




# Population Pharmacokinetics of Intravenous and Oral Acyclovir and Oral Valacyclovir in Pediatric Population To Optimize Dosing Regimens

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**ABSTRACT** Acyclovir is an antiviral currently used for the prevention and treatment of herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections. This study aimed to characterize the pharmacokinetics (PK) of acyclovir and its oral prodrug valacyclovir to optimize dosing in children. Children receiving acyclovir or valacyclovir were included in this study. PK were described using nonlinear mixed-effect modeling. Dosing simulations were used to obtain trough concentrations above a 50% inhibitory concentration for HSV or VZV (0.56 mg/liter and 1.125 mg/liter, respectively) and maximal peak concentrations below 25 mg/liter. A total of 79 children (212 concentration-time observations) were included: 50 were taking intravenous (i.v.) acyclovir, 22 were taking oral acyclovir, and 7 were taking both i.v. and oral acyclovir, 57 for preventive and 22 for curative purposes. A one-compartment model with first-order elimination best described the data. An allometric model was used to describe body weight effect, and the estimated glomerular filtration rate (eGFR) was significantly associated with acyclovir elimination. To obtain target maximal and trough concentrations, the more suitable initial acyclovir i.v. dose was 10 mg/kg of body weight/6 h for children with normal renal function (eGFR  $\leq$  250 ml/min/1.73 m<sup>2</sup>) and 15 to 20 mg/kg/6 h for children with augmented renal clearance (ARC) (eGFR > 250 ml/min/1.73 m<sup>2</sup>). The 20-mg/kg/8 h dose for oral acyclovir and valacyclovir produced effective concentrations in more than 75% of children; however, a 15-mg/kg/6 h dose, if possible, is preferred. These doses should be prospectively confirmed, and therapeutic drug monitoring could be used to refine them individually. (This study has been registered at ClinicalTrials.gov under identifier NCT02539407.)

**KEYWORDS** antiviral agents, children, population pharmacokinetics

Acyclovir {9-[(2-hydroxyethoxy)-methyl]guanine} is an antiviral used for curative or prophylactic treatment of herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections and diseases. In some cases, it can also be used as a preventive treatment against cytomegalovirus (CMV) infections and diseases following solid organ or hematopoietic stem cell transplantation (1, 2), with the knowledge that immunocompromised patients are at risk of viral infections (3). The guanosine analogue

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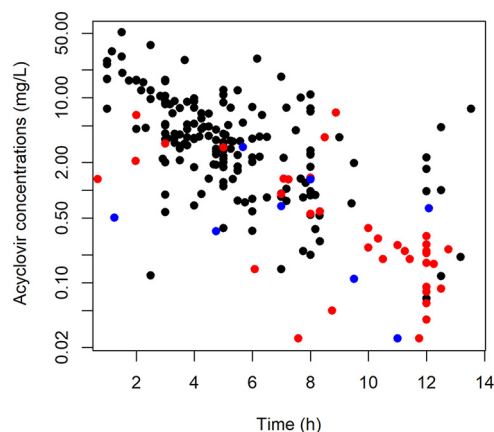
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**FIG 1** Acyclovir concentrations as a function of time after dose of acyclovir i.v. (black circles), oral acyclovir (blue circles), and oral valacyclovir (red circles).

structure of acyclovir shows a selective affinity for the HSV and VZV enzyme thymidine kinase, which allows inhibition of viral DNA replication (4, 5). Due to its low bioavailability ( $F$ ), between 15% and 30% (6), acyclovir is used mostly in an intravenous (i.v.) form. Valacyclovir, a prodrug of acyclovir, is more lipophilic than acyclovir owing to the addition of an  $L$ -valyl ester and enables an increase in bioavailability up to 54%. Valacyclovir is more adapted to oral dosing because it is metabolized by intestinal and hepatic esterase to acyclovir (7, 8).

Acyclovir is poorly metabolized by the liver, and its metabolite, 9-carboxymethoxyguanine, has no antiviral activity. Up to 90% of acyclovir is directly eliminated via renal excretion, with an elimination half-life between 1.43 and 2.48 h in the pediatric population (9–11).

Depending on the indications, the usual recommended doses for the pediatric population range from 5 mg/kg to 20 mg/kg of body weight every 8 h with a 1-h infusion for the acyclovir i.v. dosing and from 20 mg/kg every 8 h to 2,000 mg every 12 h for the oral valacyclovir dosing. Renal impairment is taken into consideration, with dose adjustments when creatinine clearance is lower than 50 ml/min (12, 13). Augmented renal clearance (ARC) is present in 20 to 65% of critically ill patients and is characterized by increased creatinine clearance and elimination of renally eliminated medications. No recommendation is made for these patients.

