Single-Dose Pharmacokinetics of Famiclovir in Infants and Population Pharmacokinetic Analysis in Infants and Children

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A multicenter, open-label study evaluated the single-dose pharmacokinetics and safety of a pediatric oral famciclovir (prodrug of penciclovir) formulation in infants aged 1 to 12 months with suspicion or evidence of herpes simplex virus infection. Individualized single doses of famciclovir based on the infant’s body weight ranged from 25 to 175 mg. Eighteen infants were enrolled (1 to <3 months old [n = 8], 3 to <6 months old [n = 5], and 6 to 12 months old [n = 5]). Seventeen infants were included in the pharmacokinetic analysis; one infant experienced immediate emesis and was excluded. Mean $C_{\text{max}}$ and AUC0–6 values of penciclovir in infants <6 months of age were ∼3- to 4-fold lower than those in the 6- to 12-month age group. Specifically, mean AUC0–6 was 2.2 μg·h/ml in infants aged 1 to <3 months, 3.2 μg·h/ml in infants aged 3 to <6 months, and 8.8 μg·h/ml in infants aged 6 to 12 months. These data suggested that the dose administered to infants <6 months was less than optimal. Eight (44.4%) infants experienced at least one adverse event with gastrointestinal events reported most commonly. An updated pharmacokinetic analysis was conducted, which incorporated the data from infants in the present study and previously published data on children 1 to 12 years of age. An eight-step dosing regimen was derived that targeted exposure in infants and children 6 months to 12 years of age to match the penciclovir AUC seen in adults after a 500-mg dose of famciclovir.

Manifestations, sequelae, and risk of mortality and morbidity of herpes simplex virus type 1 (HSV-1) and HSV-2 infections differ among newborns, infants, and immunocompetent versus immunocompromised children (7, 12, 20, 23, 31, 32). At presentation, clinical symptoms range from infections limited to the skin, eye, and mouth to disseminated disease and encephalitis. Acyclovir, valacyclovir, and famciclovir are effective and safe options for the treatment of HSV infections (32). Despite being considered as a gold standard, acyclovir’s pharmacokinetic profile is less than ideal for oral administration to children (e.g., limited bioavailability requires frequent dosing) (9). Administration of valacyclovir, the prodrug of acyclovir, provides higher serum levels of acyclovir (13). Valacyclovir is not approved in children less than 12 years of age for the treatment of herpes labialis and in children less than 2 years old with chickenpox. Penciclovir, the active component of the prodrug famciclovir, has activity against HSV-1, HSV-2, and varicella-zoster virus (VZV) (30) and a higher affinity for viral thymidine kinase than does acyclovir (4, 8). Viral thymidine kinase phosphorylates penciclovir or acyclovir to a monophosphate, which is then converted by cellular kinases to the respective triphosphate. The triphosphate inhibits viral replication (8). Penciclovir triphosphate has a longer intracellular half-life in infected cells compared to acyclovir triphosphate (7 to 20 h versus 1 h, respectively) (8). The pharmacokinetics of penciclovir in earlier studies with adults show that peak penciclovir concentration and exposure (AUC) increase linearly with dose after the administration of famciclovir (10, 16). Famciclovir is approved for use in immunocompetent adults based on findings from clinical trials for herpes zoster, recurrent genital herpes, recurrent herpes labialis, and mucocutaneous HSV infections in human immunodeficiency virus-infected patients (1, 3, 5, 6, 18, 21, 24, 29).

An experimental famciclovir oral formulation (i.e., “sprinkle” hard gelatin capsules containing famciclovir oral granules) was developed for use in pediatric trials. The capsules were to be opened and the granules sprinkled on OraSweet syrup vehicle before the mixture was ingested. Sáez-Llorens et al. (19) recently reported the findings of single-dose pharmacokinetic and multiple-dose safety evaluations with the pediatric famciclovir formulation in HSV- and VZV-infected children aged 1 to 12 years. In brief, these studies revealed that the average systemic exposure to penciclovir was similar (6 to 12 year olds) or slightly lower (1 to <6 year olds) than that in adults receiving a 500-mg dose of famciclovir. The pharmacokinetic data in children 1 to 12 years old provided initial information to guide dose selection for an exploratory single-dose pharmacokinetic study in infants.

The present study has two main purposes: (i) to describe the pharmacokinetics, safety, and tolerability of a single dose of famciclovir in infants 1 to 12 months of age who are at risk of, or who have HSV infection, and (ii) to present an updated population pharmacokinetic model of penciclovir in infants and children with HSV or VZV infection. The updated model, which combined data in children aged 1 to 12 years with those...
from infants 1 to 12 months, was used to derive a new dosing scheme for infants and children to match exposure in adults.

### MATERIALS AND METHODS

#### Study design and treatment.
A multicenter, open-label, single-dose trial was conducted to evaluate the pharmacokinetics of famciclovir after administration to infants aged 1 to 12 months. Infants could have been hospitalized or dosed as outpatients. The individualized single dose of famciclovir was based on the infant’s body weight (BW) (Table 1). The dosing algorithm used was based on pharmacokinetic data recently obtained in children aged 1 to 12 years (19) and took into account physiological changes of renal function with age. The contents of the appropriate number of capsules, provided as 25- and 100-mg sprinkle capsules, were mixed with 5 ml of OraSweet just prior to dosing and administered within 1 h. Study site personnel administered and supervised the famciclovir dosing. The infant’s intake of food and beverages was restricted. Administration of up to 90 ml (3 oz) of one of the following was permitted up to 1 h prior to dosing: breast milk, formula, or a suitable milk substitute. Water was allowed ad libitum. Normal feeding was permitted 1 h postdose. Infants could be redosed 12 h after the initial administration of study drug if they did not ingest the entire dose or if significant emesis occurred within 30 min of dosing. Although an 8-h washout of current antiviral therapy was recommended, concomitant use of antiherpes nucleoside analogue treatments was permitted if deemed appropriate by the investigator.

