Published in final edited form as:

Pediatr Infect Dis J. 2014 January ; 33(1): 42–49. doi:10.1097/01.inf.0000435509.75114.3d.

Population Pharmacokinetics of Intravenous Acyclovir in Preterm and Term Infants

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Abstract

Background—Acyclovir is used to treat herpes infections in preterm and term infants; however, the influence of maturation on drug disposition and dosing requirements is poorly characterized in this population.

Methods—We administered intravenous acyclovir to preterm and term infants <31 days postnatal age and collected plasma samples. We performed a population pharmacokinetic analysis. The primary pharmacodynamic target was acyclovir concentration ≥3 mg/L for ≥50% of the dosing interval. The final model was simulated using infant data from a clinical database.

Results—The analysis included 28 infants (median 30 weeks gestation). Acyclovir pharmacokinetics was described by a 1-compartment model: clearance (L/h/kg) = 0.305 × (postmenstrual age [PMA]/31.3 weeks)$^{3.02}$. This equation predicts a 4.5-fold increase in clearance from 25 to 41 weeks PMA. With proposed dosing, the pharmacodynamic target was achieved in 91% of infants: 20 mg/kg every 12 hours in infants <30 weeks PMA; 20 mg/kg every 8 hours in infants 30 to <36 weeks PMA; 20 mg/kg every 6 hours in infants 36–41 weeks PMA.

Conclusions—Acyclovir clearance increased with infant maturation. A dosing strategy based on PMA accounted for developmental changes in acyclovir disposition to achieve the surrogate pharmacodynamic target in the majority of infants.

Keywords

herpes simplex virus; preterm infants; acyclovir

Intravenous acyclovir is routinely used to treat herpes simplex virus (HSV) infection in preterm and term infants. Although acyclovir has reduced mortality from neonatal HSV

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Conflicts of interest and sources of funding: This work was funded under NICHD contract HHSN2752010000031 for the Pediatric Trials Network.

infections, neurodevelopmental impairment among survivors remains high.[1–3] Persistence of HSV in the cerebrospinal fluid following completion of intravenous antiviral therapy is an independent risk factor for worse outcomes,[4] suggesting that poorer outcomes may be related to inadequate antiviral exposure.[5]

Acyclovir dosing recommendations for infants vary. The Food and Drug Administration (FDA) label-approved dosing (10 mg/kg every 8 hours) differs from more recent evidence showing reduced mortality with a higher dose (20 mg/kg every 8 hours), the current standard of care.[2,6] Pediatric dosing handbooks recommend a 20 mg/kg/dose with variable dosing intervals determined by age stratifications: Redbook and Lexicomp recommend an 8-hour dosing interval for all infants, whereas the Harriet Lane Handbook and Neofax recommend dosing intervals stratified by gestational age (GA) and postmenstrual age (PMA), respectively.[7–10] More importantly, pharmacokinetic (PK) trials supporting acyclovir dosing are limited, especially in preterm infants.

Acyclovir is primarily cleared renally through a combination of glomerular filtration and tubular secretion. In adults, volume of distribution (V) at steady state is about two thirds of body weight,[11] and linear PK are observed in the range of 0.5–15 mg/kg/dose.[11,12] In adults with normal renal function, acyclovir's elimination half-life ($t_{1/2}$) is 3 hours.[12] In infants with normal renal function, elimination $t_{1/2}$ is approximately 4 hours as reported by 2 studies that did not report the GA distribution[12,13] and 5 hours in a study including preterm infants (median GA 38 weeks).[14] In a cohort of 22 infants <3 months of age with a history of HSV infection, all HSV isolates had an acyclovir half maximal inhibitory concentration (IC50) of <1 mg/L.[15] Acyclovir levels in cerebrospinal fluid (CSF) are approximately 30–50% of corresponding plasma levels.[12] Dosing designed to maintain plasma concentrations ≥3 mg/L would be necessary to maintain an acyclovir concentration ≥1 mg/L in the CSF. For safety, plasma acyclovir concentrations of 50–70 mg/L have been associated with neurotoxicity in a small subset of patients.[16–18]

Small sample sizes and infrequent inclusion of preterm infants in prior acyclovir PK studies prevented the characterization of acyclovir PK in the setting of rapid physiologic maturation. This study aims to characterize acyclovir PK and dosing requirements in preterm and term infants.

METHODS

Study Design

Two studies contributed the data for this report. Study 1 was a single-center, open-label, PK study of infants 23–42 weeks GA and <61 days postnatal age (PNA) with suspected systemic infection. Study 2 was a multi-center, open-label, PK study of infants 23–34 weeks GA and <45 days PNA with suspected HSV infection. Exclusion criteria included: history of anaphylaxis attributed to acyclovir; renal dysfunction indicated by serum creatinine (SCR) >1.7 mg/dL; and urine output <0.5 mL/kg/hour over the previous 12 hours (Study 2 only). Acyclovir was administered intravenously as a 1-hour infusion for up to 3 days. Dosing in Study 1 was 500 mg/m^2 every 8 hours. Dosing in Study 2 was determined by GA and PNA: 10 mg/kg every 12 hours (23–29 weeks GA and <14 days PNA); 20 mg/kg every 12 hours (23–29 weeks GA and 14–44 days PNA); and 20 mg/kg every 8 hours (30–34 weeks GA and <45 days PNA). Clinical data collected included the following: demographics (e.g., GA, PNA, birth weight, current weight, race, sex, ethnicity), laboratory values collected as part of routine medical care (SCR, liver function tests, albumin), concomitant medications (other antimicrobials, vasopressors), and microbiological cultures. The study was approved by institutional review boards at each site and was conducted in accordance with the Helsinki Declaration; the legally authorized guardian provided informed consent.