Our study aimed to characterize the pharmacokinetics (PK) of i.v. acyclovir and oral valacyclovir with a population pharmacokinetic approach, defining relevant covariates that could explain interindividual variability (IIV). The final goal was to assess current dose recommendations for children and to suggest appropriate dosing for optimal exposure.

## RESULTS

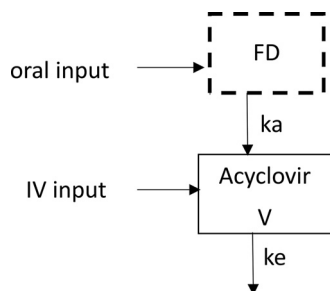
**Plasma concentration data.** From the 79 patients, 212 acyclovir plasma concentrations were measured (1 to 10 samples per patient) (Fig. 1). Of the 79 children, 48 were from the pediatric immune-hematology unit (IHU), 19 were from the pediatric intensive care unit (PICU), 10 were from the department of pediatric surgery, and 2 were from the department of pediatrics of the Necker-Enfants Malades Hospital (Paris, France). Forty-six samples came from patients with oral dosing, and 166 samples came from patients with i.v. dosing. Table 1 summarizes patients' characteristics (sex, age, body weight, height, body mass index, glomerular filtration rate [eGFR]), and indications for acyclovir treatment. Administration routes were i.v. for 50 patients, oral for 22 patients, and both i.v. and oral for 7 patients. Of the 29 patients who received the oral dose, 7 received acyclovir and 22 received valacyclovir tablets. The median (interquartile range [IQR]) administered doses were 51 (5 to 101) mg/kg/day and 22 (17 to 63) mg/kg/day for i.v. and oral administration, respectively.

**TABLE 1** Characteristics of the population

Characteristic	Median (range)
No. of patients (no. of samples)	79 (212)
Administration route (oral/i.v./i.v. and oral) (no. of patients)	22/50/7
Sex (no. of males/females)	48/31
Age (yr)	4.1 (0.02–18)
Age at inclusion (no.): 0–1 yr/1–12 yrs/12–18 yrs	20/41/18
Wt (kg)	15 (3.1–66)
Ht (cm)	108 (49–169)
Body mass index (kg/m <sup>2</sup> )	16.9 (11.5–50.0)
Plasmatic creatinine (μmol liter <sup>-1</sup> )	29 (10–172)
eGFR (ml/min/1.73 m <sup>2</sup> )	164 (56–399)
No. using acyclovir as a curative treatment	
Against HSV-1/2	17
Against VZV	5
No. using acyclovir as a preventive treatment	
After hepatic transplantation	8
After pulmonary transplantation	1
After hematopoietic stem-cell transplantation (medullar)	6
After peripheral stem cell transplantation	4
After bone marrow transplantation	36
Others	2

**Population pharmacokinetics. (i) Structural model building.** A one-compartment model with first-order absorption and elimination best described the data (Fig. 2). The parameters of the model were bioavailability ( $F$ ), absorption rate constant ( $k_a$ ), volume of distribution ( $V$ ), and clearance ( $CL$ ). Only three acyclovir concentrations were lower than the limit of quantification (LOQ), accounting for 1.4% of the data; thus, only the method of half of the LOQ was tested. The available data were not sufficient to estimate IIV for bioavailability and  $k_a$ , and fixing the variance of these random effects to zero had no influence on the objective function value (OFV). The residual variability was best described by a proportional error model. An allometric model was added to the structural model, with a decrease in the OFV of 60 U and decreases from 0.73 to 0.434 for IIV in  $CL$  and from 0.738 to 0.496 for IIV in  $V$ . eGFR was added to  $CL$  because it decreased the OFV by 51 U (and the IIV from 0.46 to 0.389), whereas the addition of the plasma creatinine decreased the OFV by 29 U and the addition of both plasma creatinine and height decreased the OFV by 48 U. The effect of other covariates was not statistically significant. Final PK parameter estimates are summarized in Table 2.

**(ii) Model assessment.** Diagnostic plots from the final model are shown in Fig. 3. Very high concentrations were not correctly fitted by the model. Prediction-corrected visual predictive check (pc-VPC) of the final population PK model showed the comparison between the 5th, 95th, and 50th predicted percentiles for the 1,000 simulations



**FIG 2** Pharmacokinetic compartmental model for acyclovir plasma concentration after oral or i.v. dose.  $D$ ,  $F$ , bioavailability of acyclovir;  $k_a$ , first-order absorption rate constant;  $V$ , acyclovir distribution volume;  $k_e$ , acyclovir elimination rate constant.

