Pharmacokinetics of Oral Acyclovir in Neonates and in Infants: a Population Analysis

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Acyclovir is approved for the treatment of herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections in children by the intravenous and oral routes. However, its use by the oral route in children younger than 2 years of age is limited due to a lack of pharmacokinetic data. The objectives of the present study were to determine the typical pharmacokinetics of an oral suspension of acyclovir given to children younger than 2 years of age and the interindividual variabilities in the values of the pharmacokinetic parameters in order to support the proposed dosing regimen (24 mg/kg of body weight three times a day for patients younger than 1 month of age or four times a day otherwise). Children younger than age 2 years with HSV or VZV infections were enrolled in a multicenter study. Children were treated for at least 5 days with an acyclovir oral suspension. Plasma samples were obtained at steady state, before acyclovir administration, and at 2, 3, 5, and 8 h after acyclovir administration. Acyclovir concentrations were measured by radioimmunoassay. The data were analyzed by a population approach. Data for 79 children were considered in the pharmacokinetic study (212 samples, 1 to 5 samples per patient). Acyclovir clearance was related to the estimated glomerular filtration rate, body surface area, and serum creatinine level. The volume of distribution was related to body weight. The elimination half-life decreased sharply during the first month after birth, from 10 to 15 h to 2.5 h. Bioavailability was 0.12. The interindividual variability was less pronounced when the parameters were normalized with respect to body weight. Hence, dosage adjustment by body weight is recommended for this population. Simulations showed that the length of time that acyclovir remains above the 50% inhibitory concentration during a 24-h period was more than 12 h for HSV but not for VZV. The proposed dosing regimen seems adequate for the treatment of HSV infections, while for the treatment of VZV infections, a twofold increase in the dose seems necessary for children older than age 3 months.

Acyclovir is currently used for the prevention and treatment of herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections (7). It is available at different dosages in the form of tablets, oral suspensions (containing 200, 400, or 800 mg in 10 ml), and injectable solutions. About 20 clinical studies have documented the use of acyclovir in children (for a review, see reference 24). Most frequently, acyclovir has been administered intravenously. Hintz et al. (8) recommended 10 mg/kg of body weight every 8 h (q8h) for neonates, while Blum et al. (2) recommended 250 mg/m² (for HSV infections) and 500 mg/m² (for HSV encephalitis and VZV infections) q8h in children between 3 months and 12 years of age. Owing to the ease of its administration and dosage adjustment, the oral suspension is also used in children. The recommended dosage in neonates is 100 mg four times a day (q.i.d.) (HSV infections) and 200 mg q.i.d. (for VZV infections). In the latter case, it is

also possible to give 20 mg/kg q.i.d., provided that the total daily dose is less than 800 mg. Oral acyclovir is also effective for the prevention of cutaneous recurrences after HSV type 2 (HSV-2) disease of the skin, eyes, and mouth in neonates at a dose of 300 mg/m² q8h (10). Despite the large amount of clinical experience, these dosage recommendations were substantiated with limited pharmacokinetic data obtained with neonates after oral administration (10, 16, 21). These preliminary data showed that the kinetics of acyclovir in neonates were probably strongly modified compared to those in adults, as expected, but acyclovir bioavailability and the interindividual variability of its pharmacokinetics could not be well characterized. As a consequence, doubt remained regarding the optimal dosing schedule for acyclovir given orally to neonates. One reason for this lack of pharmacokinetic data was ethical and practical, since it is difficult to draw many samples from neonates in a short period. Therefore, a population study of the kinetics of oral acyclovir in neonates, based on a sparse sampling design, was undertaken. The data were analyzed by a nonlinear mixed-effect modeling approach (19) in order to estimate the typical values of the pharmacokinetic parameters and their interindividual variabilities and to find the biological or demographic indices related to their variation. Ultimately, simulation techniques were used to give some support to the optimal dosing regimen for this population.

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TABLE 1. Demographic data[a]

Group, route of administration	No. of subjects	PNA (mo)	PCA (mo)	BW (kg)	H (cm)	S_{CR} (μM)
0–2 yr, per os	79	5.45 (0.10–23.10)	15.45 (8.80–33.10)	6.90 (1.80–13.0)	65.0 (43.0–95.0)	39.6 (22.0–98.0)
	5	32.8 (25.7–70.9)	41.8 (34.7–79.9)	13.6 (11.0–16.0)	91.0 (88.0–103)	61.0 (29.0–91.0)
Pediatric, intravenous	18	72.0 (3.0–204)	81.0 (10.0–213)	17.8 (2.4–62.0)	113 (37.0–168)	44.7 (35.4–72.2)

[a] Values are medians (ranges).

MATERIALS AND METHODS

Oral formulation study. The study was designed as a prospective French multicenter open study conducted in pediatric units. The study was approved by the Ethics Committee of the Bichat-Claude Bernard Hospital, Paris, France. Patients were enrolled if they were younger than 2 years of age, were immunocompetent, presented with a proven or suspected HSV or VZV infection, and their parents gave written consent. The patients were treated for at least 5 days with an oral suspension (400 mg, 10 ml) of acyclovir administered per os. Patients younger than 1 month of age received acyclovir at 24 mg/kg of body weight q8h. Patients aged between 1 month and 2 years received acyclovir at 24 mg/kg of body weight q.i.d. according to a schedule of treatment at 0, 4, 8, 12, and 24 h. These dosages were based on the limited pharmacokinetic data available (16, 21): about 25 mg/kg per dose was expected to be adequate. The value of 24 mg/kg was retained because it corresponded to three graduations of the dosing syringe.