PK Sample Collection

Blood was collected (100–200 μL) around the first dose, at steady state, and after the last dose. In Study 1, upon end of the first acyclovir infusion, samples were collected within 5 minutes, at 2–4 hours, and at 6–8 hours. Upon end of infusion at steady state (doses 5–15), samples were collected within 5 minutes, at 2–4 hours, 6–8 hours, and immediately prior to the next dose. In Study 2, upon end of the first acyclovir infusion, samples were collected within 15 minutes and within 30 minutes prior to the second dose. Upon end of infusion at steady state (doses 5–15), samples were collected within 15 minutes, at 2–3 hours, and within 30 minutes prior to the next dose. After the end of the last infusion, samples were collected at 15–18 hours.

Bioanalytical Assay

Plasma samples were analyzed for acyclovir concentrations using an LC/MS/MS bioanalytical assay validated according to FDA guidance.[19] Dicloxacillin was used as the internal standard. Drug was extracted from plasma using protein precipitation with acetonitrile. The lower limit of quantitation was 0.1 mg/L. The calibration range was 0.1–50 mg/L. The intra-day and inter-day coefficients of variation in drug concentration measurements were 14% and 8%, respectively. Samples from both studies were run with the same bioanalytical assay. Plasma samples were stored up to 22 months prior to analysis.

Population PK Analysis

Data were analyzed using nonlinear mixed effects modeling implemented in NONMEM 7 software (ICON, Ellicott City, MD, USA) using the first-order conditional estimation method with interaction. One- and 2-compartment structural models and proportional and proportional plus additive residual error models were explored. Random effects on structural model parameters were considered supported by the data if shrinkage was <30%. Weight was included a priori as a covariate for V and clearance (CL) in the base model. Diagnostic plots included the following: observed concentration versus predicted concentration and versus individual predicted concentration; weighted residuals and conditional weighted residuals versus predicted concentration and versus time after dose; conditional weighted residuals histogram; and observed versus predicted and individual predicted concentrations by infant. Diagnostic plots and objective function value (OFV) were used to assess goodness of fit.

Once the base model was identified, covariates were investigated for their influence on PK parameters (e.g., CL and V). Continuous covariates evaluated were PNA, GA, PMA, and SCR; categorical covariates included race, ethnicity, sex, and use of concomitant vasopressin, dopamine, or epinephrine. Missing covariate values were imputed using the closest value available for that participant using either a carry-forward approach or back-fill approach depending on which date was closest. If there was a tie in the number of days from the prior and next available value, then the prior available value was used (i.e., carried forward). Individual participant ηCLs and ηVs were plotted against covariates to graphically assess relationships between variability in PK parameters and covariates. Covariates with a discernible graphical relationship to ηCL and ηV were evaluated for inclusion in the final model. The threshold for significance of a single covariate was reduction of the objective function by more than 3.84 ($P<0.05$). A forward-addition, backward-elimination approach to covariate selection was planned for use if more than 1 covariate was found to be significant for CL or V.

Model Evaluation

The robustness and stability of the final PK model was assessed by nonparametric bootstrap using WINGS for NONMEM version 7 (Auckland, NZ), where the original data were resampled, with each individual participant being a sampling unit. One thousand datasets were generated and fit to the final model to assess precision of the PK parameters and agreement between final model and bootstrap parameter estimates.

A standardized visual predictive check (VPC) was conducted to compare observed acyclovir concentrations at each time point as a percentile of 1000 simulated datasets from the final model.[20] One advantage of the standardized VPC is that binning of concentrations into arbitrary time intervals is unnecessary, and differences in dosing are accounted for as the data represent percentiles. The threshold for good agreement between simulated and observed data was <15% of observed concentrations falling outside the 5^{th} to 95^{th} percentile range.

Dose-exposure Assessment

The surrogate efficacy pharmacodynamic (PD) targets were acyclovir maximum concentration at steady state ($Cmax_{ss}$), steady-state plasma concentrations at 50% of the dosing interval ($C50_{ss}$), and minimum concentration at steady state ($Cmin_{ss}$) ≥3 mg/L and ≥1 mg/L. $C50_{ss}$ was chosen as a conservative, primary surrogate PD target due to the severe morbidities associated with HSV encephalitis in infants.[21] These PD targets were chosen based on HSV IC50 = 1 mg/L[15] and reported acyclovir central nervous system penetration of approximately 30–50%.[12] Based on case report data in children and adults, surrogate safety targets of $Cmax_{ss}$ <50 mg/L (primary) and <70 mg/L were chosen.[16–18] Study dosing and individual Bayesian estimates of PK parameters for each infant in the study population were used to calculate PD target attainment. The following equations were used:

$Cmax_{ss}=((Dose/t_{in})/CL) * (1-e^{(-Ke*tin)}) * (1/1-e^{(-Ke*tau)})$, where dose (mg) is the first administered dose, t_{in} is infusion duration (1 hour for both studies), Ke (h^{-1}) is elimination rate constant, and t_{au} (h) is the dosing interval;

$C50_{ss}= Cmax_{ss} * e^{(-Ke*(tau-tin)*0.5))}$;

$Cmin_{ss}= Cmax_{ss} * e^{(-Ke*(tau-tin))}$.