**TABLE 2** Pharmacokinetic parameters for a body weight of 15 kg, with a  $CL_{CR}$  of 164 ml/min/1.73 m<sup>2a</sup>

Population parameter	Estimated value	RSE <sup>b</sup> (%)
Fixed population effects		
Absorption rate constant (h <sup>-1</sup> )	0.376	11
Clearance (liters/h)	5.15	8
Vol of distribution (liters)	16.2	13
Bioavailability	1 <sup>c</sup>	
Oral valacyclovir on bioavailability	0.768	17
Oral acyclovir on bioavailability	0.397	24
eGFR effect on clearance	0.658	11
Interindividual variability		
For clearance	0.389	14
For vol of distribution	0.434	28
Residual variability		
Residual proportional error	0.48	6

<sup>a</sup>The equations used were as follows:

$$CL_i = CL \times \left(\frac{BW_i}{15}\right)^{0.75} \times \left(\frac{eGFR_i}{164}\right)^{0.658}$$

$$V_i = V \times \left(\frac{BW_i}{15}\right)^1$$

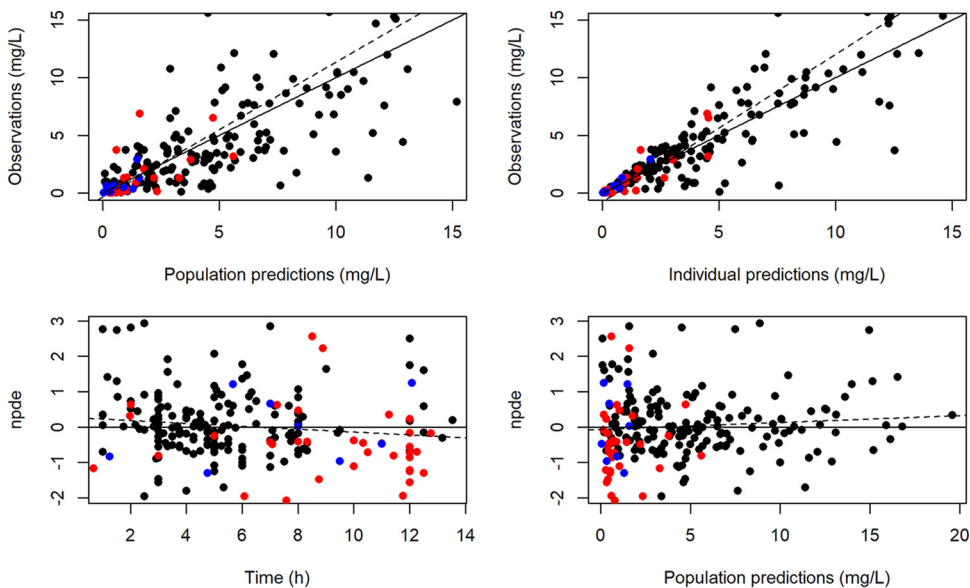
$F_i = F \times 0.768^{OV} \times 0.397^{OA}$ , with OV equal to 1 for oral valacyclovir administration, and OA equal to 1 for oral acyclovir administration and 0 if not.

<sup>b</sup>RSE, relative standard error.

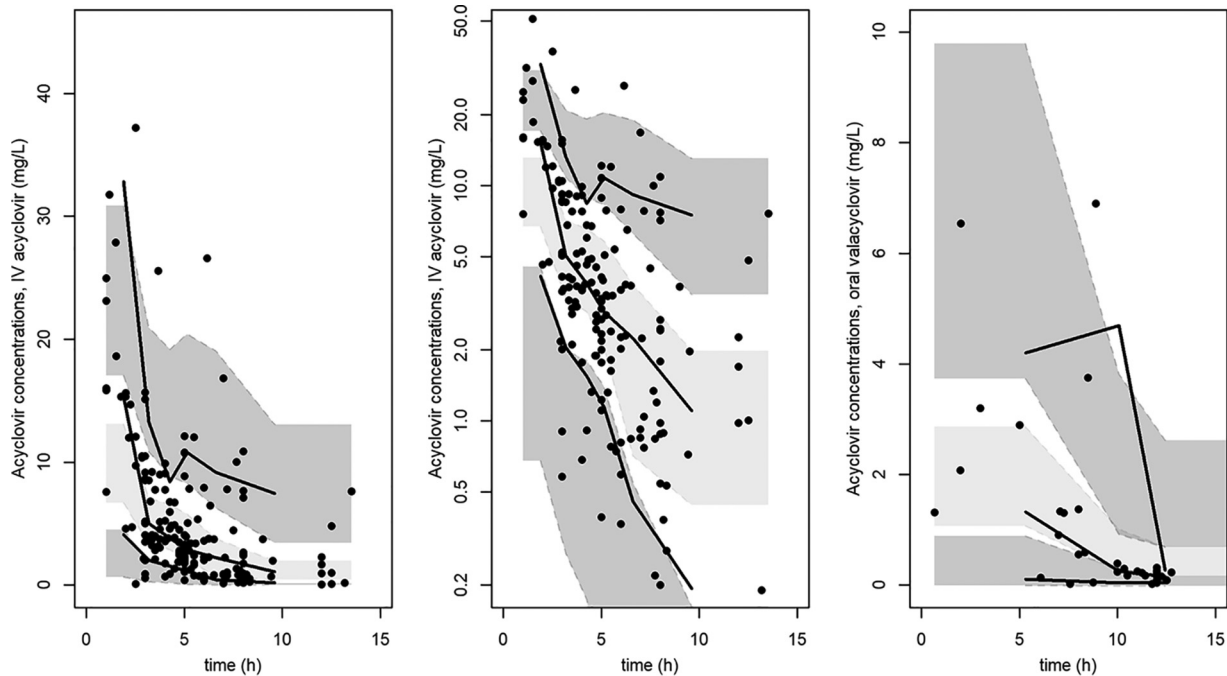
<sup>c</sup>Bioavailability is fixed to 1 for i.v. administration.

