometric scaling to weight was superior to both height and BSA scaling, with an AIC lower by 25.6 and 52.1, respectively. Clearance was further affected by renal function; scaling clearance to GFR estimated by the Cockcroft-Gault equation resulted in a lower AIC by 1.8 and 2.2, respectively, as compared to the new and old Schwartz formulae, even though this was a pediatric population. The other covariates tested did not improve the model fit of the data; sex on peripheral volume of distribution, lag time and bioavailability increased the AIC by 25.3, 29.5, and 6.1, respectively. Age on peripheral volume of distribution and clearance increased the AIC by 9.4 and 18.5 and type of organ transplanted (kidney vs. liver) on volume of distributions increased the AIC by 81.7.

Population model validation

The external validation indicates that the model appropriately describes the pharmacokinetics of GCV in pediatric SOT recipients after receiving v-GCV dosing. Comparing the data from the 61 new “external” patients with the 43 patients that provided data for development of the model showed only marginal differences in predictive bias and imprecision. The population bias and imprecision was 0.112 and 0.369 in the external data set. The median individual PE was -0.003 (IQR: 0.155) mg/L for the internal data and -0.095 (IQR: 0.999) mg/L for the external data.

The external validation data also included heart transplants and one combined kidney–liver-transplanted patient, even though the model only was developed on data from single kidney and liver transplants. The 48 kidney- or liver-transplanted patients in the external data set showed a median PE of -0.098 (IQR: 0.920) mg/L not different from that of the 13 other patients who showed a median PE of -0.086 (IQR: 1.179) mg/L.

The parameter estimates of the combined model (including the internal and external data sets), in total 104 patients, are shown in Table 3. The model converged after 9517 cycles to 90 support points. The final cycle AIC was 740 and the population bias and imprecision were 0.189 and 0.669, respectively.

v-GCV dosing simulations

Based on the final non-parametric model, the following algorithm is suggested for CMV prophylactic dosing of v-GCV in pediatric patients:

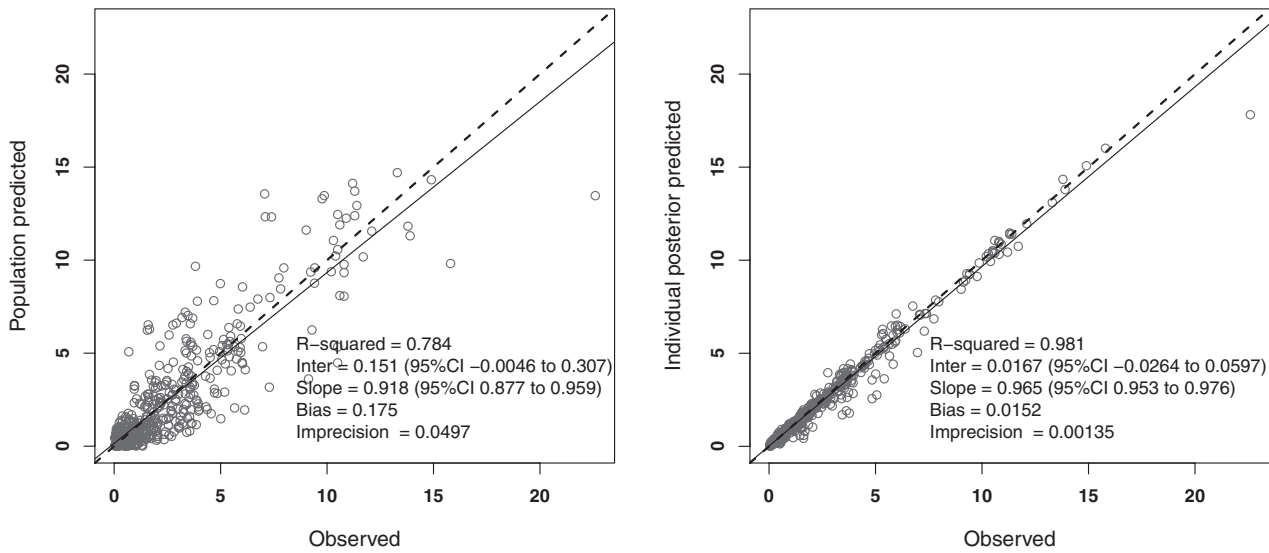


Fig. 1. Population (left) and individual (right) predicted vs. observed concentration (mg/L) plots of the final model.

