Case Report: Application of Acyclovir Serum Concentrations and Herpes Simplex Virus Inhibitory Concentrations in the Treatment of Neonatal Disseminated Herpes Simplex Virus with Concomitant Extracorporeal Membrane Oxygenation and Continuous Venovenous Hemodiafiltration

Kathryn G Merkel, PharmD, BCPS, AQ ID; Rachel D Quick, RN, MSN, CNS; Sarah Casey, CPNP; Kartik Pillutla, MD; Carolyn Ragsdale, PharmD, BCPS; Marisol Fernandez, MD; Patrick Boswell; Sarmistha B Hauger, MD
Seton Healthcare Family- Austin, Texas

Dell Children's Medical Center of Central Texas
kgmerkel@seton.org
Phone: 512-324-0000 extension 87076

dell children's medical center of central texas
A member of the Seton Family of Hospitals

Seton Healthcare Family

Abstract

Background:
Disseminated neonatal herpes simplex virus (HSV) is associated with significant morbidity and mortality therefore prompt adequate treatment with antiviral therapy is of great importance. There is little pharmacokinetic/pharmacodynamic data available to guide acyclovir dosing recommendations for neonates maintained on continuous venovenous hemodiafiltration (CVVHDF) and extracorporeal membrane oxygenation (ECMO).

This report follows the course of two full-term, previously healthy male neonates who were treated with acyclovir for disseminated HSV infection at about 1 week of age. Both were placed on CVVHDF and one on ECMO for their progressive illness. We measured serum acyclovir concentrations and HSV inhibitory concentrations to ensure adequate dosing when receiving these therapies.

Methods:
Intravenous acyclovir was given to both neonates at the recommended dose of 20mg/kg/dose. The dosing frequency in the neonate receiving ECMO and CVVHDF was every 8 hours and in the neonate receiving CVVHDF alone was every 12 hours. Acyclovir serum peak and trough concentrations were drawn to assess the efficacy and safety during CVVHDF and ECMO treatment. HSV inhibitory concentrations (IC) were measured to assess resistance to acyclovir.

Results:
The HSV2 IC for the neonate receiving ECMO and CVVHDF was 3 mcg/mL with serum peak concentration 23 mcg/mL and trough concentration 17 mcg/mL. The HSV1 IC for the neonate receiving CVVHDF was <0.25 mcg/mL with serum peak concentration 31 mcg/mL and trough concentration 15 mcg/mL. Assuming acyclovir levels in the cerebrospinal fluid (CSF) are 30-50% of serum levels the desired minimum serum levels were 10 mcg/mL and 0.83 mcg/L, respectively. Minimum serum trough concentrations were achieved and serum peak concentrations did not exceed the safety threshold of 50 mcg/mL. Both infants died as a result of their profound illness, despite early initiation of acyclovir and adequate serum concentrations.

Conclusion:
Optimal acyclovir serum concentrations can be achieved in the presence of CVVHDF and ECMO with 20 mg/kg/dose at intervals of every 8 and every 12 hours for the treatment disseminated neonatal HSV1/2 with variable resistance.

Introduction

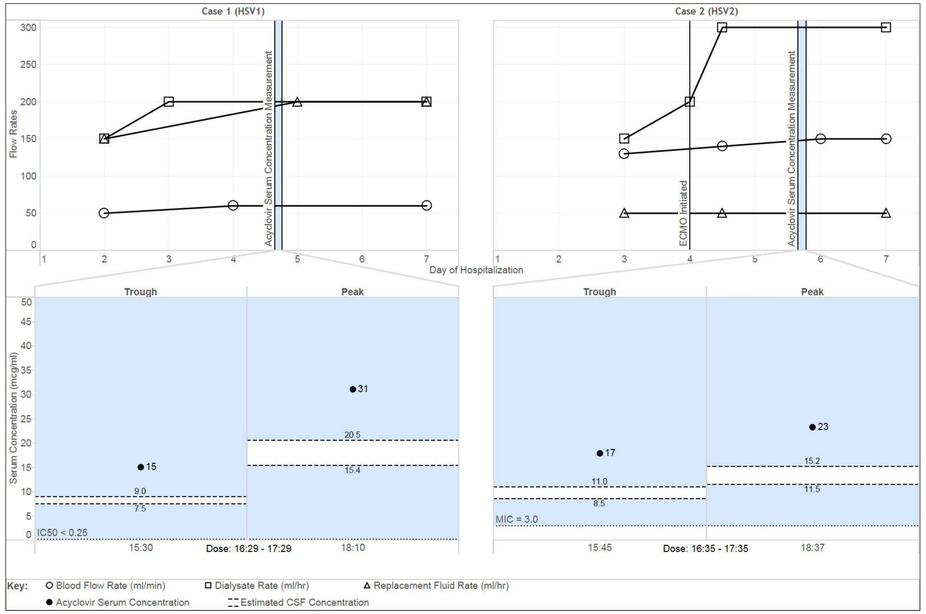
- Optimal acyclovir dosing is a critical factor in the outcome of neonatal disseminated HSV infections as previous studies have demonstrated reduced mortality with acyclovir dosing of 20 mg/kg/dose intravenously (IV) every 8 hours, the current standard of care.
- CVVHDF and ECMO can alter the clearance and volume of distribution of acyclovir such that dosage adjustments may be necessary. The following pharmacokinetic parameters should be considered:
  - Small molecule
  - Low protein binding
  - Water soluble
  - Renal excretion
- The efficacy of acyclovir is best described as time dependent killing such that the recommended dosing regimen must ensure serum drug concentrations remain above the HSV IC at the primary site of infection.