and the observed concentrations of acyclovir. This evaluation method provided good proof of the model adequacy (Fig. 4).

**(iii) Subpopulation definition.** An eGFR limit of 250 ml/min/1.73 m<sup>2</sup> was chosen to identify children with normal and augmented renal clearance. This limit was high compared to the 130 ml/min/1.73 m<sup>2</sup> value classically used in adults. Children consid-



**FIG 3** (Upper graphs) Observation data versus population predictions (upper left) and versus individual predictions (upper right) in the final model, after doses of acyclovir i.v. (black circles), oral acyclovir (blue circles), and oral valacyclovir (red circles). The solid black line is the identity line. (Lower graphs) Normalized prediction distribution error (npde) versus time (lower left) and predictions (lower right), after doses of acyclovir i.v. (black circles), oral acyclovir (blue circles), and oral valacyclovir (red circles). The solid horizontal line is the theoretical mean (0), and the dashed line corresponds to regression.



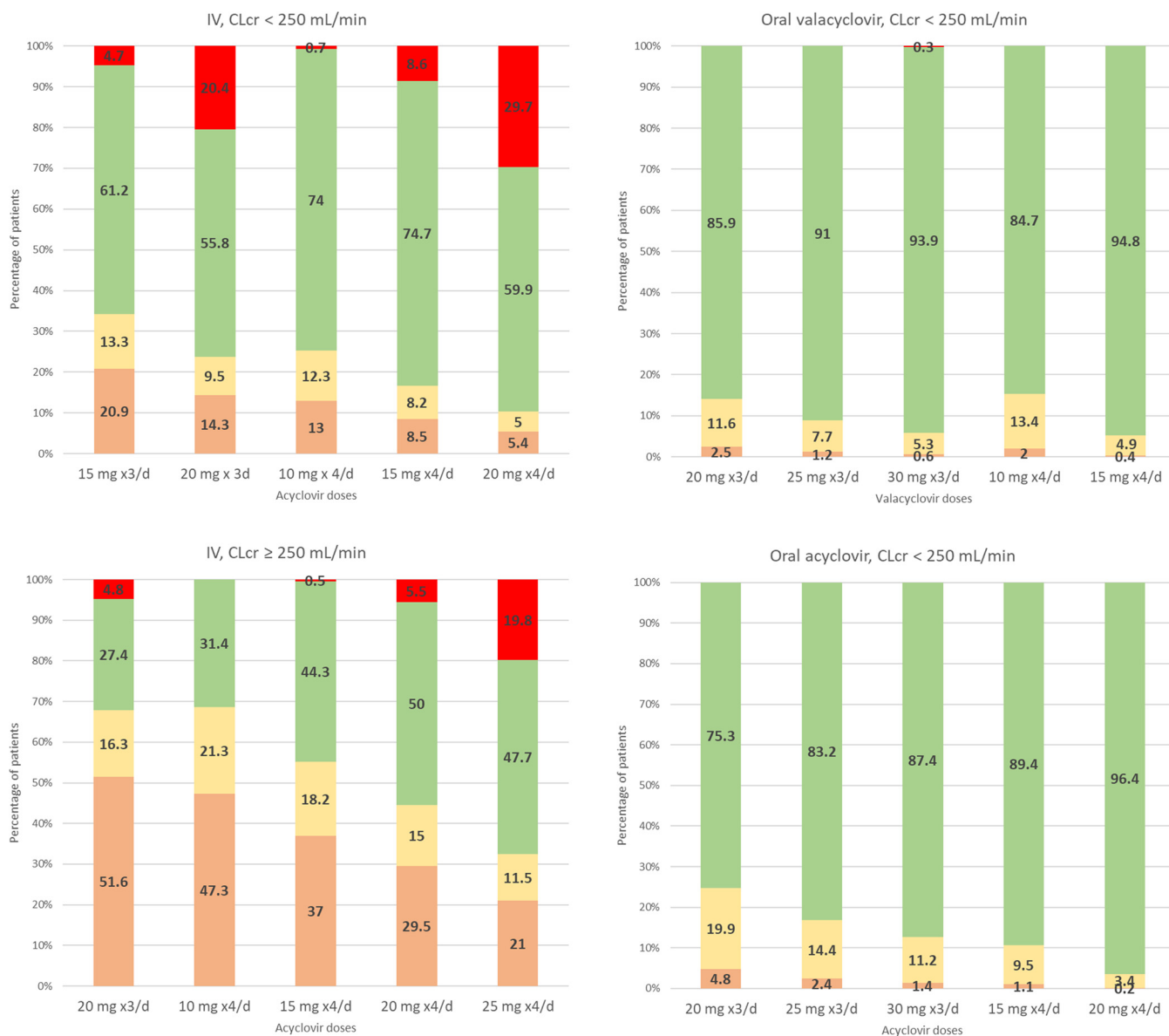
**FIG 4** Prediction-corrected visual predictive check for acyclovir concentrations, following an i.v. acyclovir dose in linear scale (left) and in log-linear scale (middle) and an oral valacyclovir dose in linear scale (right). Colored areas represent 95% confidence intervals (CIs) of 5th, 95th (dark grey), and 50th (light grey) simulated percentiles. Lines indicate empirical (observed) 5th, 50th, and 95th percentiles. Dots represent observed data.