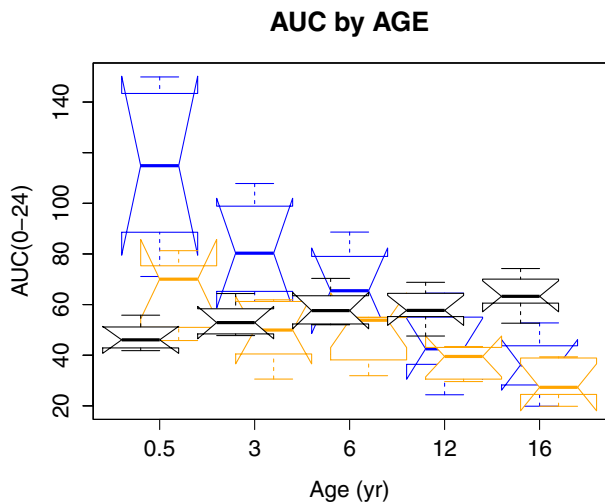


Fig. 2. Notched boxplots of simulated AUC_{0-24} values by age of the patient and dosing algorithms: Pescovitz (blue), Seattle (orange), and new candidate (black). Within each age group, one patient with the 5% and one with the 95% quintile height and weight for the ages (WHO data) with a GFR of 25, 75, or 125 mL/min/1.73 m² were used as template for the simulations (in total 30 000 simulated patients).

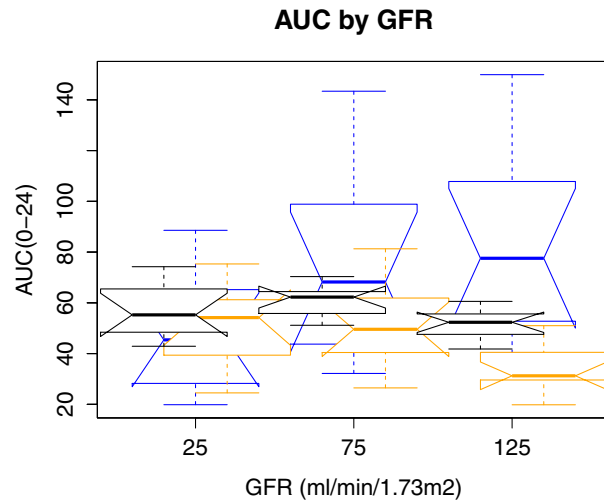


Fig. 3. Notched boxplots of simulated AUC_{0-24} values by age of the patient and dosing algorithms: Pescovitz (blue), Seattle (orange), and new candidate (black). Within each renal function group, patients with the following ages: 0.5, 3, 6, 12, and 16 yr and with the 5% or the 95% quintile height and weight for the respective age (WHO data), were used as template for the simulations (in total 30 000 simulated patients).

$$v\text{-GCV dose [mg]} = \text{body weight [kg]} * (0.07 * \text{GFR[mL/min]} + k),$$

where $k = 5$ for $\text{GFR} \leq 30$ mL/min, $k = 10$ for $\text{GFR} > 30$ mL/min and weight > 30 kg and $k = 15$ for $\text{GFR} > 30$ mL/min and weight ≤ 30 kg.

The resulting AUC_{0-24} from simulations with the two current dosing algorithms and our candidate algorithm are presented by age in Fig. 2 and

by eGFR in Fig. 3. The plots show relevant differences between the algorithms, especially in the youngest patients (an half yr), with the Pescovitz algorithm providing overly high AUC_{0-24} . The differences between the two current algorithms diminishes as age increases, but they are both out of the therapeutic window for some age groups. The new candidate algorithm results in AUC levels more within the target range over the different age and eGFR groups. As shown in Fig. 4, the percentage of patients achieving AUCs within