Venous blood samples were drawn after at least 30 h of treatment. The sampling schedule depended on the status of the child. For hospitalized children, blood samples were drawn before dosing and at 2, 3, 5, and 8 h before dosing. For ambulatory children, a sample was obtained 4 h after dosing. Dosing history and sampling times were recorded precisely by a nurse for inpatients, while theoretical times were recorded for outpatients. The accuracies and consistencies of the records were further assessed for all patients by a pharmacist. All plasma samples were stored and kept frozen (−20°C) until analysis.

Acyclovir levels were measured by radioimmunoassay at the Laboratory of Pharmacology, René Huguenin Center, St. Cloud, France. The limit of quantification of the assay (determined as the lowest concentration with a variability of less than 15%) was 0.01 μM, and the variability (coefficient of variation [CV]) was less than 12% over the entire calibration range.

Intravenous treatment study. Data from a previous multicenter study with 18 immunocompromised pediatric patients (S. Liao, M. R. Blum, D. A. Page, and P. De Miranda, Acyclovir (Zovirax) multiple-dose pharmacokinetic analyses in pediatric patients with herpes virus infections, internal document, Glaxo Wellcome Co.) treated with intravenous acyclovir for a HSV, VZV, or cytomegalovirus infection were also considered in order to improve the population model building. Patients received acyclovir by a 1-h intravenous infusion at 250 or 500 mg/m² q8h for 5 days. Blood samples were taken before each infusion, at the end of each infusion, and at 0.5, 1, 2, 4, 8, 16, and 24 h after the end of the last infusion. Acyclovir levels were measured by the same radioimmunoassay used in the study with the oral formulation.

Database. The following items were recorded: time of each event, acyclovir dose (in micromoles), acyclovir concentration (in micromolar), body weight (BW; in kilograms), height (H; in centimeters), sex, postnatal age (PNA) and postconceptional age (PCA), body surface area (BSA; in square meters), serum creatinine level (S_{CR}; in micromolar), blood urea nitrogen level (in millimolar), and intake of antacids.

Acyclovir doses were calculated by taking into account the exact titer of each lot and the exact volume of oral suspension administered. Acyclovir concentrations below the limit of quantification were recorded as half the lower limit of quantification (i.e., 0.005 μM). This event never occurred more than once in each patient. All measured values of the demographic and biological indices were recorded in the database at the corresponding time of measurement. Ages (PCA and PNA) were expressed in months by using the following rules: 1 year = 12 months and 1 month = 30 days = 4.33 weeks, so that 1 year = 52 weeks. BSA was calculated according to the formula $BSA = 0.02667 \cdot H^{0.38217} \cdot BW^{0.53937}$, i.e., the formula of Gehan and Georges for children younger than age 5 years (5). S_{CR} and the BUN level at each time were calculated by linear interpolation between known values. Other missing values were estimated as follows. H, which had not been measured for seven patients, was recorded as the ideal height according to sex (6). S_{CR}, which had not been measured for eight patients, was recorded as the mean value according to gestational age and PNA (18). For all patients older than age 3 months, PCA was calculated as PNA + 9.

With the exception of BUN levels and intake of antacids, the same items were

recorded for the intravenous treatment study. Only the data from the last administration were considered in the analysis.

Pharmacokinetic modeling. Since the infrequent sampling schedule did not enable individual pharmacokinetic parameters to be estimated by usual methods for most patients, a population pharmacokinetic method based on a nonlinear mixed-effect modeling approach was used (19). Two levels of variability (intra- and interindividual) were considered. The details are described in the Appendix.

Numerous previous pharmacokinetic studies have shown that acyclovir disposition is adequately described by a one-compartment (oral route) or a two-compartment (intravenous route) open model with first-order rate constants (2, 11, 14). Therefore, only these pharmacokinetic models were considered. The basic parameters were the elimination clearance (CL), volume of distribution (V), and the absorption rate constant (k_a) for the one-compartment model. Additional parameters for the two-compartment model were V of the central compartment (V_c), V of the peripheral compartment (V_p), and the distribution clearance (CL_d; which describes the rate of diffusion between the two compartments). Bioavailability (more precisely, the fraction of the dose that reached the systemic circulation) was denoted as F. These models enabled the computation of the acyclovir concentration at any time for any given dosing regimen (23). Elaboration of the covariate model was based on the following rationale. Acyclovir is primarily eliminated by the renal route, by glomerular filtration and tubular secretion (11). Because of knowledge of the evolution of renal function after birth, acyclovir clearance was expected to exhibit a linear or hyperbolic relationship with age and especially with PCA. The inverse S_{CR} was also expected to be correlated with acyclovir clearance. Finally, a measure of body volume (such as H, BW, or BSA) was expected to be a third covariate of acyclovir clearance, although it is highly correlated with age. The V of acyclovir corresponds to total body water (14). Therefore, V was expected to be correlated with a measure of body volume, but BW is usually the better covariate in this respect (9). The absorption rate constant was not expected to vary with any of the demographic or biological indices. By contrast, F was found in one study (3) to be saturable and dose dependent for doses between 100 and 600 mg. This phenomenon could be related to the poor solubility of acyclovir or to a carrier-mediated active absorption. Therefore, appropriate covariate models relating F to dose and/or age were also considered.