The proportions of infants in the study population meeting the PD and safety targets were determined.

We used data from a de-identified dataset containing information on infants from more than 300 neonatal intensive care units to simulate acyclovir exposures in a larger population. The analysis was approved by the Duke University Institutional Review Board without the need for written informed consent as the data were collected without patient identifiers.[22,23] The ranges of GA, PNA, PMA, and SCR (see Table 1) in our study population were used to identify infants for our simulations. Infants lacking a blood culture or exposure to antibiotic therapy were excluded. A random sample of 1000 infants, from the remaining dataset, was included in the simulations. The proportions of infants meeting the PD and safety targets were determined.

Safety

The safety cohort consisted of infants who received ≥1 dose of study medication. All adverse events (AEs) were recorded from the time of first study drug administration through 3 days following the last dose of study drug. All suspected AEs and serious AEs (SAEs) were recorded from time of first study drug administration through 10 days following the last study drug administration.

RESULTS

Study Population and PK Specimens

Ninety-two plasma samples from 30 infants were obtained. Nine (9.8%) samples were suspected to be drawn during infusion or flush and were excluded prior to model development. The final model was used to screen for extreme outlier concentrations (>10-fold difference from predicted concentration), suggesting sample contamination or other collection or dosing error. Two additional (2.2%) samples were identified as outliers and excluded after identification of the final model. This resulted in exclusion of 2 participants (each with 1 plasma sample). The final dataset included 81 samples from 28 infants with relatively normal renal function: 36 samples from 12 infants in Study 1 and 45 samples from 16 infants in Study 2. The median (range) number of samples per infant regardless of GA at birth (<34 vs. ≥34 weeks) was 3 samples (1–5). The critically ill status of the infants and timing of PK samples with standard-of-care laboratory tests prevented the collection of all planned timed samples. Demographics at the time of first PK sample are shown in Table 1. The median (range) duration of drug administration was 1.0 hour (0.4–1.2), and the median acyclovir concentration was 5.8 mg/L (0.7–110).

Population PK Model Building

A 1-compartment base model was selected, as a 2-compartment model did not significantly improve goodness of fit. A proportional residual error model was selected over a proportional plus additive model because the latter did not improve goodness of fit. As a plot of individual participant deviations from the typical population PK parameter values (η) for CL and V suggested correlation, covariance between these parameters was estimated. Random effects were supported on CL and V with shrinkage <6%. Covariate models for weight were explored with an estimated or fixed (3/4 or 1) exponent; an exponent of 1 was included in the base model.

Plots of PMA, PNA, GA, and SCR were suggestive of a relationship with ηCL; no covariates were suggestive of a relationship with ηV other than weight. PMA was identified as the most significant age covariate for acyclovir CL. SCR was the only significant non-age covariate during the univariate analysis for CL. Addition of SCR to the PMA model did not significantly reduce the OFV. Thus the final model includes weight and PMA as covariates for CL and weight as the covariate for V. The final model predicts a 4.5-fold increase in CL (and a 4.5-fold decrease in $t_{1/2}$) from 25 to 41 weeks PMA. Covariate models for weight were again explored with an estimated or fixed (3/4 or 1) exponent in the final model. Compared with an exponent of 1, the OFV decreased by 9.38 for an estimated exponent (1.46) and increased by 7.74 for an exponent of 3/4. An exponent of 1 was included in the final model. Final model diagnostic plots show minimal bias in observed vs. predicted concentrations or in residuals (Figure 1). Significant model-building steps are shown in Table 2.

Population PK Model Evaluation

Of 1000 final model bootstrap runs, 98.8% converged. All bootstrap runs were included in the analysis. The final model had a high level of precision between all final model and bootstrap parameter estimates with differences of <7.2% (Table 3). The standardized VPC indicated good agreement between observed and model-simulated concentrations, with 7.4% (6/81) of observations outside the 90% prediction interval. Observations were approximately symmetric about the 50th percentile line (Figure 2).

Individual Bayesian PK Parameter Estimates

The median empirical Bayesian post-hoc parameter estimate for CL, 0.278 L/hr/kg, was within 10% of the typical population model estimate of 0.305 L/hr/kg. Comparing the youngest and oldest PMA cohorts, CL estimates increased 2.8-fold, V estimates were unchanged, and $t_{1/2}$ estimates decreased 3.4-fold (Table 4 and Figure 3).

Dose-exposure Assessment

Using the dosing infants received in the 2 trials, 28/28 infants (100%) had $C50_{ss}$ ≥3 mg/L. $Cmin_{ss}$ was ≥3 mg/L for 18/28 (64%) infants: 7/12 (58%) in Study 1 and 11/16 (69%) in Study 2. All (28/28) infants had steady-state concentrations ≥2 mg/L (twice the secondary PD target of 1 mg/L) throughout the dosing interval. Three out of 28 (11%) infants had $Cmax_{ss}$ ≥50 mg/L; these infants were in Study 1 and received doses of 31–53 mg/kg every 8 hours.

Based on the final PK model, a PMA-based dosing regimen was developed to account for developmental changes in acyclovir disposition in infants with relatively normal renal function: 20 mg/kg every 12 hours in infants <30 weeks PMA; 20 mg/kg every 8 hours in infants 30 to <36 weeks PMA; and 20 mg/kg every 6 hours in infants 36–41 weeks PMA.