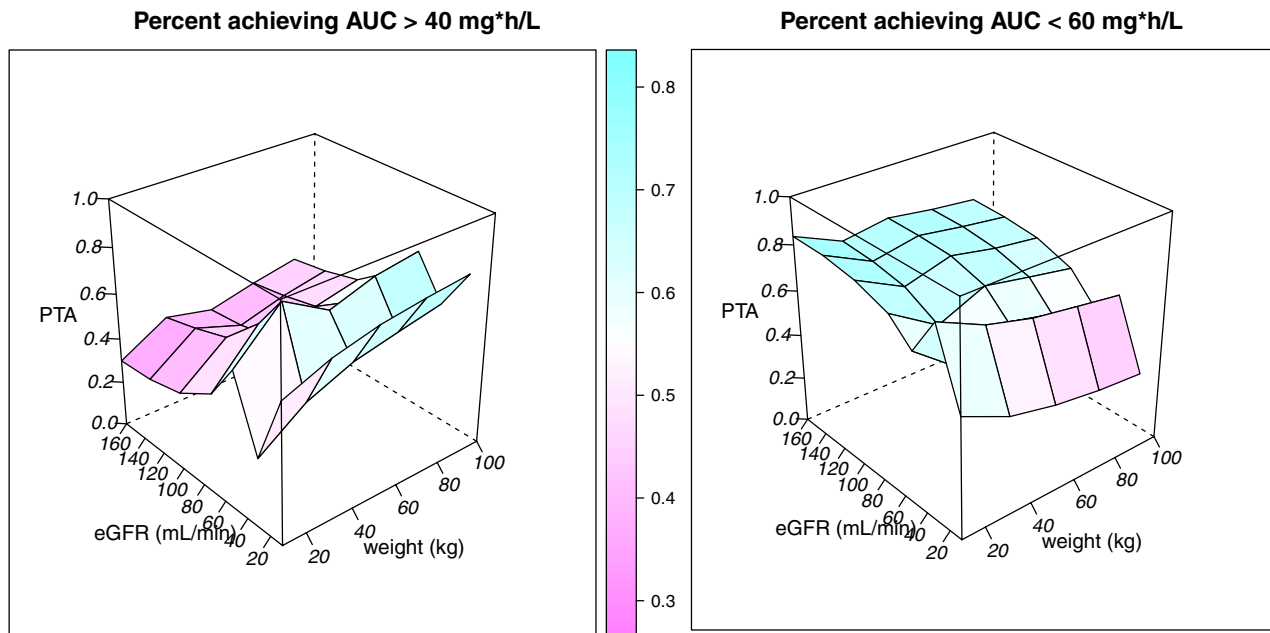


Fig. 4. Surface plots for percentage target achievement of simulated AUC_{0-24} values following prophylaxis dosing once daily with the new candidate algorithm and target set to the therapeutic window of 40–60 mg*h/L. Simulated values were assessed as described in Fig. 2.

the target AUC_{0-24} range of 40–60 mg*h/L is on average acceptable but extreme patients with regard to weight and eGFR are not perfectly covered with even the new candidate algorithm. On average, however, 21% achieved an AUC_{0-24} within the therapeutic window and 33% an exposure above.

Simulations of treatment dosing using our new candidate algorithm for twice daily v-GCV dosing resulted in a low probability of achieving an AUC_{0-12} of 40–60 mg*h/L. In addition to twice daily dosing for treatment, doses should also be increased by an additional 20% for all age and eGFR ranges (Fig. 5), i.e., 1.2 * prophylactic dose given twice daily.

Clinical v-GCV dosing

The model-calculated AUC values for the four “standard of care” clinical follow-up patients are shown in Table 2. Patient one was dosed similarly to the SCH dosing algorithm, while the rest received doses based on adult dosing schedules, adjusted for their renal function. The daily dose was however divided into two for patients 3 and 4 even though they received v-GCV as primary prophylaxis. The new candidate algorithm suggests relevant doses for all four patients. Fig. 6 shows the concentration vs. time curves for the four “standard of care” patients.