ered to have ARC in this study ( $eGFR \geq 250$  ml/min/1.73 m<sup>2</sup>) represented 16% of the children; only 24% of children were from the PICU.

**(iv) Plasma concentration simulation.** Several i.v. and oral dosing regimens were tested, i.e., from 10 to 30 mg/kg every 8 h and from 10 to 25 mg/kg every 6 h. The percentages of patients with (i) a trough concentration below 0.56 mg/liter, (ii) a trough concentration between 0.56 and 1.125 mg/liter, or (iii) a trough concentration above 1.125 mg/liter and with (iv) a peak concentration below or above 25 mg/liter are reported in Fig. 5. For all tested oral valacyclovir and oral acyclovir doses, <0.1% of children had a peak greater than 25 mg/liter. The 20-mg/kg/8 h oral acyclovir and valacyclovir administrations allowed 97.5% and 95.2% of children, respectively, to be above the target trough concentration of 0.56 mg/liter and 85.9% and 75.3%, respectively, to be above 1.125 mg/liter. The same total daily dose but given as 15 mg/kg/6 h increased these percentages. For i.v. administration, the percentage of patients with a high peak concentration is more important than for oral administration, due to bioavailabilities of 77% for valacyclovir and 40% for oral acyclovir. A 10-mg/kg/6 h i.v. dose in children with normal renal function allowed a higher percentage of children to have a trough concentration above 0.56 mg/liter, with only 0.7% of children with a peak above 25 mg/liter. A 15- to 20-mg/kg/6 h dose for children with ARC would lead to 29.5% to 37% of the children to be underdosed and 0.5 to 5.5% to be overdosed, with no child having a maximal concentration above the neurotoxic limit of 50 mg/liter. These doses are proposals for the initiation of the treatment, but therapeutic drug monitoring could help to adjust these doses individually. Proposed initial doses are reported in Table 3.

## DISCUSSION

The concentrations of acyclovir and valacyclovir were satisfactorily described by a one-compartment model with first-order absorption to represent valacyclovir administration and first-order elimination. A one- or a two-compartment model has already been used to describe acyclovir PK. PK parameters were comparable to those previously reported in immunocompromised children; clearance was 0.35 liters/h/kg in our study



**FIG 5** Simulations of trough ( $C_{trough}$ ) and peak ( $C_{max}$ ) concentrations according to the route of administration (i.v. or oral) and renal function (eGFR of <250 or >250 ml/min/1.73 m<sup>2</sup>). Color code: red,  $C_{max}$  of >25 mg/liter; green,  $C_{trough}$  of >1.125 mg/liter and  $C_{max}$  of <25 mg/liter; yellow,  $C_{trough}$  of <1.125 mg/liter and  $C_{max}$  of <25 mg/liter; orange,  $C_{trough}$  of <0.56 mg/liter and  $C_{max}$  of <25 mg/liter.

of children with a median body weight of 15.6 kg, compared to 0.2 liters/h/kg reported by Zeng et al. (9) and 0.5 liters/h/kg reported by Eksborg et al. (11) and Nadal et al. (10) in children with a mean body weight of 20 kg. The volume of distribution was 1.2 liters/kg in our study, compared to 0.4 liters/kg in the study by Zeng et al. and 1.2 to 1.3 liters/kg in the studies by Eksborg et al. and Nadal et al. An allometric model was also used, and the effect of eGFR was demonstrated on elimination clearance by Zeng et al., using the Counahan-Barratt formula [eGFR calculated as  $(0.43 \times \text{height in m}^2) \times \text{eGFR}$ ].