Model building. The population model was built step by step. At each step, a specific assumption was tested (e.g., one-compartment versus two-compartment model). The main criterion of decision was the likelihood ratio test (25). The level of significance was 0.05. Secondary criteria were the aspects of the various residual plots and the values of the random-effects variances. Possible correlations between the demographic or biological indices and the pharmacokinetic parameters were explored by the three-step approach (12, 13).

Assessment of goodness of fit. The final population model was considered adequate when several criteria were met: (i) adequate fit of each individual concentration-versus-time curve compared to the experimental data, (ii) linear pattern of observed versus predicted acyclovir concentrations, (iii) absence of trend in the weighted residuals-versus-time plot, and (iv) an approximately normal distribution of the weighted residuals. For the last three criteria, concentrations were calculated by reference to the typical parameters [i.e. $f(\overline{P}_j, t_{ij})$, where f is the function describing the pharmacokinetic model, $\overline{P}_j$ is the typical value for a individual pharmacokinetic parameters, and t_{ij} is the time of i-th sample in j-th individual].

Simulations. The final population model was used to generate acyclovir concentration-versus-time curves for 500 fictitious individuals by simulation for several age ranges. Each "individual" had a different set of pharmacokinetic parameters, which were sampled from the distribution of values for the pharmacokinetic parameters defined by the population model. The 5th, 50th (median), and 95th percentiles of the acyclovir concentration were then calculated for several "sampling" times from the 500 individual values. Likewise, the times that the concentration remained above 2.5 and 5 μM were calculated for each individual, and the percentiles of these distributions were calculated.
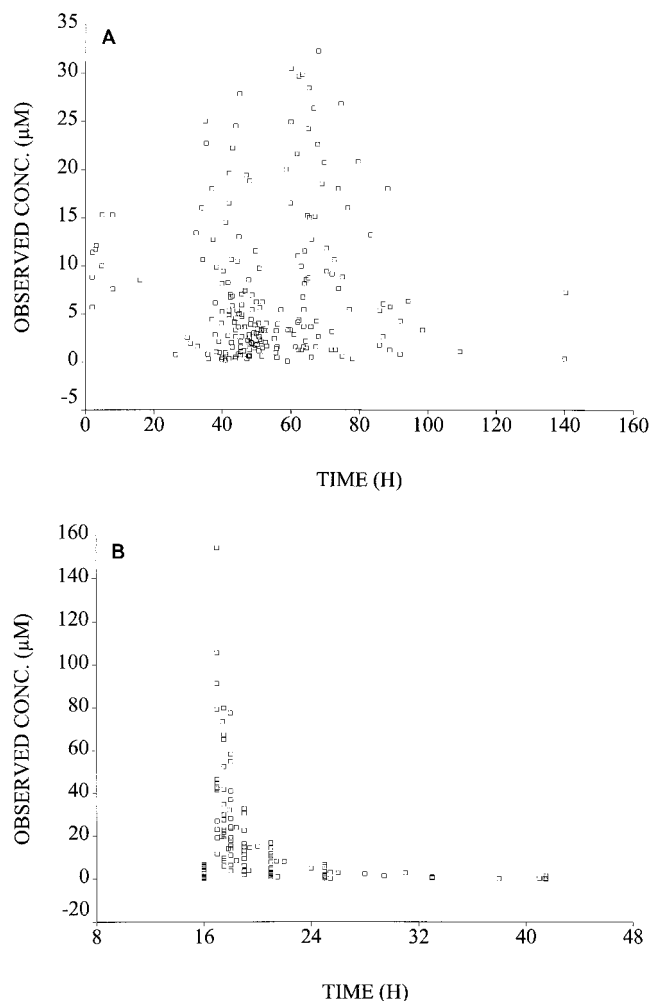
FIG. 1. Distribution of acyclovir concentrations after oral administration to 79 children (A) and after intravenous administration to 18 pediatric patients (B).

Programs. Fitting of the population model and individual Bayesian estimations were made by using the NONMEM IV software (1). The first-order method was used for model building. Once the final model was found, the parameters were estimated by the first-order conditional estimation method, taking into account the η-ε interaction. Analysis of covariate models, statistical tests, and relevant graphs were computed by using SPSS for Windows (release 6.1; SPSS

France, Boulogne, France). Simulations were performed with our POPSIM software (22).

RESULTS

Patients. A total of 90 patients was enrolled in the study. However, data for six patients were not included in the pharmacokinetic database because the dosing and/or sampling times had not been recorded and the data for five patients were discarded from the per-protocol analysis because they were older than 2 years of age. Therefore, data for 79 patients could be considered for the main analysis of the disposition of acyclovir in neonates and infants after oral administration. The data for these 79 patients were combined with those for the 5 patients older than age 2 years treated per os and with those for the 18 pediatric patients treated intravenously for the global analysis ($n = 102$) of acyclovir disposition. The demographic data are summarized in Table 1.