Discussion

The main finding of the present analysis is that TDM is warranted to achieve GCV exposure within the therapeutic window. The current available dosing algorithms will only, at the very best, be valid for about one-third of the patients. In addition, we showed that the commonly used Pescovitz algorithm (Dose = $7 \cdot BSA \cdot CL_{creat}$) (9) overdoses almost all young children and underdoses most of the older pediatric patients. The recently suggested dose strategy from SCH (11) has better target achievement as compared with the Pescovitz algorithm for the youngest children, but is still inferior to our new candidate algorithm. Even though the total number of patients reaching the therapeutic window is not that different between the three algorithms the new candidate algorithm shows a more even distribution over all age and renal function groups investigated.

The non-parametric population model developed described the data correctly, and the estimated model parameters were comparable to those previously presented by a parametric model (9). For example, bioavailability in the present analysis was estimated to be just below 60%. Even though the model was developed on data from kidney and liver SOT, no relevant difference was seen with regards to heart transplants in the external validation. It is however

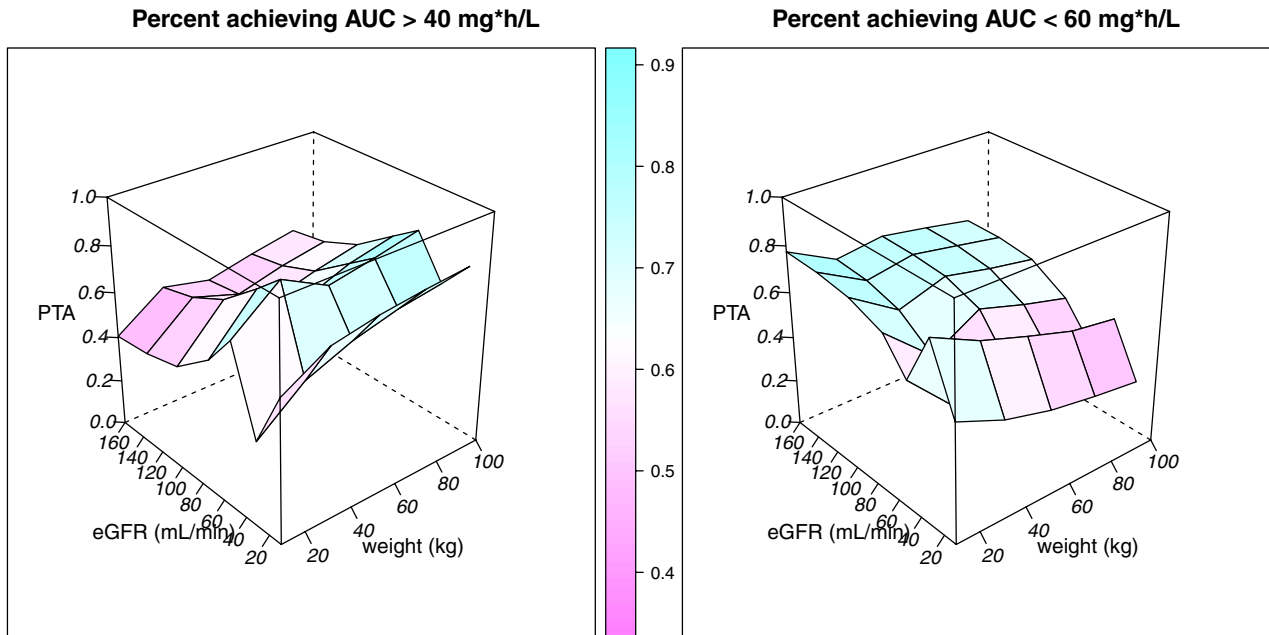


Fig. 5. Surface plots for percentage target achievement of simulated AUC_{0-12} values following treatment dosing twice daily using 1.2 time the new candidate algorithm and with target set to the therapeutic window of 40–60 $mg \cdot h/L$. Simulated values were assessed as described in Fig. 2.