#### Approval of the study protocol and consent form was obtained from each investigator’s independent ethics committee or institutional review board and the Ministry of Health (Guatemala), and all study activities were conducted in accordance with good clinical practice and the Declaration of Helsinki. The parent or legal guardian provided written informed consent.

#### Study population.
Infants were enrolled and stratified by age (1 to <3 months, 3 to <6 months, and 6 to 12 months); age grouping was used for recruitment purposes to ensure an approximately even distribution of infants across the age ranges. The study population consisted of a representative group of infants who had active, suspected, or latent HSV-1 or HSV-2 infection and who were candidates for antiviral therapy, regardless of their immune status. Infants who were starting or using acyclovir therapy were eligible for the study.

Infants were excluded from study participation if they (i) were aged 1 month to <3 months with a gestational age <35 weeks or 3 to 12 months with a gestational age <32 weeks, (ii) were unable to swallow (e.g., infants who had extensive gingivostomatitis in whom drinking was impaired), (iii) had a history of malabsorption or previous gastrointestinal surgery or a history of radiation therapy that could affect drug absorption or metabolism, (iv) had clinically significant hepatic or renal disorders, or (v) had any of the following age-adjusted clinical or hematologic laboratory and blood chemistry abnormalities: an aspartate amino-transferase or an alanine transaminase more than three times the upper limit of normal (ULN), a total bilirubin level >2-fold the ULN, a serum creatinine level >2-fold the ULN, an absolute white blood cell count of <4,000/mm³, a platelet count of <50,000/mm³, a hemoglobin level of <7 g/dl, or a significant blood volume loss (>3% of calculated blood volume) in the previous 30 days. Probenecid use was prohibited due to its effects on renal physiology and because of its propensity to elevate plasma levels of penciclovir.

#### Acceptability, tolerability, and safety assessments.
Immediately after swallowing the formulation, the caregiver and the person who administered the drug rated the apparent acceptability of the formulation using a five-point subjective scale (1 = very bad/unacceptable, 2 = bad but accepted, 3 = neither good nor bad, 4 = well accepted, and 5 = very well accepted). The study personnel who administered the dose also rated tolerability 30 min after dosing using a four-point scale (1 = significant emesis occurred; 2 = the infant spit out most of the dose, ingesting less than half of what was administered; 3 = the infant spit out some of the dose, but ingested at least 50% of what was administered; and 4 = the infant was able to ingest and retain the dose administered).

Safety assessments consisted of monitoring and recording all adverse events (AEs), serious AEs, physical examination, and vital sign measurements. AEs were recorded at serial times up to 8 h postdose; at 24 h after completion of therapy if the infant prematurely withdrew, did not ingest the full dose, or underwent significant emesis and was not redosed; and at the time of the day 8 or 38 follow-up telephone call. Clinical laboratory (e.g., hematology and clinical chemistry) tests were performed for all infants at screening, at 24 h after completion of therapy for infants specified above, and if a repeat follow-up visit was required. Laboratory toxicity grading (1 to 4) was based on modified Division of Microbiology and Infectious Diseases (November 2007) and Division of AIDS (December 2004) pediatric toxicity criteria.

#### Pharmacokinetic assessment and analysis.
Blood samples (1.0 ml each) were drawn for measurement of penciclovir concentrations at 0.5, 1, 4, and 6 h after the famciclovir dose using tubes containing EDTA as the anticoagulant; a zero time sample was not obtained in order to minimize the amount of blood withdrawn. Plasma was separated using centrifugation and kept frozen at −20°C until analysis. Penciclovir and 6-deoxypenciclovir concentrations in plasma were determined using a validated liquid chromatography-tandem mass spectrometry method. The intra- and interbatch precision of the method as characterized by the coefficient of variation (CV) ranged between 1.2 and 3.4% for plasma samples spiked with penciclovir or 6-deoxypenciclovir (prestudy assay validation). Intra- and interday accuracy was determined together with the study samples. The CV ranged between 1.1 and 5.9%. The limit of quantification was 0.15 µg/ml for each compound. 6-Deoxypenciclovir is an inactive metabolite of famciclovir and the precursor of the active metabolite penciclovir (10, 22).

Plasma drug-concentration-time data were used to derive the following pharmacokinetic parameters of penciclovir: Cmax (maximum concentration), Tmax (time to Cmax), and AUC0–t (area under the plasma drug-concentration-time curve calculated as the time-weighted area under analytic curve, AUC0–t, using WinNonLin Professional Version 5.2 (Pharsight Corp., Mountain View, CA) and noncompartmental methods. Since no predose plasma sample was collected, the 0-h concentration of penciclovir was assumed to be zero for the calculation of AUC0–t.

#### Population pharmacokinetic modeling.
An updated population pharmacokinetic model for penciclovir in pediatric patients was generated based on pooled pharmacokinetic data from the infant study described in the present study and two previous studies in older children aged 1 to 12 years (19). A weight-based dose table for infants and children that would provide AUC exposures comparable to adults was subsequently derived.

Model building was performed by using NONMEM version VI Level 1.3 with Method 1 Interaction (NONMEM user guides, Icon Development Solutions, Berkeley, CA, MD). A one-compartment model with first-order input and parameters to be estimated for apparent clearance (CL), apparent volume (V), and input rate constant (k1) was selected for the population pharmacokinetic analysis based on a previous interim analysis reported in children 1 to 12 years of age (19). CL and V are used here synonymously with CL/F and V/F, where F is the oral bioavailability. An input lag time (ALAG1) equal to 0.21 h, and clearance and volume allometrically scaled by BW to the 0.75 and 1.0 power (2), respectively, were assumed as in the previous analysis.

