Valacyclovir Versus Acyclovir for Herpes Simplex Virus Suppression Following Neonatal Infection

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ABSTRACT

Background: Anecdotal experience suggests efficacious valacyclovir use for neonatal herpes simplex virus (HSV) suppression, with limited published literature. The objective of this study was to evaluate HSV recurrence rates between valacyclovir and acyclovir for suppression of HSV following neonatal infection.

Methods: We conducted a single center, retrospective cohort analysis of patients less than 6 weeks old with a positive HSV polymerase chain reaction who received oral acyclovir or valacyclovir. Demographics, dosing, and recurrence rates were analyzed.

Results: Six patients received acyclovir and 13 received valacyclovir. The recurrence rate was similar in both groups.

Discussion: Valacyclovir may be an alternative to acyclovir for suppression of neonatal HSV, offering less frequent dosing and increased compliance. Larger studies are needed to confirm valacyclovir efficacy for neonatal HSV suppression.

BACKGROUND

Neonatal herpes simplex virus (HSV) is a viral infection affecting 1 per 3200 live births.[1] HSV can present as disseminated, central nervous system (CNS), and/or skin, eye, and/or mucous membrane (SEM) disease. The American Academy of Pediatrics (AAP) recommends intravenous (IV) acyclovir 20 mg/kg/dose every 8 hours for 14 days for SEM treatment and a minimum of 21 days for CNS or disseminated disease in neonates. HSV establishes latency in sensory ganglia following primary infection. It is not known if the virus may also subclinically reactivate in the brain after neonatal CNS infection. However, infants with CNS involvement who received oral suppressive therapy with acyclovir for 6 months were demonstrated to have improved neurodevelopmental outcomes compared to those infants who did not receive suppressive therapy.[2] While neurodevelopmental benefits were not observed for those babies solely with SEM disease, they benefitted from a significant decrease in cutaneous recurrence and presumably the socioeconomic benefits from that.[2] For these reasons, oral suppressive therapy has become relatively standard after neonatal HSV infection. Dosing is 300 mg/m^2/dose 3 times daily for a minimum of 6 months following completion of IV acyclovir.[3] Valacyclovir has not been studied for longer than 5 days in infants.[4] However, valacyclovir is sometimes prescribed for neonatal HSV suppression off-label.[4] Valacyclovir is a nucleoside analogue DNA polymerase inhibitor that rapidly converts to acyclovir and has a similar mechanism of action.[5] Valacyclovir offers the potential benefits of increased bioavailability and less frequent dosing, which could result in improved compliance compared to acyclovir.[5]

There is little published literature comparing the efficacy of valacyclovir and acyclovir for neonatal HSV suppression. However, local anecdotal experience suggests off-label valacyclovir for HSV suppression in infants has been efficacious. The primary objective of this study was to evaluate for a difference in clinical recurrence between valacyclovir and acyclovir for suppression of recurrent HSV following neonatal infection.

METHODS

We retrospectively reviewed records of children less than 6 weeks of age with a positive HSV polymerase chain reaction (PCR)

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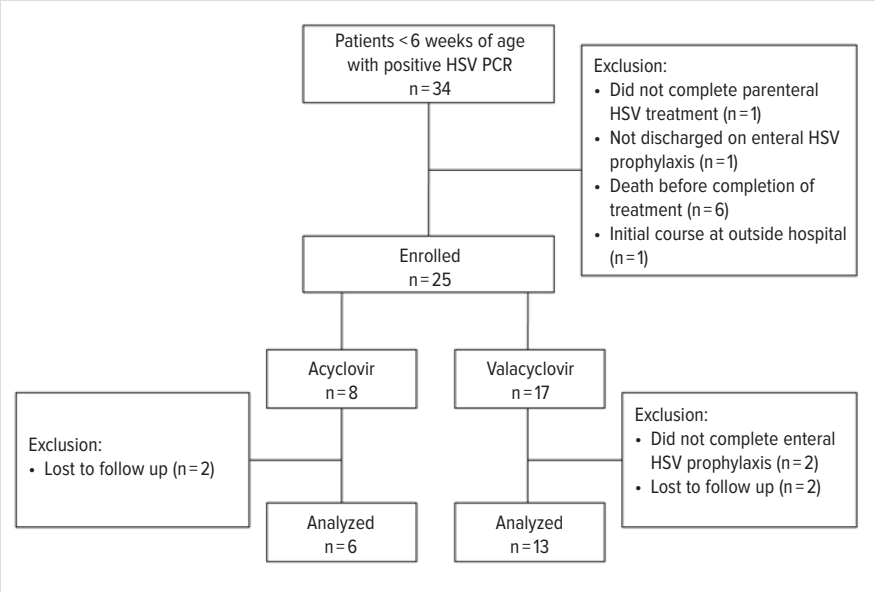
test who completed parenteral and suppressive therapy from November 2012 to July 2021. Information was collected from patients at a 298 bed children's hospital with a level IV neonatal intensive care unit with 72 licensed beds. Those who were lost to follow-up, died prior to beginning suppressive therapy, or started the course of medication therapy at an outside hospital were excluded. We collected age at diagnosis, sex, type of HSV, antiviral agent and dose, and duration of therapy. We also evaluated medication changes as a surrogate for medication intolerance or failure of therapy. Patients received acyclovir or valacyclovir suppressive therapy at the discretion of the medical provider. Duration of suppressive therapy was also determined by the medical provider. Valacyclovir was dosed at 40-50 mg/kg/day divided twice daily. Acyclovir was dosed at 300 mg/m^2/dose 3 times daily. Patients prescribed the same antiviral agent were analyzed as a cohort. We compared the incidence of recurrence during suppression, as well as time to recurrence. Recurrence was defined as a positive HSV PCR or documentation of a lesion consistent with HSV in the electronic medical record. This project was reviewed by our Institutional Review Board and determined to be a quality improvement project.