**TABLE 3** Proposed initial doses according to the route of administration (i.v. or oral) and renal function (eGFR of <250 or >250 ml/min/1.73 m<sup>2</sup>)

eGFR (ml/min/1.73 m <sup>2</sup> )	i.v. acyclovir doses	Oral acyclovir doses	Valacyclovir doses (oral)
<250	10 mg/kg/6 h	15 to 20 mg/kg/6 h	10 to 15 mg/kg/6 h
≥250	15 to 20 mg/kg/6 h		

cm)/serum creatinine concentration]. All patients were cotreated with various drugs according to their conditions, but none of those drugs are known to interact significantly with acyclovir (14).

Renal excretion is an important elimination pathway for acyclovir, and thus the influence of renal function on acyclovir CL was expected. eGFR was calculated according to the Schwartz formula. However, use of the Schwartz formula, based on serum creatinine, to evaluate renal function may have limitations, especially for critically ill children. Factors such as age, gender, muscle mass, nutritional and/or hydration status, and liver dysfunction interfere with serum creatinine concentrations. Serum creatinine concentrations may therefore have low sensitivity in evaluating renal function in this specific population (15). Endogenous biomarkers such as cystatin C or exogenous markers such as renal inulin or radiolabeled agent clearance might have made a better alternative (16, 17) but were not recorded in our study and are not commonly used. The most appropriate method to estimate the GFR is creatinine clearance ( $CL_{CR}$ ), calculated with both urine ( $U_{CR}$ ) and plasmatic ( $S_{CR}$ ) creatinine concentrations. Unfortunately, missing data on  $U_{CR}$  and urine output does not allow calculation of the  $CL_{CR}$  (18). In our model, two groups of patients could be distinguished according to their renal function, those with eGFRs of  $<250$  ml/min/1.73 m<sup>2</sup> and those with eGFRs of  $>250$  ml/min/1.73 m<sup>2</sup>, corresponding to ARC. With an incidence between 16% and 80%, ARC (usually defined as  $>130$  ml/min/1.73 m<sup>2</sup>) appears to be a common phenomenon found in critically ill patients (16, 19). Elevated renal clearances were also reported in a pediatric liver transplant population before surgery and within 3 months posttransplantation (20). Several potential mechanisms may contribute to the occurrence of ARC, including endogenous responses to increased metabolism and solute production, alterations in neurohormonal balance, and therapeutic maneuvers such as fluid resuscitation; the precise mechanism of ARC is not completely resolved. But, for many drugs, especially antibiotics such as vancomycin or  $\beta$ -lactam, underexposure had been pointed out in cases of ARC, increasing the risk of treatment failure (21). Any renally cleared drugs are potentially vulnerable to this phenomenon. Acyclovir is almost exclusively eliminated by renal excretion and seems to not be an exception. Increased acyclovir clearance had also been reported during infant maturation (22).

Target values were chosen for peak and trough acyclovir concentrations. Goals were to maintain trough concentrations above the recommended 50% inhibitory concentrations for HSV and VZV (0.56 mg/liter and 1.125 mg/liter, respectively) and to maintain peak concentrations below 25 mg/liter, the limit considered to result in moderate or severe adverse side effects such as nausea, abdominal pain, vomiting, renal failure, and neutropenia (23). A peak higher than 50 mg/liter has been proposed for an increase in neurotoxicity (24).

Dosing adaptations are currently prescribed only for renal impairment below 50 ml/min. In contrast, no recommendations exist for patients with enhanced renal function, and thus our work has an important impact, providing dosing recommendations for this population. Furthermore, simulated data flagged the potential inefficiency of current doses for the ARC group. Considering all our results, the oral form is less likely to produce toxic peak concentrations even with a dosing regimen of 30 mg/kg/8 h. Since the absorption phase is absent from the i.v. route, maximal concentrations must be excessively high in order to maintain the plasma concentration above the maximum efficacy threshold of 1.125 mg/liter or 0.56 mg/liter throughout treatment for patients with elevated GFR. We suggest that the dosing regimens be adapted depending on the renal function of the patient.

The more suitable initial doses to ensure a trough concentration of  $>1.125$  mg/liter and a peak concentration of  $<25$  mg/liter were 10 mg/kg/6 h of i.v. acyclovir for children with normal renal function ( $eGFR \leq 250$  ml/min/1.73 m<sup>2</sup>) and 15 to 20 mg/kg/6 h of i.v. acyclovir for children with augmented renal clearance (ARC) ( $eGFR > 250$  ml/min/1.73 m<sup>2</sup>). The 20-mg/kg/8 h dose oral for oral acyclovir and valacyclovir produced effective concentrations in more than 75% of children; however, a 15-mg/kg/6 h dose, if possible, is preferred to increase this percentage. A higher dose of acyclovir than

valacyclovir was needed to result in the same percentage of children in the target (Table 3).