The population model added random effects for the pharmacokinetic parameters in order to recognize differences among individuals and similarities across observations corresponding to the same subject. Intersubject random effects for CL, V, and k1 (\(\eta_1\), \(\eta_2\), and \(\eta_3\), respectively) were assumed normally distributed with means of zero and with \(\eta_1\) correlated with \(\eta_2\) but both were uncorrelated with \(\eta_3\). The individual pharmacokinetic parameter for clearance was reparameterized in terms of its typical value (TV) = TVCL as CL = TVCL · exp(\(\eta_1\)). Other pharmacokinetic parameters used similar representations. A combined residual error model was adopted in this analysis. In this case, the residual error is normally distributed with mean 0 and variance \(\sigma_r^2 + \sigma_x^2 \cdot C_e^2\), where \(C\) is the individual predicted plasma penciclovir concentration at a specific time point, \(\sigma_r\) is the approximate standard deviation of the residual error when \(C\) is small, and \(\sigma_x\) is the approximate residual CV when \(C\) is large.

#### Pharmacokinetic data recently obtained in children aged 1 to 12 years (19) and took into account physiological changes of renal function with age. The contents of the appropriate number of capsules, provided as 25- and 100-mg sprinkle capsules, were mixed with 5 ml of OraSweet just prior to dosing and administered within 1 h. Study site personnel administered and supervised the famciclovir dosing. The infant’s intake of food and beverages was restricted. Administration of up to 90 ml (3 oz) of one of the following was permitted up to 1 h prior to dosing: breast milk, formula, or a suitable milk substitute. Water was allowed ad libitum. Normal feeding was permitted 1 h postdose. Infants could be redosed 12 h after the initial administration of study drug if they did not ingest the entire dose or if significant emesis occurred within 30 min of dosing. Although an 8-h washout of current antiviral therapy was recommended, concomitant use of antiherpes nucleoside analogue treatments was permitted if deemed appropriate by the investigator.

### TABLE 1. Famciclovir dosing regimen by BW

<table>
<thead>
<tr>
<th>BW (kg)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4.5</td>
<td>25</td>
</tr>
<tr>
<td>4.6–6.4</td>
<td>25</td>
</tr>
<tr>
<td>5.5–6.4</td>
<td>50</td>
</tr>
<tr>
<td>6.5–7.4</td>
<td>75</td>
</tr>
<tr>
<td>7.5–8.4</td>
<td>100</td>
</tr>
<tr>
<td>8.5–9.4</td>
<td>125</td>
</tr>
<tr>
<td>9.5–10.4</td>
<td>150</td>
</tr>
<tr>
<td>10.5–11.4</td>
<td>175</td>
</tr>
<tr>
<td>11.5–13.4</td>
<td>200</td>
</tr>
</tbody>
</table>

\(a\) BW, body weight.
TABLE 2. Demographic and baseline characteristics by age group for infant single-dose study (safety population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1: age 1 to &lt;3 months (n = 8)</th>
<th>Group 2: age 3 to &lt;6 months (n = 5)</th>
<th>Group 3: age 6 to 12 months (n = 5)</th>
<th>Total (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects with confirmed HSV infection (%)</td>
<td>5 (62.5)</td>
<td>3 (60.0)</td>
<td>4 (80.0)</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td>No. of subjects with HSV identification confirmation (%)</td>
<td>3 (37.5)</td>
<td>2 (40.0)</td>
<td>1 (20.0)</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>PCR</td>
<td>1 (12.5)</td>
<td>1 (20.0)</td>
<td>1 (20.0)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Culture</td>
<td>1 (12.5)</td>
<td>1 (20.0)</td>
<td>3 (60.0)</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Clinical diagnosis only</td>
<td>2 (25.0)</td>
<td></td>
<td></td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>No. of male subjects</td>
<td>5 (62.5)</td>
<td>3 (60.0)</td>
<td>3 (60.0)</td>
<td>11 (61.1)</td>
</tr>
<tr>
<td>Median age in mo (range)</td>
<td>1 (1–2)</td>
<td>3 (3–4)</td>
<td>8 (7–12)</td>
<td>3 (1–12)</td>
</tr>
<tr>
<td>Race, no. of subjects (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>4 (50.0)</td>
<td>3 (60.0)</td>
<td>1 (20.0)</td>
<td>8 (44.4)</td>
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<tr>
<td>Black</td>
<td>3 (37.5)</td>
<td>1 (20.0)</td>
<td>1 (20.0)</td>
<td>5 (27.8)</td>
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<tr>
<td>Native American</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (12.5)</td>
<td>1 (20.0)</td>
<td></td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Ethnicity, no. of subjects (%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>1 (12.5)</td>
<td></td>
<td>3 (60.0)</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Mixed</td>
<td>1 (12.5)</td>
<td></td>
<td></td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (75.0)</td>
<td>5 (100.0)</td>
<td>2 (40.0)</td>
<td>13 (72.2)</td>
</tr>
<tr>
<td>Median wt in kg (range)</td>
<td>4.0 (3.2–6.0)</td>
<td>5.9 (5.5–7.7)</td>
<td>7.9 (6.9–11.5)</td>
<td>5.9 (3.2–11.5)</td>
</tr>
</tbody>
</table>

concentration data were simulated based on covariate data and actual milligram doses and times of doses and samples in the actual data set. Final population parameters were fixed at their final estimates in the simulation (i.e., assuming no uncertainties in the population parameters), but incorporating variability in individual parameters and observational (residual) error. SAS PROC UNIVARIATE was used to compute the 5th, 50th, and 95th percentiles of the simulated penciclovir concentrations by three weight groups (>3 to 7 kg, >7 to 12 kg, and >12 kg) and elapsed time after dose. Finally, S-Plus was used to display the visual predictive check with observed data superimposed over the percentiles.

The final model was used to predict pharmacokinetic exposure measures (AUC, the area under the plasma concentration-time curve from time zero to infinity, and C_{max}) and related pharmacokinetic parameters for penciclovir for each patient in the population pharmacokinetic analysis population using actual doses, as well as various proposed alternative dosing tables designed to match AUC for infants and children with adults. SAS release 8.2 was used for all nongraphical descriptive summaries. S-Plus version 6.2 was used for all graphical analyses.