Proportions of patients with various characteristics were compared between those who received acyclovir versus those who received valacyclovir using Fisher exact tests. Continuous/numeric variables were compared in the 2 groups using Mann-Whitney tests. Quartiles were calculated using "Tukey's Hinge" method in SPSS. IBM SPSS Statistics 20 (Armonk, New York) was used for statistical analysis.

Figure. Consort Diagram



Abbreviations: HSV, herpes simplex virus; PCR, polymerase chain reaction.

Out of 34 patients who had a positive HSV PCR at less than 6 weeks of age, 9 patients were excluded. Following intravenous therapy, included patients were given oral suppression. In the acyclovir arm, 2 patients were excluded resulting in 6 included patients. In the valacyclovir arm, 4 patients were excluded resulting in 13 patients with complete data for analysis.

Table 1. Demographics

Characteristic	Overall	Acyclovir	Valacyclovir	*P* value
Total, N (%)	19	6 (32)	13 (68)	n/a
Female, N (%)	7 (37)	4 (67)	3 (23)	0.13
Birth weight (kg), median (IQR)	3.26 (2.85–3.52)	3.40 (3.22–3.52)	3.20 (2.78–3.52)	0.38
Gestational age (weeks), median (IQR)	38.0 (36.5–38.5)	38 (38–39)	37 (36–38)	0.12
Herpes simplex virus (HSV) type N (%)				
Type 1	9 (47)	5 (83)	4 (31)	
Type 2	10 (53)	1 (17)	9 (69)	0.06
Diagnosis				
SEM, N (%)	10 (53)	4 (67)	6 (46)	0.63
CNS, N (%)	11 (58)	3 (50)	8 (62)	1.00
Disseminated, N (%)	15 (79)	5 (83)	10 (77)	1.00
Dose, median (IQR)	n/a	900 (900–900) mg/m^2/day	50.0 (40–50) mg/kg/day	n/a
Duration (months), median (IQR)	6 (6–12)	6 (6–6)	11.5 (6–12)	0.03

Abbreviations: SEM, skin, eye, and/or mucous membrane; CNS, central nervous system; IQR, interquartile range.

RESULTS

A total of 34 patients had a positive HSV PCR at less than 6 weeks of age, of which 25 met inclusion criteria (Figure 1). Following IV therapy, included patients received oral suppression with acyclovir (n = 8) or valacyclovir (n = 17). In the acyclovir arm, 2 patients were lost to follow-up, resulting in 6 included patients. In the valacyclovir arm, 2 patients did not complete oral HSV suppression (presumably for adherence) and 2 were lost to follow-up, resulting in 13 patients with complete data for analysis. Patients were lost to follow-up if they did not have documented clinic notes in the electronic health record. There were no differences in demographics between the 2 groups, with the exception of duration of therapy, which was longer in patients prescribed valacyclovir (Table 1). Initial dosing of the antiviral agent was appropriate for both groups. Recurrence while on suppressive therapy was similar between groups (Table 2). Among those who did have a recurrence, the median time to recurrence was 102 days

from diagnosis. Only 1 patient required a medication switch during suppressive therapy, and this was due to nothing by mouth status prior to a procedure, requiring a change to IV acyclovir. No patients had a prescribed change in suppressive therapy for a documented adverse effect.