Results

Table 1. Patient Demographics and Case Information

	Day of Life / Sex / Birth History	Acyclovir Dosing	HSV Diagnostics	CVVHDF Circuitry	ECMO Circuitry
Case 1	6 days Male Full term, Normal delivery No known maternal HSV history	20 mg/kg/dose Every 12 hours 1 hour infusion	• (+) HSV PCR (serum) • (+) HSV surface culture (skin/nasopharynx) • CSF unable to be obtained	Gambro Prismaflex Filter: HF 1000	N/A
Case 2	8 days Male Full term, Normal delivery No known maternal HSV history	20 mg/kg/dose Every 8 hours 1 hour infusion	• (+) HSV PCR (serum) • (+) HSV surface culture (nasopharynx) • CSF unable to be obtained	Gambro Prismaflex Filter: HF 1000	• Sorin SIII (roller pump) • Maquet Quadrox D Softline Coating • Terumo tubing pack with Xcoating

Figure 1. Continuous Renal Replacement Therapy (CRRT) Flow Rates and Acyclovir levels



Methods

- A literature search was performed to identify recommended acyclovir dosage adjustments. Despite patients receiving CVVHDF and/or ECMO the acyclovir dose was not changed from 20 mg/kg/dose due the inconsistencies in the literature, however the dosing interval selected was influenced by the presence or absence of ECMO.
- An efficacy pharmacodynamic target was established based on comparison of serum acyclovir concentrations in relationship to in vitro IC for HSV clinical isolates:
  - HSV1 0.02-1.9 mcg/mL → target acyclovir trough concentration > 2 mcg/mL
  - HSV2 0.3-2.9 mcg/mL → target acyclovir trough concentration > 3 mcg/mL
- Acyclovir concentrations in the CSF are approximately 30-50% of corresponding serum concentrations, therefore serum acyclovir trough concentrations must be higher to ensure adequate CSF penetration.
- A toxicity pharmacodynamic target was established at 50 mcg/mL based on a small subset of patients experiencing neurotoxicity at acyclovir serum concentrations of 50-70 mcg/mL.

Summary and Conclusion

- Empirically the current standard of care dosing (20 mg/kg/dose IV every 8 hours) may be both safe and effective in patients receiving CVVHDF and ECMO.
- The efficacy pharmacodynamic target was exceeded in the presence of CVVHDF and/or ECMO with both dosing regimens (Figure 1).
- Therapeutic drug monitoring should be considered to help determine appropriate acyclovir dosage adjustments in patients receiving CRRT and/or ECMO.
- Limitations:
  - Quantitative HSV DNA levels were not measured which may have been useful to track the response to treatment.
  - Acyclovir CSF concentrations were not directly measured to ensure adequate concentrations relative to the IC at the site of infection.
  - Generalizability limited by the CVVHDF and ECMO prescriptions utilized in the two cases.

References

1. Kimberlin DW. Neonatal Herpes Simplex Infection. Clinical Microbiology Reviews. 2004;17(1):1-13.
2. Hintz M, Connor JD, Spector SA, et al. Neonatal Acyclovir pharmacokinetics in patients with herpes virus infections. The American Journal of Medicine, Acyclovir Symposium
3. Zeng L, Nath CE, Shaw PJ, et al. HPLC-fluorescence assay for acyclovir in children. Biomedical Chromatography 2008;22:879-887.
4. Funaki T, Miyata I, Shoji K, et al. Therapeutic drug monitoring in neonatal HSV infection on continuous renal replacement therapy. Pediatrics. 2015;136(1): e270-e274.
5. Sampson MR, Bloom BT, Lenfestey RW, et al. Population pharmacokinetics of intravenous acyclovir in preterm and term infants. Pediatr Infect Dis J 2014; 33: 42-49.
6. Choi G, Gomersall CD, Tian Q, et al. Principles of antibacterial dosing in continuous renal replacement therapy. Blood Purif 2010;30: 195-212.
7. Aoki FY, Hayden FG, Dolin R. Antiviral Drugs (Other than Antiretrovirals) In: Mandell GL, Bennett JE, Dolin R. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease, 7th ed. Philadelphia PA: Churchill Livingstone: 2010: 565-611.
8. Aronoff GR, Bennett WM, Berns JS, et al. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children, 5th ed, Philadelphia, PA: American College of Physicians, 2007.
9. Cies JJ, Moore WS, Miller K, et al. Therapeutic drug monitoring of continuous-infusion acyclovir for disseminated herpes simplex virus infection in a neonate receiving concurrent extracorporeal life support and continuous renal replacement therapy. Pharmacotherapy 2015;35(2):229-233.
10. Shann F, and Chiletti R. Neonatal herpes virus infection: Duration of extracorporeal support and the dose of acyclovir. Pediatric critical care medicine 2011;12(5):605-606.
11. American Academy of Pediatrics [Herpes Simplex]. In: Pickering LK, Baker, CJ, Kimberlin DW, Long SS, eds. Red Book: 2012 Report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics: 2012: 398-408.