**Sample size and statistical methods.** For this single-dose study, 18 infants were planned with a sample size of six participants per group based on common practice for pharmacokinetic studies in pediatric participants.

**Descriptive summaries of demographics, medical history, pharmacokinetics, safety, and medication acceptability were provided. Safety data were analyzed by Biometrical Practice BIOP AG (Basel, Switzerland), using SAS 8.2 or Windows XP. No inferential analyses were performed.**

**RESULTS**

**Participants.** A total of 18 infants were enrolled, all of whom completed the study (safety population). One infant, exactly 12 months of age, was enrolled and included in the analysis. Sixteen of the infants were inpatients, and two were outpatients.

The full dose was administered to 16 infants (88.9%) and ranged from 25 to 175 mg. One infant in the 6 to 12 months group took a dose of 175 mg instead of 200 mg, and another infant (1 to < 3 months group) did not receive the full dose secondary to significant emesis (redosing was not attempted, and pharmacokinetic samples were not obtained). Demographic and disease characteristics are outlined in Table 2. Approximately two-thirds of infants had confirmed HSV at baseline, with confirmation most commonly by PCR. Regarding HSV disease, six infants had meningoencephalitis, one had unspecified congenital herpes, three had eczema herpeticum, one had gingivostomatitis, and seven had unspecified HSV infection. Two infants were immunocompromised, both in the 1 to <3 months group (one with myeloproliferative disorder and the second with unspecified immune system disorder). The remaining 16 infants were immunocompetent. A total of 16 patients (89.0%) received concomitant acyclovir therapy including eight patients in the 1- to <3-month-old group, four patients in the 3- to <6-month-old group, and four patients in the 6- to 12-month-old group.

**Pharmacokinetics.** Seventeen infants were included in the pharmacokinetic analysis. Blood samples for penciclovir concentrations were available from seven patients in the 1- to <3-month-old group, five patients in the 3- to <6-month-old group, and five patients in the 6- to 12-month-old group. The mean famciclovir doses administered to groups 1, 2, and 3 were 6.6, 9.4, and 13.5 mg/kg, respectively.

The mean plasma concentration time profiles of penciclovir and 6-deoxy penciclovir for the three age groups are shown in Fig. 1. Concentrations of 6-deoxy penciclovir were lower than those of penciclovir and were below the limit of quantification at 4 h after dosing in 16 of the 17 infants. A summary of pharmacokinetic parameters for penciclovir by age group is presented in Table 3. The mean C_{max} and AUC_{0–6} values of penciclovir in the infants younger than 6 months of age were ~3- to 4-fold lower than those in the 6- to 12-month-old group.

In Fig. 2, the individual AUC_{0–6} values of penciclovir are plotted against BW (upper graph) or age (lower graph) of the infants of each age group; infants in both the 1- to <3-month-old and the 3- to <6-month-old groups had a lower exposure to penciclovir than infants in the 6- to 12-month-old group. As mentioned previously, one infant in the 6- to 12-month-old group...
received an incorrect dose (i.e., 175 mg instead of 200 mg, according to BW [11.5 kg]). The AUC$_{0-6}$ of penciclovir in this infant was 8.45 μg·h/ml. Assuming exposure proportionally increased with dose, the AUC$_{0-6}$ for the correct dose (200 mg) would have been 9.66 μg·h/ml, which is still well below the upper limit of the exposure range in this age group.

Acceptability, tolerability, and safety. A total of eight (44.4%) infants experienced at least one AE. All AEs occurred within 8 days, with the majority occurring 3 or more days, after single-dose famciclovir administration except for one (fever), which was reported 31 days after study drug administration. No infants discontinued the study or treatment because of AEs. Among 17 individual AEs reported, the most common were vomiting in three infants and diarrhea, pyrexia, and dehydration in two infants each. All other AEs were reported in one infant each. A total of three infants (16.7%) had at least one mild adverse event, four infants (22.2%) had at least one moderate AE, and one infant (5.6%) had a severe AE. The infant with a severe event was immunocompromised, had oral candidiasis, and was reported to have worsening HSV encephalitis. The infant’s deterioration began after 18 of 21 days of intravenous acyclovir therapy and was reported on day 3 of famciclovir single-dose administration. The encephalitis was not considered to be related to famciclovir therapy per the investigator’s judgment.

One infant was reported by the investigator to have a pos-

![FIG. 1. Mean (± the standard deviation) plasma concentration-time profiles of penciclovir and 6-deoxypenciclovir after a single oral famciclovir dose administered to infants stratified by age. Group 1, ages 1 to <3 months; group 2, ages 3 to <6 months, group 3, ages 6 to 12 months. Symbols: ■, penciclovir; ○, 6-deoxypenciclovir.](image)

![FIG. 2. Relationship between AUC$_{0-6}$ of penciclovir and body weight (BW) or age. Infant 0511_0001 received an incorrect dose, i.e., 175 mg instead of 200 mg. (Upper) Observed AUC$_{0-6}$ versus BW after single oral famciclovir dose. (Lower) Observed AUC$_{0-6}$ versus age after single oral famciclovir dose. Group 1 (■), ages 1 to <3 months; group 2 (○), ages 3 to <6 months; group 3 (▲), 6 to 12 months.](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1: age 1 to &lt;3 months ($n=7$)</th>
<th>Group 2: age 2 to &lt;6 months ($n=5$)</th>
<th>Group 3: age 6 to 12 months ($n=5$)</th>
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<tbody>
<tr>
<td>Pharmacokinetic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median $T_{\text{max}}$ in h (range)</td>
<td>1.00 (1.00–5.17)</td>
<td>4.00 (1.0–4.17)</td>
<td>1.02 (0.58–1.10)</td>
</tr>
<tr>
<td>Mean $C_{\text{max}}$ (μg/ml) ± SD</td>
<td>0.69 ± 0.41</td>
<td>0.74 ± 0.17</td>
<td>3.24 ± 1.01</td>
</tr>
<tr>
<td>Mean AUC$_{0-6}$ (μg·h/ml) ± SD</td>
<td>2.22 ± 1.23</td>
<td>3.16 ± 0.68</td>
<td>8.77 ± 2.14</td>
</tr>
<tr>
<td>Mean BW-adjusted dose (mg/kg) ± SD</td>
<td>6.6 ± 1.4</td>
<td>9.4 ± 2.1</td>
<td>13.5 ± 2.0</td>
</tr>
</tbody>
</table>

$^a$ BW, body weight.
sible drug-related AE. The infant had vomiting of moderate intensity on day 1 soon after taking the medication, which resolved on the same day without intervention.