Acyclovir doses and levels. In the oral formulation study ($n = 79$), the median (range) of the actual dose of acyclovir was 164 mg (43 to 292 mg), corresponding to 24.1 mg/kg (21.7 to 32.6 mg/kg) or 446 mg/m^2 (280 to 574 mg/m^2). In the intravenous study ($n = 18$), the actual doses ranged from 83 to 500 mg/m^2. A total of 212 samples were analyzed in the main study (1 to 5 samples per subject), while 131 samples (7 or 8 samples per subject) were considered for the intravenous study. There were 351 samples in the global analysis ($n = 102$). Figures 1A and B show the data for the oral and intravenous studies, respectively.

Model building for oral disposition. The main models and hypotheses tested are described in Table 2. The two-compartment model was not superior to the one-compartment model. Therefore, the one-compartment model was used to describe oral data. The typical value of the apparent clearance of acyclovir ($\overline{CL}/F$) was found to be related to the estimated glomerular filtration rate (GÎR), BSA, and S_{CR}, $\overline{CL}/F = \theta_1 \cdot$ GÎR $\cdot$ (BSA/1.73) (40/S_{CR}), where GÎR $= (7.2 \times $ PCA$^{\theta_3})/(\theta_2^{\theta_3} +$ PCA$^{\theta_3}$) (θ_1, θ_2, and θ_3 are defined below), while the interindividual variability of $\overline{CL}/F$ was expressed as $CL_j/F = (\overline{CL}/F) \cdot \exp(\eta_{CL_j})$

The GÎR was estimated as a function of PCA. With this relationship, GFR tends to a maximal value in adults, in whom it reaches 7.2 liters/h/1.73 m^2, i.e., 120 ml/min/1.73 m^2. The parameter θ_2 is the PCA at which GFR reaches half its max-

TABLE 2. Main steps in population model building for oral data[a]

Step[b]	Model	Objective function[c]	Commentary
1	Monocompartmental CL, V, k_a	1,016	$\sigma^2 = 7.61$
2	$\overline{CL}$ linearly related to PNA	666	$\sigma^2 = 0.470$; PNA influences $\overline{CL}$
3	$\overline{CL}$ linearly related to PNA, $\overline{V}$ linearly related to BW	648	$\sigma^2 = 0.291$; BW influences $\overline{V}$
5	$\overline{CL}$ linearly related to PNA, $\overline{V}$ proportional to BW	650	$\sigma^2 = 0.288$; $\overline{V}$ is proportional to BW
8	$\overline{CL} = \theta_1 \cdot$ GFR $\cdot$ (BSA/1.73)/($\theta_2^{\theta_3} +$ PCA$^{\theta_3}$), GFR $= (7.2 \times$ PCA$^{\theta_3})/(\theta_2^{\theta_3} +$ PCA$^{\theta_3}$)	560	$\sigma^2 = 0.219$; this clearance model is better
10	$\overline{CL} = \theta_1 \cdot$ GFR (BSA/1.73) $\cdot$ (40/S_{CR})	583	$\sigma^2 = 0.202$; scatterplots are better than those in step 8
16	Similar to step 10, but with zero-order absorption rate	596	$\sigma^2 = 0.554$; the fit is worse than that in step 10
17	Bicompartmental model: $\overline{CL} = \theta_1 \cdot$ GFR (BSA/1.73) $\cdot$ (40/S_{CR}) $\overline{V} = \theta_2 \cdot$ BW $\overline{k_a} = \theta_3$ $\overline{CL_d} = \theta_4 \cdot$ BW $\overline{V_t} = \theta_5 \cdot$ BW	577	$\sigma^2 = 0.183$; not significantly better than the one-compartment model

[a] Abbreviations: θ_1 to θ_6, population parameters to be estimated; σ^2, common error variance. To simplify notations, the subscript j on typical parameter values and covariates, the normalization of the covariates with respect to their median, and the ratio with F have been omitted. After step 5, $\overline{V}$ has the same definition in all remaining steps. After step 8, GFR has the same definition in all remaining steps.

[b] Some steps have been omitted for brevity.

[c] Function to be minimized. The critical change is 3.84 for 1 degree of freedom at the 0.05 level.

TABLE 3. Values of population pharmacokinetic parameters for acyclovir from data for patients younger than age 2 years receiving the drug by the oral route[a]

Model and value	θ_1	θ_4 (liters)	θ_5 (h^{-1})	b	θ_2 (mo)	θ_3	Var (η_{CL})	Var (η_V)	Var (η_{k_a})	σ^2
Fixed effects										
Estimate	25.5	37.0	0.277	0.760	13.4	6.17				
SE[b]	2.9	5.3	0.018	0.066	0.58	0.60				
Random effects										
Estimate							0.245	0.324	2.98×10^{-8}	0.210
SE							0.051	0.222	1.97×10^{-3}	0.050

[a] θ_1, θ_3, and b are dimensionless parameters. See text for definitions of θ_1 to θ_5.
[b] SE, standard error of estimate.

imal value. The parameter θ_3 is a sigmoidicity coefficient, which is proportional to the steepness of the sigmoid curve at PCA equal to θ_2. The coefficient (BSA/1.73) transforms the estimated GFR into liters per hour. The last term ($40/S_{CR}$) takes into account the deviation of a given individual from the median S_{CR} for this population to correct the estimated clearance. Finally, θ_1 is a scaling factor which accounts for the unknown F and for the fact that acyclovir clearance is higher than GFR owing to the tubular secretion of acyclovir.

