Population Pharmacokinetics of Intravenous Acyclovir in Premature and Term Infants

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Disclosures: see right panel

Abstract

Acyclovir is used to treat herpes infections in preterm and term infants; however, the influence of maturation on drug disposition and dosing requirements are poorly characterized in this population. We administered intravenous acyclovir to preterm and term infants <61 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. The analysis included 28 infants (median 31 weeks gestation). Acyclovir pharmacokinetics was described by a 1-compartment model: clearance (L/h/kg) = 0.305 x (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– <36 weeks PMA; 20 every 6 hours in infants 36–41 weeks PMA.

Background

- Acyclovir is routinely used to treat herpes simplex virus (HSV) infections in premature and term infants
- Although acyclovir has reduced mortality from neonatal HSV infections, morbidity remains high
- Acyclovir is primarily renally cleared, and the influence of maturational factors on drug disposition are poorly characterized
- Trials supporting acyclovir dosing in infants are limited, especially in premature infants

Methods

- Two multicenter, open-label, pharmacokinetic studies of acyclovir in 28 premature and term infants
- Inclusion criteria: gestational age <42 weeks, postnatal age <61 days, and suspected HSV infection
- Exclusion criteria: history of anaphylaxis to acyclovir; serum creatinine >1.7 mg/dL; urine output <0.5 mL/kg/hour
- Acyclovir 10-50 mg/kg every 8 hours was administered IV over 1 hour
- Sparse plasma samples were obtained around the first and after multiple dosing
- Population PK analysis was performed using NONMEM 7. The final model was evaluated by bootstrapping (Wings for NONMEM) and visual predictive check
- Intermittent infusion equations, infant PK parameters, and infant dosing were used to predict acyclovir steady-state peak ($Cmax_{ss}$), 50% of the dosing interval ($C50_{ss}$), and trough ($Cmin_{ss}$) concentrations
- The surrogate pharmacodynamic target was steady-state acyclovir $C50_{ss}$ ≥3 mg/L
- Monte Carlo simulations were used to evaluate target attainment rates in a random sample of 1000 infants from a large clinical care database

Results

Table 1. Clinical data

	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)

Table 2. Final model and bootstrap pharmacokinetic parameters

		Bootstrap Confidence Intervals		
	Point Estimate	2.5%	Median	97.5%
Clearance (L/h/kg)	0.305	0.237	0.307	0.379
Volume (L/kg)	2.80	1.82	2.80	3.67
Clearance, Postmenstrual Age	3.02	2.39	3.02	4.18
Inter-individual Variability – Clearance (CV%)	52.8	35.6	53.2	84.4
Inter-individual Variability – Volume (CV%)	85.0	4.89	81.3	140
Clearance vs. Volume Correlation Coefficient	0.98	0.62	1.00	1.02
Residual Variability (CV%)	34.5	21.1	32.0	43.4

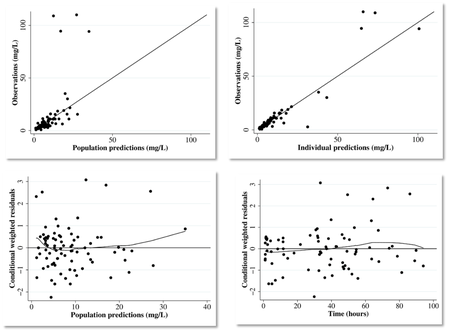
Eighty-one concentrations from 28 infants were used to estimate PK parameters. The final model had good precision between all final model and bootstrap parameter estimates with differences of <7.2%.

Table 3. Target attainment rate for proposed and handbook dosing regimens

Source	Dose (mg/kg)	GA (weeks)	PMA (weeks)	N	% Subjects ≥3mg/L: $Cmax_{ss}$	$C50_{ss}$	$Cmin_{ss}$
Proposed dosing	20 q 12 h	Any	<30	218	100	97	89
	20 q8 h		30– <36	373	98	94	75
	20 q6 h		36–41	409	96	86	56
			Total	**1000**	**98**	**91**	**71**
FDA label	10 q8 h	Any	<30	218	95	91	81
			30– <36	373	80	53	15
			36–41	409	66	18	0
			Total	**1000**	**77**	**47**	**23**
Redbook and Lexicomp	20 q8 h	Any	<30	218	100	100	100
			30– <36	373	98	94	74
			36–41	409	94	70	10
			Total	**1000**	**97**	**85**	**53**
Harriet Lane	20 q12 h	<34	NA	450	96	90	55
	20 q8 h	≥34	NA	550	95	77	22
			Total	**1000**	**96**	**83**	**37**
Neofax	20 q12 h	<37	<34	441	97	89	55
	20 q8 h	Any	≥34	559	94	77	22
			Total	**1000**	**95**	**82**	**37**

Using the final model and 1000 infants from a clinical care database, the proportion of infants meeting the PD target was computed. All doses are a 1-hour infusion. PMA = postmenstrual age.

Figure 1. Goodness of fit plots – Final Model



Final Model (1-compartment): Clearance (L/h/kg) = 0.305 x (postmenstrual age (weeks)/31.3)$^{3.02}$ and Volume of distribution (L/kg) = 2.8.

Figure 2.

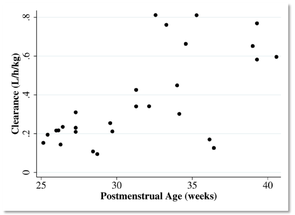
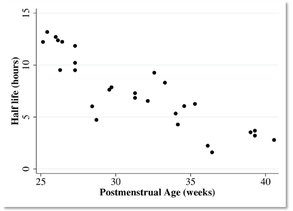


Figure 3.



Conclusions

- Acyclovir clearance increased with infant maturation
- A dosing strategy based on postmenstrual age was developed to account for developmental changes in acyclovir disposition to achieve the surrogate pharmacodynamic target in the majority of infants:

  20 mg/kg every12 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

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