A 4-month-old male with eczema herpeticum, experienced two serious AEs, which led to hospitalization: dehydration and worsening of constitution both reported on day 2 of the study. The infant was treated with intravenous fluids; each event resolved after 15 days. Neither of these events was suspected to be related to study medication.

There were no meaningful changes from baseline in vital signs. For hematology and clinical chemistry tests, changes from baseline were generally small and not clinically meaningful overall. A 1-month-old male shifted from normal at baseline for hemoglobin to grade 3 toxicity posttreatment. The same patient shifted from abnormal at baseline for neutrophils to grade 3 toxicity posttreatment. No changes to grades 3 or 4 toxicities were reported for clinical chemistry values.

Most infants appeared to like the taste of the famciclovir formulation administered. After the first dose was given, the majority of caregivers (66.6% [12 of 18]) indicated that the medication was “well accepted” or “very well accepted” by the infant. Three caregivers rated the medication as being of neutral acceptability. Two caregivers stated that the medication was taken “badly but accepted” or “very badly, unacceptable” (one in the 1- to <3-month-old group and the second in the 6- to 12-month-old group). Similar results were seen in the acceptability responses from study personnel. Overall, 17 patients (94.4%) were considered by study personnel to have been able to ingest the study medication and retain the dose. One patient as mentioned above had significant emesis after receiving the single dose. **Updated pediatric population pharmacokinetic model.**

A total of 67 patients (50 children aged 13 months to 12 years, 5 infants aged 6 to 12 months, and 12 infants aged <6 months) comprised the data set, which included 316 postdose penciclovir plasma concentrations. Children averaged 4.26 years in age (median, 3.67 years; range, 0.09 to 11.94 years); BW averaged 17.5 kg (median, 15.4 kg; range, 3.2 to 61.7 kg) and was correlated with age. Males slightly outnumbered females 35 (52.2%) to 32 (47.8%). Racial diversity prevailed: 21 (31.3%) Caucasian, 18 (26.9%) Black, 3 Native American (4.5%), 1 (1.5%) Asian, and 24 (35.8%) mixed or other. Each patient contributed three to five blood samples to the pharmacokinetic analysis.

The one-compartment model was fitted with clearance and volume allometrically scaled by BW to the powers 0.75 and 1.0, respectively, as had been done in the previous pediatric study (19). Diagnostics plots for the model (model 1) indicated clearances in infants needed no adjustment, but the $k_a$ was smaller in infants than in older children.

A new model was proposed (model 2) which incorporated two additional parameters for the effect of a maturation factor (MF) on TVKA as follows:

$$\text{MF} = \frac{\text{PCA}^{0.5}}{(\theta_0 + \text{PCA}^{0.5})}$$

$$\text{TVKA} = \theta_0 \cdot \text{MF}$$

Full maturity is indicated by $\text{MF} = 1$. MF increases from 0 to 1 based on a sigmoid $E_{\text{max}}$ model parameterized in terms of $\theta_a$, the sigmoidicity parameter, and $\theta_0$, the postconceptional age to reach half of full maturity. Model 2 was fitted and its goodness of fit as measured by the log likelihood function was significantly better than model 1 ($\chi^2 = 586.463 - 541.555 = 44.908$, $P < 0.0001$).

Models with additional parameters (model 3, model 4, model 5, and model 6) were proposed, but the additional parameters were not statistically significant. Three parameters to estimate the bioavailability fraction ($F1$) as a function of MF (two parameters for the MF and one parameter for the variance of the random effect related to $F1$) were not significant when added to model 1 or model 2 (model 3 versus model 1: $\chi^2 = 543.361 - 541.555 = 1.806$, $P > 0.2$; model 4 versus model 2: $\chi^2 = 586.552 - 586.463 = 0.089$, $P > 0.2$). Two parameters added to model 2 for a separate MF on CL were not statistically significant (model 5 versus model 2: $\chi^2 = 586.499 - 586.463 = 0.036$, $P > 0.2$). An added parameter to estimate the exponent for BW in the expression for clearance was estimated as 0.767 and was not statistically significant different than the assumed value of 0.75 (model 6 versus model 2: $\chi^2 = 586.681 - 586.463 = 0.218$, $P > 0.2$). Model 2 was adopted as the final model based on these statistical comparisons (Table 4). The CV for unexplained intersubject variability in apparent clearance was 21%. The residual CV ranged from 13% to 18% at expected concentrations from 5.0 to 0.5 $\mu g/ml$.

The visual predictive check by BW groups (>3 to 7 kg, >7 to 12 kg, and >12 kg) showed good agreement of the observed concentration data and model with the data centered near the 90th percentile (median) and ~10% of the 316 observations outside the 90% prediction intervals. Estimates of pharmacokinetic exposure (i.e., AUC and $C_{\text{max}}$) subsequently were computed using model 2 (Table 5). Model-based estimates of penciclovir exposure in infants <6 months averaged less than one-half (AUC) or one-third ($C_{\text{max}}$) of that for all other age groups for infants and children. Infants <6 months in age ($n = 12$) had a mean AUC = 3.69 ± 1.19 $\mu g \cdot h/ml$ and a mean $C_{\text{max}} = 0.79 \pm 0.31 \mu g/ml$.