The final PK model and proposed dosing regimens were used to predict acyclovir concentrations in 1000 randomly selected infants from a clinical care database. The PMA-based dosing regimen predicted 91% and 100% of infants would have $C50_{ss}$ ≥3 mg/L and ≥1 mg/L, respectively. Predicted $Cmax_{ss}$ safety thresholds of 50 and 70 mg/L were exceeded by 0.9% and 0.3% of infants, respectively. The PMA-based dosing regimen was superior to regimens found in commonly used pediatric dosing sources, including the FDA label. None of the earlier dosing regimens consistently achieved the PD target of $C50_{ss}$ ≥3 mg/L for ≥90% of infants (Table 5). Due to high correlation between ηCL and ηV and higher-than-expected inter-individual variability in V observed in the final model, simulations were also performed without inter-individual variability on V and showed similar results (data not shown).

Safety

Acyclovir was well tolerated. The safety cohort included 32 infants. This critically ill cohort had a history of the following conditions at baseline: respiratory, thoracic, and mediastinal disorders (78%); nervous system disorders (37%); and metabolic acidosis (19%). None of the evaluations for HSV (surface cultures [n=19], CSF polymerase chain reaction [PCR] [n=7]) were positive. Overall, 38 AEs were reported in 66% of the participants. Infants <14 days PNA and 23–29 weeks GA had the highest proportion of AEs (90%). Only 1 AE was considered related to study drug (worsening SCR), and study drug was discontinued in this participant. A total of 4 SAEs were reported in 4 infants (13%). Two of the SAEs were infant deaths: 1 due to nonketotic hyperglycinaemia and 1 due to sepsis. The other 2 SAEs were neuroblastoma and neonatal asphyxia. No SAEs were determined to be related to study drug. No episodes of neutropenia were reported as AEs. Fifteen infants (47%) received >80 mg/kg/day of acyclovir (range 87–158). Infants with SAEs received 75–103 mg/kg/day. One of 4 infants with SAEs had a predicted $Cmax_{ss}$ >50 mg/L.

DISCUSSION

This study evaluated the population PK of acyclovir in 28 preterm and term infants. A 1-compartment model appropriately described the data and was precise as evidenced by population CL and V point estimates nearly identical to the median bootstrap values and narrow 95% confidence intervals. A maturational change in acyclovir CL was included in

the final model through the PMA covariate. From 25–41 weeks PMA, the final model predicts a large (4.5-fold) increase in CL, and equivalent decrease in $t_{1/2}$.

This association was expected as acyclovir is primarily renally eliminated, and renal function rapidly develops with both advancing GA and PNA during the first months of life.[14,24] GA and PNA can vary considerably for a given value of PMA; however, the sample size of this study likely precluded identification of separate covariate effects of GA and PNA on CL. SCR was also a significant covariate (though with smaller effect than PMA), consistent with a prior study in 16 infants of median (range) 38 (27–40) weeks GA.[14] This study was limited to infants with relatively normal renal function; a study of infants with renal dysfunction would likely result in a stronger association between acyclovir clearance and SCR. While creatinine clearance is a good measure of renal function in adults, methods for calculating creatinine clearance in infants are sub-optimal, and we relied only on SCR for PK/PD modeling. There were no apparent age-related effects on acyclovir V; however, the ability to detect such a relationship may have been limited by the small sample size.

The acyclovir population CL estimates in the present study were similar to estimates reported in another population that included premature infants (typical CL 0.265 L/kg/h for an infant 38 weeks GA).[14] The median (range) V Bayesian estimates were 3.34 (0.29–10.85) L/kg, which is larger than values previously reported in adults (0.7 L/kg)[12] and in a study of 16 infants up to 3 months PNA (median [range] 1.0 [0.4–6.5] L/kg).[13] The differences in V in this study could be related to higher content of total body water and the critical condition of these infants.[25]

Inter-individual variability estimates for CL (52.8%) and V (85.0%) were larger than expected. For example, in a study of intravenous ganciclovir in 27 infants, inter-individual variability estimates for CL and V were 35% and 30%, respectively.[26] In another study of intravenous ganciclovir and oral valganciclovir in 24 infants, the estimated inter-individual variability CL was 28%.[27] A study of 9 infants (4 term and 5 preterm) found acyclovir levels varied widely among infants receiving the same dose but were correlated with the expected renal maturity of the individual infant.[28] However, it is possible that the large variability observed is an accurate reflection of variability in acyclovir disposition in preterm and term infants. In spite of this variability, however, the proposed dosing regimen achieved pre-specified surrogate efficacy targets.

Simulations of our proposed dosing regimens, compared with prior studies in adults and infants, predict more variable peak concentrations and overlapping trough concentrations. At doses of 15 mg/kg every 8 hours, reported $Cmax_{ss}$ in 2 adults and 4 infants was mean ± standard deviation 23 ± 0.2 mg/L and median (range) 22.7 (16.2–33.7) mg/L, respectively; $Cmin_{ss}$ was 2.0 ± 0.1 mg/L and 4.4 (1.5–23.9) mg/L, respectively.[12,28] Simulations of our proposed dosing regimen in infants with PMA 36–41 weeks predicts median (range) $Cmax_{ss}$ of 9.0 (1.3–79.6) mg/L and $Cmin_{ss}$ of 3.3 (0.8–9.7) mg/L.

