Dose-Safety Relationship for Acyclovir in the Treatment of Neonatal Herpes Simplex Virus

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Abstract

Background: The current US FDA label recommends 30 mg/kg/day of acyclovir for treatment of neonatal herpes simplex virus (HSV) disease. Due to improved survival, 60 mg/kg/day has been the standard of care since 2001 and some centers use even higher doses.

Objective: Evaluate the safety of high dose acyclovir in infants with neonatal HSV disease.

Methods: We identified all infants <90 days of age with neonatal HSV disease discharged from 4 children's hospitals from 2002 to 2014. We obtained demographic and acyclovir dosing information from medical records along with new medical diagnoses and laboratory results on days with acyclovir exposure. Diagnostic AEs were: rash, hypotension, seizure, renal failure or death first occurring after the start of acyclovir and laboratory AEs were abnormal laboratory values as defined *a priori* occurring on a day with acyclovir exposure. We determined the number and proportion of infants with each AE and calculated the median daily acyclovir dose for each AE.

Results: We identified 49 infants with neonatal HSV disease treated with acyclovir. The median gestational and postnatal ages were 38 weeks (range: 24-41) and 8 days (0-90), respectively. The median daily dose was 77 mg/kg/day (20-441), and the median duration of therapy was 22 days (1-82). Rash was the most common diagnostic AE occurring in 37% of infants. Thrombocytopenia (platelet count <100,000/mL) was the most common laboratory AE, occurring in 43% of infants. For all laboratory AEs, the median daily acyclovir dose for infants with the AE was ≤ to the daily dose for infants without the AE. Nine (18%) infants died. Infants who died had a lower median daily dose of acyclovir than those who survived, 60 mg/kg/day (20-60) and 82 mg/kg/day (59-441), respectively, P<0.01.

Conclusion: Infants treated with higher acyclovir doses had improved survival compared to those treated with currently recommended doses. Acyclovir dose was not associated with AEs.

Background

- The current Food and Drug Administration label recommends an acyclovir dose of 30 mg/kg/day for neonatal herpes simplex virus (HSV) disease[1]
- Improved mortality and neurodevelopmental outcomes have been demonstrated with high dose (HD) (60 mg/kg/day) acyclovir.[2]
- 1500 mg/m^2/day is occasionally used in lieu of weight-based dosing[3]

Objective

- Evaluate the safety of HD acyclovir in infants with neonatal HSV disease

Methods

- We identified all infants with confirmed or suspected neonatal HSV disease cared for at 4 children's hospitals from 2002-2014
- Inclusion criteria:
  - < 90 days of age
  - Neonatal HSV disease
  - Treated with IV acyclovir for ≥14 days
- Primary outcome: median dose for infants with and without any adverse event (AE)
- Secondary outcomes:
  - Median dose for infants with and without each AE
  - Frequency (number) of any AE by maximum daily dose

Methods

- Definitions:
  - Diagnostic AE: new diagnosis of rash, hypotension, seizure, renal failure or death after acyclovir exposure
    - Seizure: clinical diagnosis of seizure, EEG was not required
    - Hypotension: required a vasoactive medication
    - Renal failure: diagnosis recorded in medical record
    - Death: death at hospital discharge
  - Laboratory AE: abnormal laboratory value occurring on a day with acyclovir exposure
- Statistics:
  - The number and proportion of infants with each AE was determined
  - The median maximum daily acyclovir doses for infants with and without each AE were compared using nonparametric Wilcoxon rank sum tests

Results

- We identified 49 infants with neonatal HSV treated with acyclovir for ≥ 14 days (Table 1)
- Median mean daily acyclovir dose was 59 mg/kg/day (range: 20-441)
- At least 1 laboratory AE occurred in 37% of infants
- Rash was the most common diagnostic AE (37%)
- Acyclovir dose was not associated with the daily number of AEs (Figure 1)
- Nine infants died (18%)
- Infants who survived had a higher median daily dose of acyclovir than those who died, 82 mg/kg/day (59-441) versus 60 mg/kg/day (20-60), P<0.01

Table 1. Demographics

	N=49 (%)
Gestational age, weeks, median (range)	38 (24, 41)
Birth weight, g, median (range)	2990 (590, 4054)
Male	25 (51)
Cesarean section	21 (43)
Herpes simplex virus type	
Type 1	16 (33)*
Type 2	28 (58)*
Unspecified	5 (11)
Site of positive diagnostic test†	
Blood	18 (38)
Cerebrospinal fluid	19 (40)
Conjunctivae	3 (6)
Mouth	4 (8)
Nasopharynx	8 (17)
Rectum	9 (19)
Skin or mucus membrane lesion	20 (42)

*1 infant had both HSV type 1 and type 2; †each infant could have >1 positive test

Results

Figure 1. Daily frequency of any adverse event by maximum daily dose (mg/kg

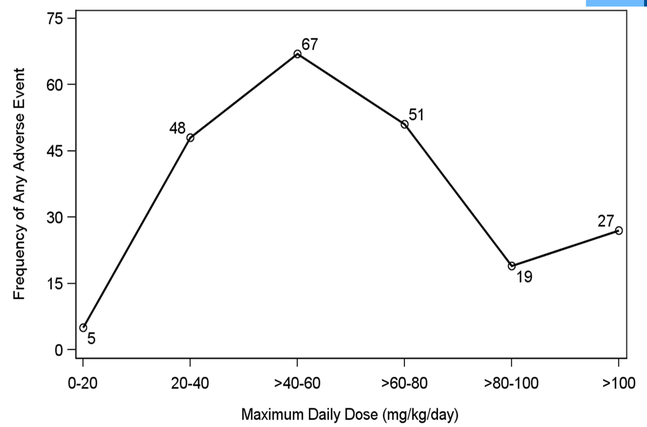

Table 2. Median daily dose of infants with and without each adverse event

Adverse Event	N=49 (%)	Dose for infants with Adverse Event Median (Range)	Dose for Infants without Adverse Event Median (Range)	P
Rash	18 (37)	51 (20-121)	61 (20-441)	0.11
Hypotension	12 (24)	50 (20-182)	80 (20-441)	<0.01
Death	9 (18)	60 (20-60)	82 (59-441)	<0.01
Seizure	7 (14)	60 (19-127)	78 (20-441)	0.42
Hypernatremia	2 (4)	60	77 (20-441)	0.12
Hyponatremia	6 (12)	60 (40-182)	80 (20-441)	0.08
Hyperkalemia	5 (10)	40 (19-441)	80 (20-318)	0.08
Hypokalemia	9 (18)	96 (60-221)	64 (20-441)	0.15
Elevated BUN	4 (8)	96 (60-221)	65 (20-441)	0.24
Elevated creatinine	10 (20)	60 (58-221)	80 (20-441)	0.38
Elevated ALT	18 (37)	60 (19-102)	80 (20-441)	<0.01
Elevated AST	11 (22)	60 (20-102)	80 (20-441)	<0.01
Leukopenia	14 (29)	60 (40-96)	80 (20-441)	<0.01
Neutropenia	0 (0)		77 (20, 441)	

Conclusions

- Acyclovir was not associated with AEs even when doses > 80 mg/kg/day were used
- Infants who survived had higher median daily doses of acyclovir than those who died

References

[1]Kimberlin, *Pediatrics* 2001. [2]Acyclovir Sodium Injection. *APP Pharmaceuticals* 2012. [3]Tiffany *J Perinatology* 2005.

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