The typical value of the apparent volume of distribution ($\overline{V}/F$), was related only to BW: $\overline{V}/F = \theta_4$(BW/6.9), where 6.9 is the typical value of BW for this population. None of the demographic or biological indices was found to be related to the typical value of k_a: $\overline{k_a} = \theta_5$ and $k_{aj} = \overline{k_a} \exp(\eta_{k_{aj}})$.

Allowing for covariance between the η values did not improve the fit; therefore, covariances were fixed to zero. The values of the parameters of the final model, based on the data for 79 patients, are summarized in Table 3. The interindividual CVs of the CL and V of acyclovir after having taken into account the covariates were 49 and 57%, respectively. The variability of k_a was estimated to be near zero. This should not be interpreted as reflecting the absence of interindividual variability in k_a but, rather, as the inability to estimate the variability owing to the small amount of information on the absorption phase because of the sparse amount of data as a result of the sampling schedule.

A graph of the predicted concentrations versus the observed concentrations is presented in Fig. 2. No systematic deviation from the line of y equal to x is observed. The plot of the weighted residuals of the concentrations versus time (data not shown) showed no systematic deviation from the line of y equal to 0. Other validation scatterplots did not reveal any particular trend (data not shown), so that the population model fit the data reasonably well. Individual curves based on post hoc estimates were also adequate.

According to the definition of the residual error model, the residual variabilities of the acyclovir concentrations, expressed as a CV, were 61% at 0.3 μM, 35% at 3 μM, and 20% at 30 μM.

The distribution of individual pharmacokinetic parameters for acyclovir (more precisely, of the post hoc estimates) is summarized in Table 4. The dispersion of the individual values was very large, even after normalization with respect to BW or BSA.

Figure 3 illustrates the variation of typical values for pharmacokinetic parameters for acyclovir as a function of age; the

steep variation in the elimination half-life ($t_{1/2}$) in the first month of life as well as the large value for premature infants is clearly visible. The concomitant variations of BSA and BW are also represented, after scaling for the sake of clarity.

Model building for intravenous disposition. The two-compartment model was found to be much more adequate than the one-compartment model for description of the acyclovir disposition after intravenous dosing (difference in objective function values [DOFVs], 125). Relating the typical value of CL to $G\hat{F}R$, BSA, and S_{CR} and that of V_c to BW by relationships similar to those used in the oral disposition population model increased further the adequacy of the model (DOFV, 133). Finally, typical values of CL_d and V_p were modeled as being proportional to BW, which yielded a DOFV of 20. With this final model, the adequacy of the fit to the data was very good. The various scatterplots revealed no systematic deviation (data not shown). The distribution of the individual pharmacokinetic parameters (post hoc estimates) for acyclovir is summarized in Table 5.

Analysis of acyclovir F. The data for the 102 patients were combined in order to estimate the acyclovir F. A one-compartment model and a two-compartment model were first compared. In these two models, the typical values of the parame-
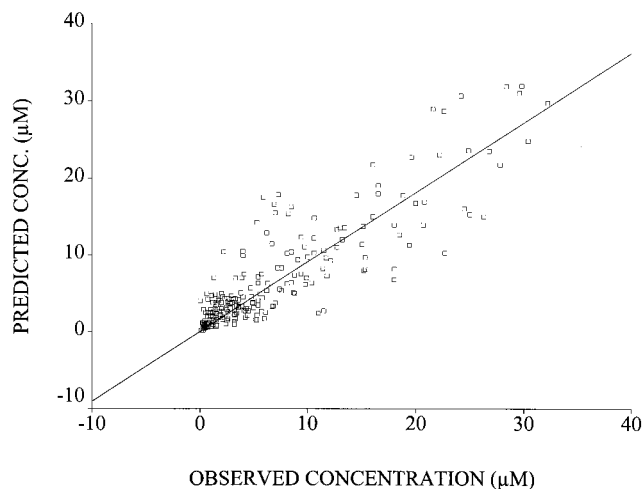

FIG. 2. Scatterplot of predicted versus observed acyclovir concentrations for data for administration by the oral route. Predicted concentrations were calculated by using the population model, the covariates for each patient, and the patient's dosing history.

TABLE 4. Median and 5th to 95th percentiles of individual pharmacokinetic parameters (post hoc estimates)
for acyclovir after oral administration

Value	CL/F (liters/h)	CL/F (liters/h/kg)	CL/F (liters/h/m^2)	V/F (liters)	V/F (liters/kg)	V/F (liters/m^2)	k_a (h^{-1})
Median	20.9	3.1	56.3	37.3	5.4	93.2	0.28
5th to 95 percentile	1.7–93.9	0.6–9.8	7.5–201	12.1–81.4	3.5–8.2	54.1–170	0.28–0.28
CV (%)	98	79	86	53	27	31	

ters were related to the covariates in the same way that they were in the final oral and intravenous models, respectively. The two-compartment model was found to be more adequate than the one-compartment model (DOFV, 231). The point estimate and standard error of F were 0.118 and 0.026, respectively, while the interindividual variability of F was 16%. Individual estimates of F were plotted against the dose and the covariates to examine possible relationships. Specific models relating F to dose and age were then tested, but these relationships were not found to be significant.