Validated PD targets for acyclovir are lacking. In the absence of such targets, surrogate efficacy is often assessed by comparison of in vivo acyclovir concentrations to in vitro IC_{50} values for HSV clinical isolates. $C50_{ss}$ was chosen as a primary target in this study as a balance between a stringent target such as $Cmin_{ss,}$ while being more conservative than $Cmax_{ss}$.

Any acyclovir efficacy target must account for CSF penetration. A post-treatment reservoir of HSV in the central nervous system would increase the risk of recurrence and its attendant risks of poor neurodevelopmental outcomes for infants.[29] However, data relating CSF HSV PCR status to acyclovir CSF concentrations pre- and post-treatment are minimal in adults

and lacking in premature and term infants. In a study of nine adults with positive CSF HSV PCR at time of enrollment treated with 21 days of 1000 mg oral valacyclovir (acyclovir prodrug) three times daily, serial CSF HSV PCR measures on days 2, 10, and 20 were obtained. Four patients completed treatment and had a negative CSF HSV PCR status by day 10. The mean ± standard deviation of CSF concentrations collected from all patients peaked on day 2 at 1.46 ± 1.01 mg/L and were at a minimum (and nearly identical) on days 0 and 20 (∼0.8 ± 0.38 mg/L). Assuming similar CSF penetration in premature and term infants compared to adults, these data are supportive of our choice of 1 mg/L as an effective acyclovir concentration in CSF.[30] Future studies are needed in infants to identify the acyclovir exposure metrics in plasma, CSF, and other target organs that maximize efficacy.

Acyclovir concentrations associated with toxicity are not well defined in any age group. AEs reported with acyclovir include renal dysfunction, injection site reactions, seizures, and rare leucopenia and thrombocytopenia. Following acyclovir treatment for viral mucocutaneous infection or pneumonia, plasma acyclovir concentrations of 50–70 mg/L have been associated with toxicity in a small subset of patients.[16–18] Although 3/28 (10.7%) infants in the study population exceeded $Cmax_{ss}$ ≥50 mg/L with trial doses of 30–50 mg/kg every 8 hours, simulations in 1000 infants predict <1% of infants would exceed this safety target with the proposed dosing scheme.

We recommend a higher acyclovir dose (20 mg/kg every 6 hours) for infants 36–41 weeks PMA than has been prospectively shown to be safe.[2] Fifteen infants in our study received >80 mg/kg/day of acyclovir dosed every 8 hours, and none had SAEs attributed to acyclovir. The adverse effects most commonly associated with acyclovir are neutropenia and nephrotoxicity. Neutropenia can be easily detected by laboratory monitoring, and acyclovir dosing modifications in the setting of renal dysfunction are available. Considering the risk of death and long-term neurodevelopmental impairment associated with HSV infection, we think the risk-to-benefit ratio favors aggressive acyclovir dosing to ensure adequate exposure.

Acyclovir dosing for infants is improved, optimized, and simplified by this study. Of the 2 trials comprising this dataset, Study 1 used body surface area dosing unstratified by age, and Study 2 used 3 different weight-based dose levels in 3 age strata based on GA and PNA. Our proposed weight-based dosing regimen simplifies dosing to include only PMA. In addition, the use of real infant information from a clinical care database for simulations increases the likelihood that our simulation results will match results in clinical practice because the demographic distribution arises from infants with presumed systemic infections. Our proposed dosing achieves plasma acyclovir $C50_{ss}$ ≥3 mg/L in >90% of infants and outperforms dosing regimens found in current pediatric dosing handbooks. Our proposed dosing is consistent with a study of 66 infants (mean GA 38 weeks and 33% premature) with HSV that observed improved survival with a dose of 60 mg/kg/day vs. 30 mg/kg/day.[2]

The population PK of acyclovir in infants shows that PMA is associated with CL. A dosing strategy based on PMA was developed to account for developmental changes in acyclovir disposition in infants with relatively normal renal function: 20 mg/kg every 12 hours in infants <30 weeks PMA, 20 mg/kg every 8 hours in infants 30 to <36 weeks PMA, and 20 mg/kg every 6 hours in infants 36–41 weeks PMA. This dosing strategy achieved the surrogate PD target in the majority of infants.

Acknowledgments

The PTN Administrative Core Committee

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Dr. Sampson was supported by training grant T32GM086330 from the National Institute of General Medical Sciences. Dr. Lenfestey has received grant support from the Children’s Miracle Network. Dr. Kashuba has received support from Bristol-Myers Squibb, Boehringer Ingelheim, Merck, and GlaxoSmithKline. Dr. Anand receives support from Government Contract HHSN267200700051C (PI: Benjamin). Dr. Benjamin receives support from the United States government for his work in pediatric and neonatal clinical pharmacology (1R01HD057956-05, 1K24HD058735-05, and NICHD contract HHSN275201000003I) and the nonprofit organization Thrasher Research Fund for his work in neonatal candidiasis (www.thrasherresearch.org); he also receives research support from industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp). Dr. Capparelli receives salary support from the United States government (U54 HD071600-01) and research support from Trius, Cerexa Pharmaceuticals, Abbott, and Theravance. Dr. Cohen-Wolkowiez receives support for research from the National Institutes of Health (1K23HD064814), the Food and Drug Administration (1U01FD004858-01), the nonprofit organization Thrasher Research Fund (www.thrasherresearch.org), and from industry for drug development in adults and children (www.dcri.duke.edu/research/coi.jsp). Dr. Smith receives salary support for research from the National Institutes of Health and the U.S. Department of Health and Human Services (NICHD 1K23HD060040-01, DHHS-1R18AE000028-01, and HHSN267200700051C); he also receives research support from industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp). The remaining authors have no conflicts of interest to disclose.