DISCUSSION

Our data reveal similar rates of recurrence during suppressive therapy when either oral acyclovir or valacyclovir were prescribed. Though oral acyclovir is the drug of choice recommended by the AAP for suppression following neonatal HSV infection, oral valacyclovir is sometimes used off-label. A study completed by Kimberlin et al assessed the safety and pharmacokinetics of valacyclovir dosing.[6] Patients 1 month through 5 years old received one 25 mg/kg dose of valacyclovir. Patients 1 year to 11 years old received 10 mg/kg twice daily or 20 mg/kg 3 times daily for 3 to 5 days. After the authors' pharmacokinetic evaluation, no dosing recommendations could be concluded in patients younger than 3 months old. The authors concluded that valacyclovir 20 mg/kg/dose provided similar exposure of blood concentrations for children aged 3 months to 11 years compared to acyclovir. Our study based appropriate dosing on these findings, as it is the only dosing available and, thus, also what is conventionally used by clinicians for this indication. This pharmacokinetic study demonstrated valacyclovir to be safe and well tolerated. Likewise, patients in our cohort were prescribed doses of 20-25 mg/kg/dose given twice daily without reported side effects.

We did not identify any statistical differences in recurrences, though the recurrence rate while on suppressive therapy overall was low (2 of 19; 10%). This could be a result of our small sample size. Comparatively, a single-center study in the United Kingdom identified a recurrence rate of 33% among 21 infants who presented with HSV at or prior to 90 days of age.[7] The difference might be explained by more reliable follow-up documentation of recurrences given the nationalized health care system. However, most patients (all but 2) were given acyclovir prophylaxis in that study. Additionally, the study by Kimberlin et al reported 41% of babies had at least 2 cutaneous recurrences while on oral acyclovir suppression (37.5% of those infants with CNS disease and 47% of those infants with solely SEM disease).[2] Notably, in our evaluation, both recurrences were related to SEM disease and occurred in the valacyclovir group. However, 1 patient with a gestational age of 36 weeks initially presenting with CNS HSV did not have the dose adjusted for weight gain while on suppressive therapy at the time of the recurrence when nearly 4 months old, potentially explaining the recurrence. The other infant initially had CNS, disseminated, and SEM HSV, with a cutaneous recurrence at around 3 months of age. This patient had a gestational age of 27 weeks, which could impact the pharmacokinetics of the drug, as young infants experience significant kidney maturation in the first few months of life that may alter clearance.[4] Waheed et al also found recurrences in 50% of premature neonates versus 23% of term patients while on suppressive therapy, supporting our concern for dosing and metabolism in premature infants.[7]

Table 2. Outcomes

Medication	Acyclovir (n = 6)	Valacyclovir (n = 13)	*P* value
Medication change, N (%)	0 (0)	1 (8)	1.00
Recurrence while on suppression, N (%)	0 (0)	2 (15)	1.00
Time until recurrence (days), median (IQR)	n/a	102.5 (85–120)	n/a

It was interesting to note patients in our study who were prescribed valacyclovir had longer durations of therapy. Clinicians selected the drug and duration of therapy at their discretion. Given the retrospective nature of this study, we were unable to determine the reason for the selection of drug and duration. However, verbal communication with infectious disease providers suggest that differences in medication selection and duration of therapy may reflect a change in practice over time, favoring a longer duration of 1 year versus 6 months by some clinicians, as many of the valacyclovir patients were from more recent encounters.

Strengths of this study include manual review of patient charts for documentation of a recurrent lesion and/or any PCR for diagnosis of recurrence. All patients included in the analysis had documentation of adherence and were evaluated for appropriate dosing throughout the course of therapy by the authors. Although all patients in this study were reportedly adherent, twice daily valacyclovir dosing allows for ease of administration for neonates and young children, potentially improving compliance over months of therapy. Lastly, complex or questionable patients were reviewed by a pharmacist (HO) and an infectious disease physician (MM) to determine if the patient should be included in the study.

Limitations include small sample size, resulting in insufficient power to detect a potential difference in outcomes, greater number of patients in the valacyclovir arm due to clinician selection, lack of literature guiding dosing in premature neonates, lack of lab assessment for neutropenia, as well as the single center experience. Exclusion of patients who did not complete treatment or who started treatment at another hospital may affect the finding's generalizability.

However, this study provides real world experience on the safety and long-term use of valacyclovir for prevention of recurrent HSV following neonatal infection. Additionally, an ongoing phase 1, open label, single-center study is further assessing the pharmacokinetics and pharmacodynamics of valacyclovir compared to IV acyclovir in neonates.[8] Up to 10 participants aged 2 to 12 weeks with a gestational age greater than 34 weeks will be enrolled. This study may aid in determining optimal dosing of valacyclovir, including those who are late preterm.

Valacyclovir may be an acceptable alternative to oral acyclovir for suppression of neonatal HSV, offering less frequent dosing and possible increased compliance with similar outcomes. Larger studies are needed to determine if there are true differences in outcomes or adverse effects, particularly in premature infants where drug metabolism may differ.

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