A limitation of this study is that most of the children received valacyclovir as crushed tablets, which probably produce approximate doses and modify the absorption of the drug, and we did not have this information. Furthermore, we were not able to suggest dose adaptation for impaired renal function due to the lack of cases in our population. All our proposals aim to obtain the maximal efficacy/safety ratio against HSV and VZV disease and infections or as a preventive treatment. Our dosing regimen proposals need to be confirmed prospectively. Therapeutic drug monitoring, combining drug measurement with Bayesian estimation from a population model, is then a useful tool to adapt the dose individually. Indeed, in critically ill children, renal function changes quickly, and the use of these methods is helpful for individual dosing optimization.

Regarding other indications, even if it seems to provide a clinically and economically valuable alternative to valganciclovir for CMV prophylaxis in young people with solid organ and bone marrow transplantation (2, 25, 26), valacyclovir requires a much higher dose for this indication (27). Indeed, with a 50% inhibitory concentration ( $IC_{50}$ ) of 47.1 mg/liter (28) against CMV, acyclovir would not be able to obtain efficient and nontoxic concentrations for this indication.

**Conclusions.** This study provided optimal dosing stratification of acyclovir and valacyclovir PK in children with various body weights and renal clearances. Simulations from modeling suggested that dose or administration frequency be adjusted depending on eGFR. The use of our suggested dosing adaptations combined with therapeutic drug monitoring should improve clinical outcomes.

## MATERIALS AND METHODS

**Patients.** This prospective study was part of the Optimome study, which was approved by the Ethics Committee of the Necker-Enfants Malades Hospital and is registered at <https://www.clinicaltrials.gov> (ClinicalTrials registration no. NCT02539407). All children aged less than or equal to 18 years old, weighing more than 2.5 kg, and receiving oral or intravenous acyclovir, oral acyclovir, or oral valacyclovir were included. The study was conducted in the pediatric intensive care unit (PICU), the pediatric immune-hematology unit (IHU), and the department of pediatric surgery and department of pediatrics of Necker-Enfants Malades Hospital (Paris, France). Prior to inclusion, oral consent was obtained from the patient's legal representative after oral and written information. Patients with hemofiltration or extracorporeal membrane oxygenation assistance were excluded.

Baseline patient characteristics were recorded, including sex, age, body weight (BW), height (HT), body mass index, creatinine level, and reason for acyclovir administration. The estimated glomerular filtration rate (eGFR, ml/min/1.73 m<sup>2</sup>) was derived from the Schwartz formula (29), as follows:

$$CL_{CR}(\text{ml/min}/1.73 \text{ m}^2) = K_{CR} \times \frac{\text{height (cm)}}{\text{plasma creatinine concn (mg/dl}^{-1})}$$

where  $K_{CR}$  is a coefficient equal to 0.45 for patients aged <2 years and with a BW of  $\geq 2.5$  kg, 0.55 for patients aged  $\geq 2$  and <13 years and for female patients aged  $\geq 13$  years, or 0.7 for males aged  $\geq 13$  years.

**Drug administration regimens and blood sampling.** The prescribed doses refer to a child's medical history (preventive/curative treatment), the disease, the local protocol, and the route of administration. Intravenous acyclovir was diluted in 0.9% saline solution. Oral acyclovir can be given, using acyclovir (Zovirax) or valacyclovir (Zelitrex) tablets, crushed if needed. Acyclovir was mostly administered three times daily but could also be given every 6, 12, or 24 h. Median (range) daily doses were 59 (5 to 101) mg/kg/day for i.v. acyclovir, 35 (20 to 54) mg/kg/day for oral acyclovir, and 21 (17 to 63) mg/kg/day for oral valacyclovir. The median delay between drug intake and sample collection was 5.1 h, and the interquartile range was 3.5 to 8 h.

**Assay.** Acyclovir concentrations in plasma samples were measured using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Samples were centrifuged ( $4,000 \times g$ , 5 min) to yield plasma and then stored at  $-20^{\circ}\text{C}$  before analysis. The analysis was performed using TSQ Quantum discovery max chromatographic system (Fisher Scientific, Les Ulis, France). A volume of 100  $\mu\text{l}$  of each plasma sample was precipitated with 500  $\mu\text{l}$  of acetonitrile. The supernatants were evaporated to dryness under a  $+40^{\circ}\text{C}$  nitrogen flow. The residues were then reconstituted in 500  $\mu\text{l}$  of water, and a volume of 10  $\mu\text{l}$  was injected into the chromatographic system. Chromatographic separation was carried out on an Atlantis T3 C<sub>18</sub> column (Waters, Saint-Quentin, France) using a mobile phase composed of water (0.05% [vol/vol] formic acid) and methanol (0.05% [vol/vol] formic acid). The method was fully validated according to FDA guidelines for validation of bioanalytical assays. The calibration of acyclovir was linear over the range of 0.05 to 16  $\mu\text{g/ml}$  with a limit of quantification (LOQ) of 0.05  $\mu\text{g/ml}$ .