Simulation of acyclovir kinetics. The final population model describing the kinetics of acyclovir after oral administration (Table 4 was used to generate the acyclovir concentration profile for 500 fictitious individuals by simulation in order to visualize the evolution of the typical acyclovir concentration profile as a function of age. Figure 4A shows the median concentration-versus-time curves at steady state after the administration of 24 mg/kg q8h to neonates (PNA, 0 to 1 months) of various gestational ages (7, 8, or 9 months). Figure 4B shows the corresponding curves after administration of 24 mg/kg according to a schedule of 0, 4, 8, 12, and 24 h to children with various PNA ranges: 1 to 3, 3 to 12, and 12 to 24 months. The lengths of time that the acyclovir concentrations remain above 2.5 and 5 µM at steady state, according to several dosing schedules, are reported in Table 6.

DISCUSSION

The pharmacokinetics of acyclovir administered by the oral route were well described, as in earlier studies with adults, by a one-compartment model with first-order absorption and elimination. Therefore, only four parameters were needed to characterize the disposition of acyclovir, namely CL, V, k_a, and F. The population approach based on a mixed-effects modeling approach enabled the estimation of the typical values of these parameters and their interindividual variabilities; it also enabled correlation of some of the demographic and biological indices to variations in these parameters. A possible limitation of our approach is that data for the intravenous route were mainly from older children, whereas data for the oral route were mainly from younger children. Hence, the estimation of F is reliable only if the variation of CL with age is appropriately described by the covariate model. In this respect, the absence of any trend in the scatterplot of CL (actually η_{CL_j}) versus age is reassuring.

The F of acyclovir administered as an oral suspension was about 12%. This value is in the range of F values estimated for adults (20% for the 200-mg dose, 12% for the 800-mg dose) for various pharmaceutical forms (tablets, solution, etc.) (11, 24). From a practical point of view, it implies that for a given dosing regimen, mean acyclovir concentrations are about eight times
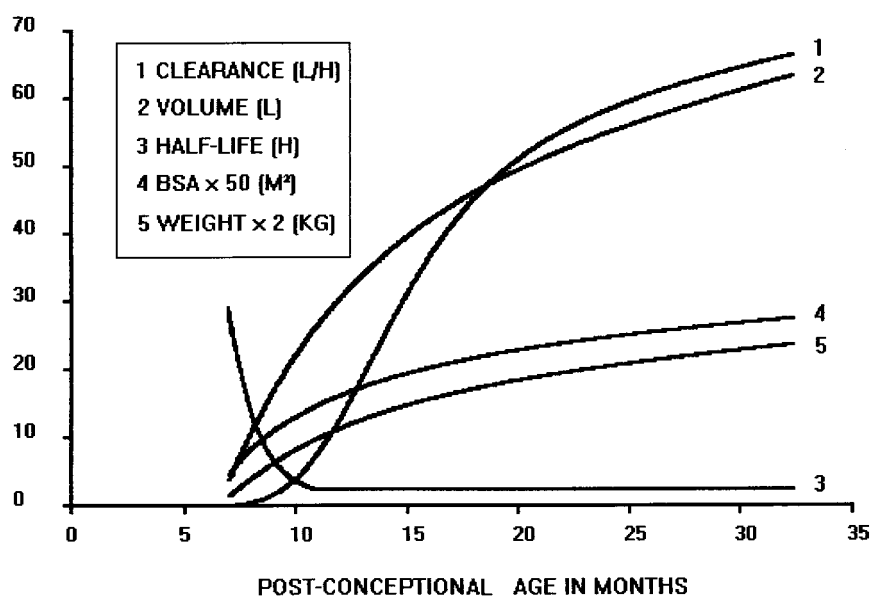

FIG. 3. Variations in the typical values of pharmacokinetic parameters for acyclovir as a function of age.

TABLE 5. Median and range of individual pharmacokinetic parameters (post hoc estimates) for acyclovir after intravenous administration

Value	CL (liters/h)	CL (liters/h/kg)	V_c (liters)	V_c (liters/kg)	CL_d (liters/h)	CL_d (liters/h/kg)	V_p (liters)	V_p (liters/kg)
Median	9.7	0.44	10.0	0.57	4.79	0.21	13.7	0.62
Minimum-maximum	0.76–22.5	0.24–0.79	1.7–27.1	0.28–0.71	0.12–18.2	0.02–0.45	1.4–25.6	0.40–1.24
CV (%)	59	32	67	20	100	62	62	27

lower after oral administration than after intravenous administration to the same patients, so that doses administered by the oral route must be about eight times higher than those administered by the intravenous route to ensure the same exposure. This relationship may not hold for higher dosages, since the F of acyclovir decreases as the dose increases owing to saturation of the absorption.