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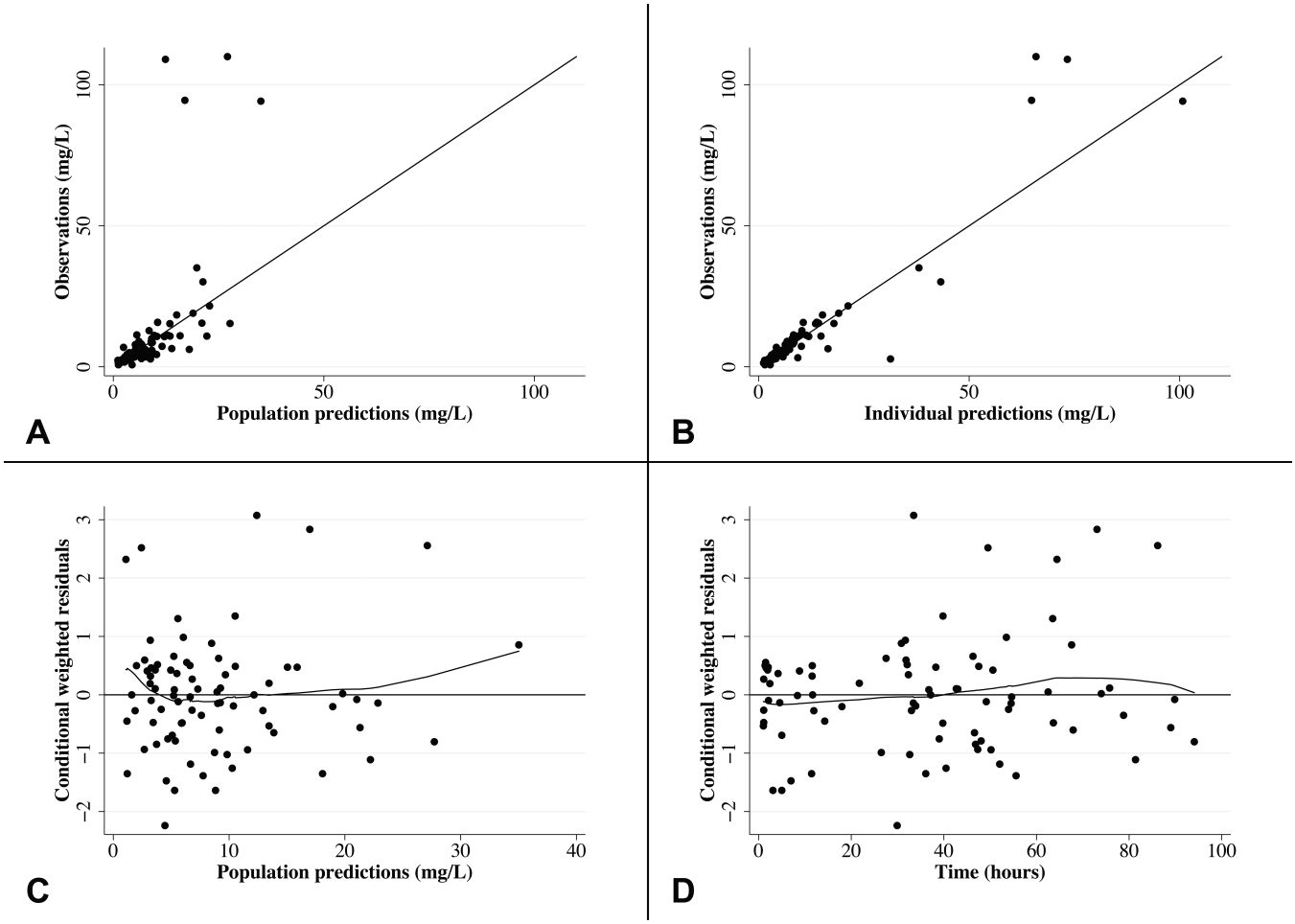

FIGURE 1.

Final population PK model diagnostic plots. (A) Observed vs. population predictions; (B) observed vs. individual predictions; (C) conditional weighted residuals vs. population predictions; (D) conditional weighted residuals vs. time since first dose. A locally weighted scatterplot smoothing line was fit to the data points in C and D.