The final model (model 2) depended upon BW in kilograms and postconceptional age in months (PCA), assuming a full-term birth at 9 months postconception. The population TV of the pharmacokinetic parameters (CL, $V$, and $k_a$) of penciclovir were expressed in terms of the penciclovir dose and were estimated in the final model as follows:

$$\text{TVCL} = 29.6 \cdot (\text{BW/20})^{0.75} \text{ liters/h}$$

$$\text{TVV} = 55.7 \cdot (\text{BW/20}) \text{ liters}$$

$$\text{TVk}_a = 5.48 \cdot (\text{BW/20}) \text{ h}^{-1},$$

where $\text{MF} = \frac{\text{PCA}^{0.87}}{(21.1^{0.87} + \text{PCA}^{0.87})}$

and $\text{PCA} = (9/12 + \text{age}) \cdot 12$ months, (1)

where age is given in units of years.

In these equations, TVCL and TVV are expressed in terms of the penciclovir dose. MF, the maturation factor on $k_a$, increases from 0 to 1, based on a sigmoid $E_{\text{max}}$ model, parameterized in terms of 3.87, the sigmoid parameter and 21.1, the PCA to reach half of full maturity.

The model can be reexpressed in terms of the penciclovir equivalent dose by multiplying both TVCL and TVV by 0.7884
to adjust for difference in molecular weight (MW) between famciclovir (321.3 g/mol) and penciclovir (253.3 g/mol). Thus, the model-based oral clearance (CL/F) of penciclovir is given by the equation:

\[
\frac{CL}{F} = \frac{MW_{penciclovir}}{MW_{famciclovir}} \cdot TVCL = 0.7884 \cdot TVCL \\
= 23.3 \cdot (BW/20)^{0.75} \text{ liters/h}
\]

and the CL/F of penciclovir for a typical 20-kg child is predicted to be 23.3 liters/h.

The relationship between the oral clearance of penciclovir (model-based) and BW in all 67 pediatric patients included in the population pharmacokinetic analysis is illustrated in Fig. 3. The data were fitted to an empirical power model (CL/F = \(A \cdot BW^\alpha\)), resulting in the following equation:

\[
\frac{CL}{F} = 2.3873 \cdot BW^{0.7658}
\]

As seen in Fig. 3, this function is practically superimposing equation 2 (“modeled CL/F”). By dividing both sides of equation 3 by BW, weight-normalized oral clearance (liters/h/kg) is seen to be inversely related to BW. Penciclovir weight-normalized oral clearance generally increased when BW decreased (Fig. 4).

### TABLE 5. Estimates of penciclovir pharmacokinetic exposure measures by age group using the population pharmacokinetic model 2

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of subjects</th>
<th>Mean ± SD AUC (μg • h/ml)</th>
<th>Mean ± SD C_{\text{max}} (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 months</td>
<td>12</td>
<td>3.69 ± 1.19</td>
<td>0.79 ± 0.31</td>
</tr>
<tr>
<td>6 to 12 months</td>
<td>5</td>
<td>8.52 ± 1.74</td>
<td>3.04 ± 0.92</td>
</tr>
<tr>
<td>13 months to &lt;2 years</td>
<td>10</td>
<td>7.77 ± 2.28</td>
<td>3.41 ± 0.61</td>
</tr>
<tr>
<td>2 to &lt;6 years</td>
<td>23</td>
<td>7.86 ± 1.77</td>
<td>3.21 ± 0.79</td>
</tr>
<tr>
<td>6 to &lt;12 years</td>
<td>17</td>
<td>9.62 ± 1.68</td>
<td>3.49 ± 0.77</td>
</tr>
</tbody>
</table>

**Updated dosing recommendations.** As presented above, the infants younger than 6 months showed considerably lower exposure than those between 6 and 12 years of age. To match the exposure (penciclovir AUC) seen in adults after a single 500-mg dose (8.94 μg • h/ml) (19), the infants younger than 6 months are predicted to require doses at least two to three times higher than those actually given in the present study. Since the safety for such higher doses of famciclovir was not established in patients younger than 6 months of age, the updated dosing scheme of famciclovir for pediatric patients covers the age range from 6 months to 12 years.

Based on the presented pharmacokinetic data above and the population pharmacokinetic model, an eight-step dosing scheme was developed for pediatric patients between 6 months and 12 years of age, aiming to achieve the target exposure (i.e., the exposure seen in adults after a single 500-mg dose). Starting from equation 1 and substituting TVCL by famciclovir exposure (penciclovir AUC) seen in adults after a single 500-mg dose)

\[
\frac{CL}{F} = \theta_1 (BW/20)^{0.75} \times \exp(\eta_{CL}) \\
V' = \theta_2 (BW/20) \times \exp(\eta_V)
\]

where CL and \(V'\) as in model 1

\[
MF = PCA^{0.06}(BW/20)^{0.75} \\
k_a = \theta_3 \times \exp(\eta_{k_a})
\]

the CL and \(V'\) as in model 1

\[
MF = PCA^{0.06}(BW/20)^{0.75} \\
F1 = \theta_4 \times \exp(\eta_{F1})
\]

and \(F1\) depend on separate MFs

\[
MF = PCA^{0.06}(BW/20)^{0.75} \\
F1 = \theta_5 \times \exp(\eta_{F1})
\]

and \(F1\) depend on separate MFs

\[
MF = PCA^{0.06}(BW/20)^{0.75} \\
F1 = \theta_6 \times \exp(\eta_{F1})
\]

and the CL depends on separate MFs.
dose/penciclovir AUC, the theoretical famciclovir dose to match the adult AUC (8.94 μg · h/ml) is given by:

\[
\text{famciclovir dose (mg)} = 29.6 \cdot (\text{BW/20})^{0.75} \cdot 8.94
\]

These theoretical doses are listed in Table 6 for the lower and upper BW limits of each of the eight BW groups, together with the proposed doses. The proposed dose is at the lower limit of the theoretical dose range for the lowest BW group (6 to 8 kg) and near the middle of the theoretical range of doses for all other BW groups.