The interindividual variability in the pharmacokinetic parameters for acyclovir in the pediatric population studied in the present investigation was found to be very large, but it depends on the way in which the variability is expressed. The "crude" variability is reflected by the dispersion of the individual values for the parameters when they are expressed in their "natural" units, i.e., liters per hour for CL and liters for V; the ratios between the 95th and the 5th percentiles are about 55 and 6.7 for CL and V, respectively (Table 4). If the individual parameters are normalized to BW or BSA, the same ratio is reduced to 16 for CL in liters per hour per kilogram and 2.3 for V in liters per kilogram but only to 27 for CL in liters per hour per square meter and 3.1 for V in liters per square meter. Hence, the values of the parameters normalized with respect to BW are less variable than those normalized with respect to BSA. Comparison of these ratios for CL and V also shows that the interindividual variability of CL is much larger than that of V, probably because V is mainly related to body size, while CL is related to body size as well as to maturity and to all the factors that influence the renal handling of acyclovir. The population model shows how several covariates are quantitatively related to CL and V: CL was found to be related to PCA, BSA, and S_{CR}, while V was related to BW. The deviation of the values of the individual parameters from the typical value (calculated according to the covariate model and the values from the covariate model for that individual) represents the residual (unexplained) variability of the parameters once the contribution of the covariates (PCA, BSA, S_{CR}, BW) has been taken into account. As described in the Results section, these residual variabilities correspond to CVs of 49 and 57% for CL and V, respectively. Hence, about half of the interindividual variability in CL and V remains unexplained, so that the uncertainty about predicted acyclovir concentrations in a given individual for a given dosing schedule remains large. However, it is possible to obtain a confidence interval of the acyclovir concentration profile by several techniques, e.g., by Monte-Carlo simulation.

We examined the acyclovir concentration profile by simulation for different age ranges. It was found that prematurity had a profound influence on the kinetics of acyclovir since within the first three PCA ranges (7 to 8, 8 to 9, and 9 to 10 months), an increase of one age range led to a twofold decrease in the acyclovir concentration. The question arises whether the dosing regimen used in the study is adequate or whether a new

dosing regimen must be proposed. The efficacy of acyclovir is dependent on the daily dose, the number of doses per day, and the 50% inhibitory concentration (IC_{50}) for the viral strain. For example, the proportions of 1,050 patients free of genital HSV recurrence after 1 year of treatment with valaciclovir at 250, 500, or 1,000 mg once daily were 22, 40, and 48%, respectively, while the mean daily areas under the concentration-time curve (AUCs) for acyclovir were 22.0, 45.8, and 80.4 $\mu M \cdot h$, respectively (15). In the same study, 50% of the patients treated with valaciclor at 250 mg twice daily (mean daily AUC for acyclovir, 55.1 $\mu M \cdot h$) were free of recurrence after 1 year of treatment; i.e., 250 mg twice daily had the same efficacy as 1,000 mg once daily, despite a lower daily AUC. This finding and other results (4) support the assumption that the length of time that the acyclovir concentration remains above a given threshold (the IC_{50}) is also an important criterion for efficacy. It has been suggested that maximal efficacy is reached when the length of time that the acyclovir concentration remains above the IC_{50} is greater than 12 h in each 24-h period of treatment (17, 20). For VZV infections, a higher acyclovir AUC is required because the IC_{50} for VZV isolates is higher. It has been shown that the time to healing in 994 adult patients is related to the daily AUC for acyclovir after oral administration of acyclovir or valaciclovir (S. Weller and M. R. Blum, Population pharmacokinetics of acyclovir after administration of valaciclovir or oral acyclovir to patients for the treatment of herpes zoster, internal document, Glaxo Wellcome Co.). The mean daily AUCs for acyclovir at the doses approved for the treatment of herpes zoster in adults are 107 $\mu M \cdot h$ (acyclovir at 800 mg five times per day) and 253 $\mu M \cdot h$ (valaciclovir at 1,000 mg q8h), respectively, with the latter treatment having a greater efficacy. On the basis of these

TABLE 6. Daily AUC and length of time that acyclovir concentration remains above 2.5 and 5 μM at steady state in a 24-h interval, calculated by simulation with data for 500 fictitious individuals

PNA (mo)	Dose (mg/kg), of times daily[a]	Median (5th–95th percentile)		
		Daily AUC[b] ($\mu M \cdot h$)	Time > 2.5 μM (h)	Time > 5 μM (h)
0–1	24, 3	441 (283–690)	24.0 (24.0–24.0)	24.0 (24.0–24.0)
1–3	24, 4	269 (185–448)	24.0 (21.1–24.0)	22.3 (17.3–24.0)
3–12	24, 4	93 (63–157)	17.8 (13.4–22.6)	8.4 (0.0–18.5)
	48, 4	186 (126–314)	—[b]	17.8 (13.4–22.6)
12–24	24, 4	76 (52–102)	16.3 (10.1–18.7)	2.6 (0.0–10.8)
	48, 4	152 (104–204)	—	16.3 (10.1–18.7)