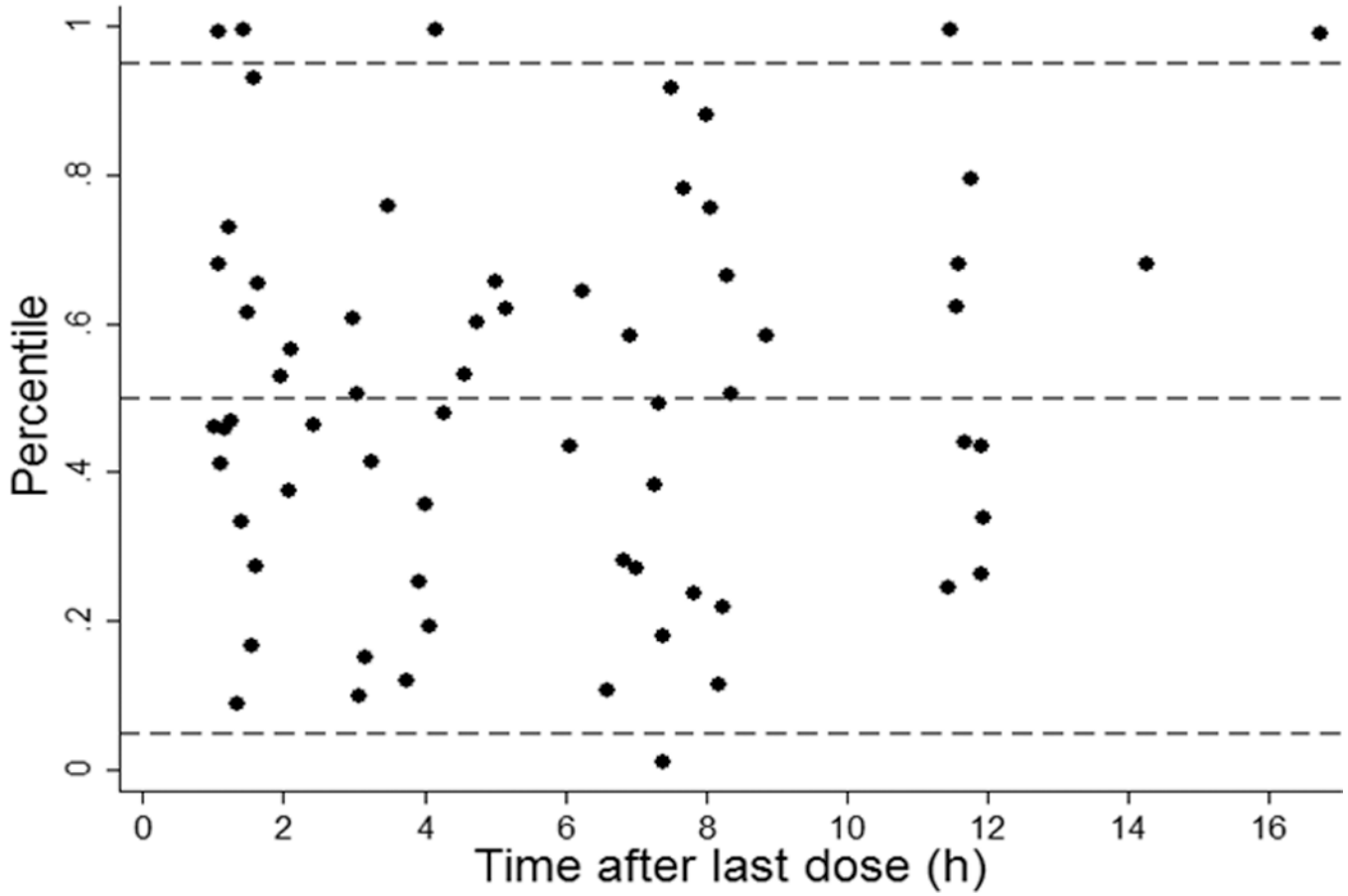

FIGURE 2.
Standardized visual predictive check. Solid black circles: observed concentrations; dashed black lines: 5th, 50th, and 95th percentiles of predicted concentration.

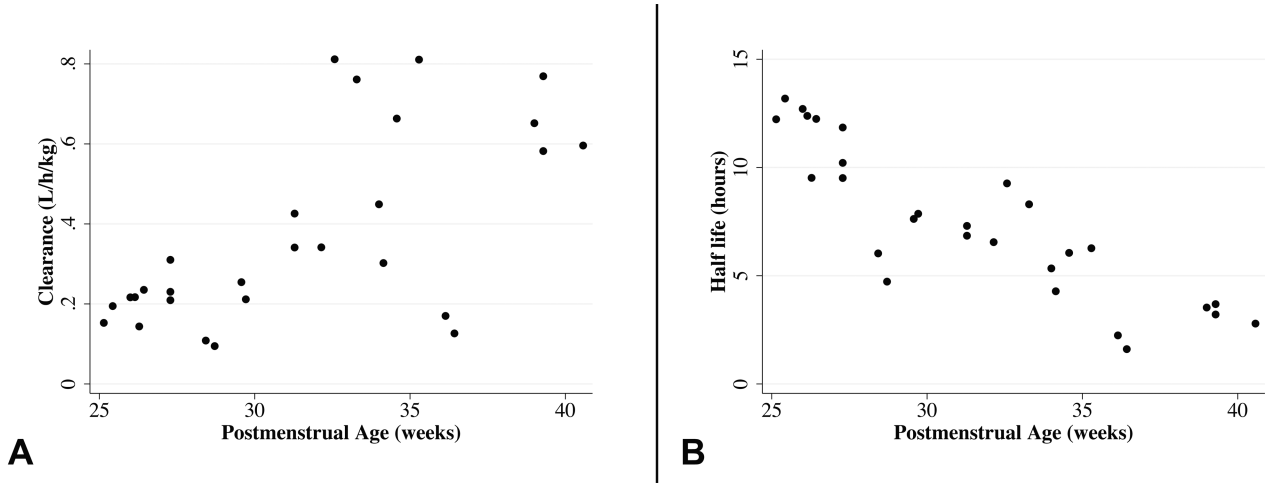

FIGURE 3.
Relationship between individual Bayesian PK parameter estimates and PMA. (A) Clearance; (B) half-life.