**Population pharmacokinetics.** Data were analyzed using the nonlinear mixed-effect modeling software MONOLIX (version 2018R1), along with the SAEM algorithm. To model acyclovir and valacyclovir



administration simultaneously, doses and concentrations were converted to molarity, dividing mass concentrations by the molarity of each compound. Analytical solutions were used to code i.v. and oral routes simultaneously. Numerical and graphical outputs were also obtained with MONOLIX software. Simulations were performed with NONMEM 7.4, using the final parameters obtained in MONOLIX. Maximal trough concentrations and the percentages of patients in each interval were calculated using R software (version 3.6.1) and represented with Excel.

**(i) Structural model building.** One- and two-compartment models were tested to describe the data. Acyclovir concentrations below the lower limit of quantification (LOQ) were set to half of the LOQ. Proportional, additive, and combined models were investigated to describe residual variability. IIV was defined by an exponential model.

Data for acyclovir and valacyclovir were then fitted jointly. Only significant interindividual variabilities of the PK parameters were kept, e.g., a decrease in the objective function value (OFV) of  $\geq 3.84$  U.

The continuous covariates considered were body weight, age, height, and eGFR by using the Schwarz formula (29).

Continuous covariates were integrated as follows:

$$\theta_i = \theta_{\text{pop}} \times \left( \frac{\text{Cov}_i}{\text{median}(\text{Cov})} \right)^\beta$$

where  $\theta_{\text{pop}}$  is the typical value of clearance or volume of distribution for a patient with the median covariate value,  $\text{Cov}_i$  is the covariate value for individual  $i$ , and  $\beta$  is the estimated influential factor for the continuous covariate estimated by the modeling software. For body weight, according to the allometric rule,  $\beta$  was fixed at 0.75 for the clearance parameter and 1 for the volume of distribution parameter (30), and median body weight was 15.6 kg. Categorical covariates such as sex were tested as follows:

$$\theta_i = \theta_{\text{pop}} \times \beta^{\text{Cov}_i}$$

where  $\text{Cov}_i$  equals 0 or 1.

A covariate was retained in the model if its effect was biologically plausible, if it produced a reduction in the variability of the PK parameter IIV, and if the OFV was decreased by at least 3.84 (equal to chi squared with 1 degree of freedom equivalent to a  $P$  value of 0.05) in the forward inclusion phase and was increased by more than 6 (equal to chi squared with 1 degree of freedom equivalent to a  $P$  value of 0.01) in the backward phase.

**(ii) Model evaluation.** For evaluation of the goodness of fit, the following graphs were plotted: observed concentrations versus population predictions and versus individual predictions, normalized prediction distribution error metrics (npde) versus time and versus predictions.

From the final model, Monte Carlo simulations were performed to compute the prediction-corrected visual predictive check (pc-VPC). The observed concentration data were overlaid on the 5th, 50th, and 95th percentiles of the simulated concentrations at each time, and a visual inspection was performed.

**(iii) Subpopulation definition.** Patients were split into two groups according to their eGFRs: children with normal renal clearance and children with augmented renal clearance. This eGFR limit was found by choosing the lowest  $P$  value for the Wilcoxon tests, comparing trough concentrations between the two eGFR groups.

**(iv) Simulations.** One thousand Monte Carlo simulations were performed, from the final population PK model, to simulate acyclovir trough and peak concentrations. According to previously published reports, curative antiviral efficiency is reached with acyclovir plasma concentrations above the *in vitro* 50% inhibitory concentration ( $\text{IC}_{50}$ , 0.56 mg/liter and 1.125 mg/liter for HSV and VZV, respectively) for more than 12 h (9, 31). Although acyclovir has a large therapeutic window, moderate and severe side effects from the drug seem to appear when peak concentrations exceed 25 mg/liter (23). Several dosing regimens were tested, from 10 mg/kg to 30 mg/kg every 8 h and from 10 mg/kg to 25 mg/kg every 6 h, for both oral valacyclovir and i.v. acyclovir. Trough concentrations were calculated using the equation of i.v. or oral concentration as a function of time at 8 h after drug intake for a thrice daily regimen, at 12 h for a twice daily regimen, and at 24 h for a once daily dose. The percentages of patients with trough concentrations below 0.56 mg/liter, between 0.56 and 1.125 mg/liter, and above 1.125 mg/liter and with a maximal or peak concentration below or above 25 mg/liter were reported.

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