[a] Dosing schedule is q8h if three times daily or at 0, 4, 8, 12, and 24 h if four times daily.
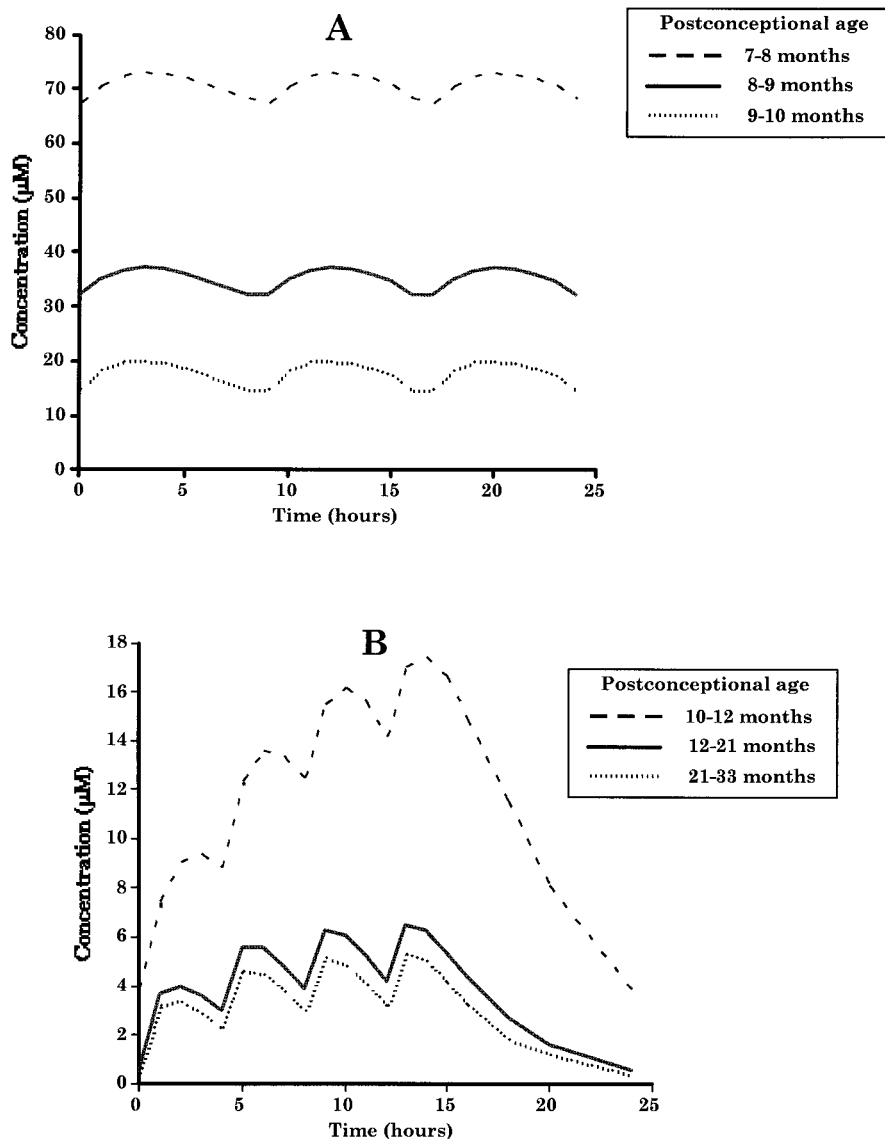[b] —, not done because the lower dose is adequate.

FIG. 4. Simulation of the median acyclovir concentration-versus-time curve at steady state from 500 fictitious individuals after oral administration of 24 mg/kg q8h to children ages 0 to 1 month (A) or after administration q.i.d. at 0, 4, 8, 12, and 24 h to children ages 1 to 24 months (B).

considerations and the results of our simulations for thresholds of 2.5 and 5 μM, which correspond to a worst-case IC_{50} for HSV strains and a bad-case IC_{50} for VZV strains (Table 6), respectively, the proposed dosing regimen (24 mg/kg q8h for patients younger than 1 month of age or q.i.d. otherwise) seems to be appropriate for the treatment of HSV-1 and HSV-2 infections in children up to age 2 years. For VZV infections, a twofold increase in the dose (i.e., 48 mg/kg according to a schedule of treatment at 0, 4, 8, 12, and 24 h) seems to be necessary in order to ensure maximal efficacy in children older than age 3 months. These suggestions should serve as starting point for the design of clinical efficacy studies.

APPENDIX

The population pharmacokinetic method based on a nonlinear mixed-effects modeling approach is as follows. Two levels of variability were considered. The first level of variability, i.e., residual (intraindi-

vidual) variability, accounted for the deviation of the observed acyclovir concentration at time i in individual j (C_{ij}) from the predicted concentration ($\hat{C}_{ij}$) according to the equations $C_{ij} = \hat{C}_{ij} + \varepsilon_{ij} \cdot \hat{C}_{ij}^{b}$ and $\hat{C}_{ij} = f(P_j, t_{ij})$, where ε_{ij} is a random variable with a normal distribution with zero mean and variance σ^2, and b is a parameter of the residual error model. σ^2 and b are parameters to be estimated. The predicted concentration is given by the pharmacokinetic model $f(\cdot)$ for a given set (vector) of individual pharmacokinetic parameters P_j. This error model assumes that residual errors are uncorrelated and that residual error variance increases as a function of concentration, a pattern which is very common in pharmacokinetics.

The second level of variability accounted for interindividual variability. Individual pharmacokinetic parameters P_j were assumed to arise from a multivariate lognormal distribution whose typical value, $\overline{P}_j$ (i.e., the median), depends on the set (vector) of covariate values of individual j (X_j) according to a covariate model $h(\cdot)$: $\overline{P}_j = h(P, X_j)$ and $P_j = \overline{P}_j \exp(\eta_j)$, where P is a set (vector) of population parameters called fixed effects ($P = \theta_1, \theta_2, \ldots$) and η_j is a set (vector) of random effects with normal distribution, zero mean, and Ω variance-covariance matrix. With this model, the distribution of the individual parameters

in all subjects having the same covariates X_j is skewed to the right and negative values are avoided. The goal of the population analysis was to determine the most adequate models for $f(\cdot)$ and $h(\cdot)$ and to estimate the parameters P, Ω, σ^2, and b.

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