TABLE 1

Participant Demographics (n=28)

	N (%) or median (range)
Gestational age (weeks)	30 (23–40)
Postnatal age (days)	3 (1–30)
Postmenstrual age (weeks)	31 (25–41)
Birth weight (g)	1295 (510–4840)
Weight (g)	1370 (578–5720)
Female	15 (54)
White	16 (57)
Serum creatinine (mg/dL)	0.9 (0.3–1.8)
Vasopressin use	1 (4)
Dopamine use	4 (14)
Epinephrine use	7 (25)

Values for PNA, PMA, and weight are at the time of first PK sample collection. Concomitant medication use refers to any time during the study.

TABLE 2

Summary of Steps in the Acyclovir Model-building Process

Description	Population model	OFV	ΔOFV
V (all models)	V(L/kg)=2.8	1500.7	-
CL base model	CL(L/h/kg)=0.299	1500.7	-
PNA on CL	$CL(L/h/kg)=0.319*(PNA/3.5)^{-0.161}$	1498.0	−2.7
SCR on CL	$CL(L/h/kg)=0.275*(0.9/SCR)^{0.577}$	1492.0	−8.7
GA on CL	$CL(L/h/kg)=0.295*(GA/30.5)^{2.35}$	1481.7	−19.0
PMA on CL	$CL(L/h/kg)=0.280*(PMA/31.3)^{3.00}$	1478.9	−21.8
GA, PNA, and SCR on CL	$CL(L/h/kg)=0.283*(PNA/3.5)^{-0.007}*(0.9/SCRE)^{0.441}*(GA/30.5)^{2.16}$	1476.2	−24.5
PMA and SCR on CL	$CL(L/h/kg)=0.269*(0.9/SCR)^{0.577}*(PMA/31.3)^{3.02}$	1475.3	−25.4
PMA on CL (2 outliers dropped)	$CL(L/h/kg)=0.305*(PMA/31.3)^{3.02}$	1408.5	−92.2

Two outliers (observed concentration >10X different from the predicted concentration) dropped in the final model. ?OFV is relative to the base model.

TABLE 3

Final Model and Bootstrap PK Parameters

Parameter	Point estimate	%RSE	Bootstrap confidence interval		
			2.5%	Median	97.5%
CL (L/h/kg)	0.305	13.9	0.237	0.307	0.379
V (L/kg)	2.80	14.8	1.82	2.80	3.67
CL, PMA	3.02	11.5	2.39	3.02	4.18
Inter-individual variability (CV%)					
CL	52.8	36.2	35.6	53.2	84.4
V	85.0	51.5	4.89	81.3	140
CL vs. V correlation coefficient	0.98	45.7	0.62	1.00	1.02
Proportional residual variability (CV%)	34.5	35.0	21.1	32.0	43.4

CV%, coefficient of variance; RSE, relative standard error.

TABLE 4

Individual Empirical Bayesian Post-hoc Parameter Estimates for Acyclovir (Median [Range])

PMA	N	CL (L/h/kg)	V (L/kg)	Half-life (h)	$Cmax_{ss}$ (mg/L)	$C50_{ss}$ (mg/L)	$Cmin_{ss}$ (mg/L)
<30	13	0.211 (0.095–0.310)	2.88 (0.646–5.30)	10.2 (4.73–13.2)	10.3 (4.59–110)	7.12 (3.38–65.7)	3.92 (2.38–39.3)
30– <36	9	0.449 (0.302–0.812)	4.49 (1.87–10.85)	6.55 (4.28–9.26)	8.83 (5.44–29.8)	6.80 (3.72–16.9)	5.10 (2.54–9.62)
36–41	6	0.589 (0.126–0.769)	2.55 (0.293–4.09)	3.00 (1.61–3.69)	12.4 (10.8–86.1)	5.82 (5.23–22.0)	2.90 (2.19–7.46)
Overall	28	0.278 (0.095–0.812)	3.34 (0.293–10.85)	7.07 (1.61–13.2)	11.1 (4.59–110)	6.33 (3.38–65.7)	4.15 (2.19–39.3)

Intermittent infusion equations, infant PK parameters, and trial dosing were used to predict concentrations.

TABLE 5

Target Attainment Rate for Proposed and Handbook Dosing Regimens

Source	Dose (mg/kg)	GA (weeks)	PMA (weeks)	N	%Participants ≥3 mg/L		
					$Cmax_{ss}$	$C50_{ss}$	$Cmin_{ss}$
Proposed dosing	20 every 12 h	Any	<30	218	100	97	89
	20 every 8 h		30– <36	373	98	94	75
	20 every 6 h		36–41	409	96	86	56
		Overall		1000	98	91	71
FDA label	10 every 8 h	Any	<30	218	95	91	81
			30– <36	373	80	53	15
			36–41	409	66	18	0
		Overall		1000	77	47	23
Redbook and Lexicomp	20 every 8 h	Any	<30	218	100	100	100
			30– <36	373	98	94	74
			36–41	409	94	70	10
		Overall		1000	97	85	53
Harriet Lane	20 every 12 h	<34	NA	450	96	90	55
	20 every 8 h	≥34	NA	550	95	77	22
		Overall		1000	96	83	37
Neofax	20 every 12 h	<37	<34	441	97	89	55
	20 every 8 h	Any	≥34	559	94	77	22
		Overall		1000	95	82	37

Intermittent infusion equations, infant PK parameters, and trial dosing were used to predict concentrations. The fraction of infants with target concentrations ≥3mg/L was computed. All doses are a 1-hour infusion.