Subsequently, all 55 patients between 6 months and 12 years included in the population pharmacokinetic analysis were assumed to receive a famciclovir dose according to the eight-step dosing scheme shown in Table 6, and the model-based individual AUC values of penciclovir for these doses were calculated. In Fig. 5, these AUCs are plotted against BW. The graph also shows the target AUC (i.e., mean and range of AUCs observed in healthy adult volunteers after a single 500-mg dose of famciclovir). The individual values are equally distributed around the target mean and 51 (93%) of the 55 patients show values within the range seen in adults.

**TABLE 6. Theoretical doses of famciclovir to achieve the target exposure in pediatric patients aged 6 months to 12 years and proposed dose according to an eight-step dosing scheme**

<table>
<thead>
<tr>
<th>Body wt (kg)</th>
<th>Theoreticala</th>
<th>According to eight-step dosing scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 to 8</td>
<td>100–139</td>
<td>100</td>
</tr>
<tr>
<td>9 to 11</td>
<td>139–175</td>
<td>150</td>
</tr>
<tr>
<td>12 to 15</td>
<td>175–219</td>
<td>200</td>
</tr>
<tr>
<td>16 to 20</td>
<td>219–270</td>
<td>250</td>
</tr>
<tr>
<td>21 to 26</td>
<td>270–327</td>
<td>300</td>
</tr>
<tr>
<td>27 to 33</td>
<td>327–370</td>
<td>350</td>
</tr>
<tr>
<td>34 to 40</td>
<td>390–449</td>
<td>425</td>
</tr>
<tr>
<td>≥41</td>
<td>≥449</td>
<td>500</td>
</tr>
</tbody>
</table>

*a Theoretical dose = 29.6 · (BW/20)0.75 · AUC, where BW is the body weight and AUC defines the mean exposure seen in adults (n = 24) after a single 500-mg dose of famciclovir (mean AUC = 8.94 μg · h/ml; range, 6.31 to 11.84 μg · h/ml). The lower (upper) BW limit used in the computation of the theoretical dose range begins at −0.5 kg (+0.5 kg) from the integer weight limit.

**FIG. 5.** Model-based estimates of AUC of penciclovir versus body weight in pediatric patients (n = 55) between 6 months and 12 years given a single dose of famciclovir according to the proposed eight-step dosing table. The squares represent the model-based individual values. The middle, lower and upper horizontal lines represent the mean (8.94 μg · h/ml), minimum (6.31 μg · h/ml), and maximum (11.84 μg · h/ml), respectively, in adults (n = 24) after a single 500-mg dose (19).

**DISCUSSION**

The present single-dose famciclovir pharmacokinetic study extends previous investigations to infants 1 to 12 months of age. The basis for dosing famciclovir in infants originated from data accumulated in older children (19), wherein BW was shown to be the most important factor in penciclovir pharmacokinetics. This is in keeping with expected characteristics of a drug with low protein binding that distributes in total body water and is predominantly renally excreted (17), as is the case for penciclovir (10). For children 1 to 12 years old, famciclovir dosing was calculated based on the established relationship between penciclovir clearance and BW in order to achieve the target exposure (i.e., the penciclovir AUC seen in adults after a 500-mg dose of famciclovir) (19). It was subsequently assumed that clearance of penciclovir in infants younger than 12 months of age would be lower than that extrapolated from the relationship between penciclovir clearance and BW in older children due to their physiologically immature kidneys (11, 25, 28). Glomerular filtration and active tubular secretion are involved in the renal elimination of penciclovir (10), and both processes have been reported to be immature at birth, reaching adult levels during the first year of life (11, 25). As such, a renal MF was introduced in the equation describing the relationship between penciclovir clearance and the infant’s BW. Accordingly, the infant dosage algorithm derived from the modified model and used in the current single-dose study resulted in relatively lower doses (mg) per BW (kg) in the infants younger than 6 months of age (mean, 6.6 and 9.4 mg/kg; see Table 3) than in the older infants (13.5 mg/kg), as well as in the children of the previous study that comprised three age groups (12.2 to 13.0 mg/kg) (19).

Actually, penciclovir concentrations in infants aged 6 to 12 months were similar to those observed in children aged 1 to 12 years and in adults after a single 500-mg dose of famciclovir (19). The mean estimate of AUC was 8.52 μg · h/ml in the 6- to 12-month age group compared to mean estimates of between 7.77 and 9.62 μg · h/ml in the age groups between 1 and 12 years (Table 5). In adults, mean AUC was 8.94 μg · h/ml. In
contrast, systemic exposure to penciclovir in infants 1 month to <6 months of age was considerably lower, the AUC estimate being 3.69 µg · h/ml (Table 5). In addition, the penciclovir concentration-time profiles were relatively flat in these infants, without a distinct peak in most profiles (Fig. 1). These observations suggest that unlike acyclovir (28), the apparent oral clearance of penciclovir is not reduced in young infants due to an immature kidney function, thus disproving the assumption that a renal MF is needed for deriving dosages in the 1- to <6-month-old age group.