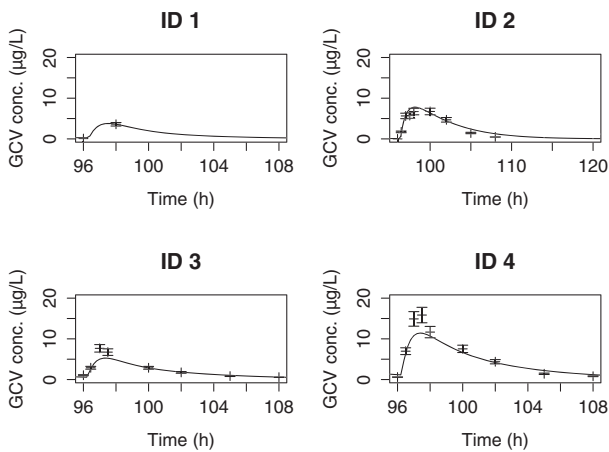


Fig. 6. Individual predicted (line) plasma concentration vs. time curves and measured GCV concentrations (+) for the four patients treated with valganciclovir in our clinic.

important to remember that only 12 heart transplants were included in the external validation data set, so some deviation may be present. Studying the two heart transplants from our “standard clinical care,” it seems obvious that the model under predicts especially peak concentrations in these patients.

Somewhat surprisingly, despite the pediatric population, the Cockcroft-Gault formula for GFR estimation slightly improved the model fit compared to the Schwartz formula. The new candidate algorithm includes body weight, and

not BSA, which is commonly used for dose adjustments in pediatric patients. However, BSA scaling is not needed when estimating GFR with the Cockcroft-Gault formula since it provides eGFR in the unit of mL/min (17) as compared with the Schwartz formula which provides eGFR in the unit of mL/min/1.73 m² (10). One can always argue about how good different eGFR algorithms predict renal function in the pediatric population and creatinine-based formulas are known to overestimate GFR (18). However, here we are most interested in finding the renal function descriptor that best describes GCV behavior, with the goal of individualized v-GCV dosing, rather than accurate GFR estimates, per se. In this regard, the Cockcroft-Gault formula outperformed the Schwartz formula, and it is similar to a comparison of eGFR algorithms to model gentamicin pharmacokinetics in adults that found Cockcroft-Gault to be similar to the Jelliffe method, and both were superior to MDRD (20). So even if the Schwartz formula is best associated with gold standard measurements of GFR (i.e., inulin clearance) in children, it is not the best descriptor of GCV behavior in this population.

However, it is important to note that no simple algorithm alone will estimate the individual correct dose for all patients due to the wide range of GCV exposures for a given dose of v-GCV. The present simulations show that the new candidate

algorithm provides a good estimate of starting doses but in order to ensure exposure within the therapeutic window, TDM is needed. Few transplant centers currently use TDM for v-GCV dose adjustments. Without TDM, at best only about 20% of the patients will receive the correct dose according to the defined therapeutic window. The effect of TDM both on drug target achievement and on clinical outcomes needs, however, to be further evaluated in prospective clinical trials.

The current dosing suggestion for v-GCV to treat CMV disease is to use the same v-GCV dose as in prophylaxis, but given twice daily instead of once daily, that is, double the total daily dose. This is based on the theoretical assumption that AUC_{0-24} will be the same as AUC_{0-12} for once- and twice-daily dosing, respectively, at steady state for a one-compartment, dose-proportional model with linear kinetics. Our simulations indicate, however, that this is not the case, and that on average the dose should be increased by about 20%, in addition to being given twice daily, to achieve high enough systemic GCV exposure in the main proportion of the population. Again, since the exposure variability is so large, TDM seems warranted. Aiming for a somewhat higher initial exposure is probably advisable in the case of CMV disease treatment, in order to quickly get control of the viral replication.

TDM can be performed in many ways but the most cost-effective would probably be to use a population model combined with an optimal sampling strategy. This will ensure quick control over individual pharmacokinetics behavior with a minimal number of blood samples (21).

In conclusion, we present a new dosing algorithm for v-GCV in the pediatric population. This algorithm provides more suitable starting doses for the suggested therapeutic window than previous algorithms. Nevertheless, TDM needs to be applied in order to individually adjust systemic exposures within the therapeutic window in this population. The non-parametric population model may be a suitable TDM tool but this needs to be tested prospectively.

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Authors' contributions

All authors have been involved in the design of the study, interpretation of results and the writing of the manuscript. AB has collected the "standard of care" patient samples and

ÅÅ has measured GCV in these samples. ÅÅ and MN performed the population modeling and simulations.

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