In order to optimize the dose of famciclovir in the pediatric population, we conducted a series of population pharmacokinetic analyses of penciclovir using data from children and most recently infants. The first analysis included 41 children with HSV and VZV infections (aged 1 to 12 years) from the study reported by Saez-Llorens et al. (19). This model estimated the typical oral clearance of penciclovir as a function of BW (i.e., CL/F = 23.8 · [BW/20]0.75), which was used to predict famciclovir doses to match the targeted penciclovir AUC. An eight-step dosing regimen was subsequently derived for pediatric patients aged 1 to 12 years and was used in the multiple-dose phase of the study reported by Saez-Llorens et al. (19). The subsequent analysis reported herein combined the data obtained in older children (19) with the 17 infants described in the first part of this study. The typical oral clearance of penciclovir in the latest model [CL/F = 23.3 · (BW/20)^0.75] was nearly identical to that described in the first model and also supported that a relationship between clearance and BW was close to proportional. Importantly, the updated model found no effect of renal maturation on apparent oral clearance. However, the updated model included a MF on the input rate k1, which depended upon postconceptual age: MF increased from 0.99. The effect of MF on the concentration-time profile of penciclovir in infants and children 1 month to 12 years of age is illustrated in Fig. 6. The profile is getting flatter and T_{max} is being shifted to later times the younger the subject.

Conversion of the prodrug famciclovir to the active metabolite penciclovir occurs in two steps (i.e., deacetylation of famciclovir to 6-deoxy penciclovir, followed by oxidation of the intermediate metabolite to penciclovir). In adults and children 1 to 12 years of age, it has been shown that famciclovir is rapidly absorbed and extensively metabolized to penciclovir (10, 15, 19, 22). Plasma concentrations of 6-deoxypenciclovir were typically lower than that of penciclovir and were detectable only for a short period after dosing (15, 19). As shown in Fig. 1, this observation is also valid for the infants in our study.

Despite the apparent similarities of 6-deoxypenciclovir to penciclovir ratios between the pediatric age groups, it is worthwhile to consider the enzymes involved in the conversion of famciclovir to penciclovir. The deacetylation is catalyzed by esterases, the oxidation by aldehyde oxidase (10). There are reports that activity of these enzymes is reduced in infants (25, 26). Tayama et al. recently reported that aldehyde oxidase activity rapidly increases with the patient’s age up to ~1 year (26). Thus, conversion of famciclovir to penciclovir could be affected in infants, resulting in a delayed appearance of penciclovir in plasma and, potentially, also in a reduction of the amount of penciclovir reaching the systemic circulation. The first effect was actually observed, as discussed above (i.e., effect of MF on k1). The second effect (i.e., smaller amount converted) may have been compensated by a somewhat slower renal elimination of penciclovir in the very young infants, so that the net affect is close to zero and apparent oral clearance is not dependent on a MF. The latter may also explain the difference in the disposition of penciclovir and acyclovir in very young infants, since acyclovir is not dependent on metabolic activation.

Another factor which could have contributed to the observed differences in the disposition kinetics of penciclovir between young infants and children is slow gastric emptying in neonates and young infants, resulting in a slower rate at which orally administered drugs are absorbed in these populations compared to older infants/children or adults (11, 25, 27). Thus, in young infants treated with famciclovir, famciclovir absorption as well as its conversion to penciclovir could be delayed to a certain extent, resulting in a delay of the time to achieve the maximal plasma concentration, as observed in our study.

The population pharmacokinetic analysis has led us to recommend an eight-step dosing scheme for oral famciclovir in pediatric patients aged 6 months to 12 years, one that targets the mean AUC in adults (i.e., 8.94 µg · h/ml) after a 500-mg dose (Table 6). The recommended dosage regimen is expected to achieve optimal penciclovir concentrations, as illustrated in Fig. 5. Although the model would allow us to derive doses also for infants below 6 months of age and weighing <6 kg, we currently cannot recommend such doses since they would be considerably higher than those actually tested in our study. The proposed dosages for infants and children 6 months to 12 years of age remain to be tested in prospective clinical trials; however, exploratory efficacy data in children with active HSV and VZV infections has been encouraging (19).

Recently, Ogungbenro et al. (14) reported another population pharmacokinetics analysis of penciclovir, which was done to develop optimal sampling windows for future pediatric studies. These authors used pharmacokinetic data from studies in 46 adults and 23 children aged 2 to 17 years. The children were either immunocompromised or had hepatitis B infection. The
population model shows some differences compared to our model. It is a two-compartment model and includes bioavailability as a separate model parameter. The clearance of penciclovir depends on BW, age, and the creatinine clearance of the patient, whereas in our model penciclovir clearance depends only on BW (see equations 1 to 3). Nonetheless, the two models seem to give similar results when used to predict penciclovir clearance for a given individual. For an 8.1-year-old child with a BW of 29.5 kg and a creatinine clearance of 58.2 mI/min (mean values for the children in the Ogungbenro paper [14]), the CL/F of penciclovir is 29.7 liters/h, whereas our model (equation 2) predicts a CL/F value of 31.2 liters/h.

Famiclovir was well tolerated in infants 1 to 12 months of age. Similar to adults and older children (1, 3, 5, 6, 19, 24), the most frequent AEs in the 18 infants given famciclovir were vomiting, diarrhea, pyrexia, and dehydration. No infants discontinued famciclovir for safety reasons, and none of the infants had serious drug-related AEs. There were no signals of significant central nervous system, hepatic, or hematologic toxicities; nor unexpected changes in hematology or clinical chemistry parameters; and no trends indicative of hepatic or renal toxicities, neutropenia, or thrombocytopenia. A 1-month-old male infant experienced a shift from normal at baseline to grade 3 toxicity for hemoglobin, although this was of questionable clinical relevance. Infants between the ages of 1 and 12 months tolerated the single-dose oral famciclovir sprinkle formulation well. Similar to that observed in older children given the oral sprinkle famciclovir formulation (19), the majority of caregivers and study personnel considered the famciclovir pediatric formulation to be well or very well accepted by the infants.

In summary, a single dose of famciclovir oral pediatric formulation was safe and well tolerated in infants 1 to 12 months of age with active, suspected, or latent HSV infection. Combining single-dose data in infants with those of older children allowed us to derive an eight-step weight-based dosage scheme for infants and children between 6 months and 12 years, achieving a target exposure similar to adults after a 500-mg dose. Famiclovir oral sprinkle formulation appears suitable for use in infants who require treatment for HSV infections.

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REFERENCES


