Exposure-safety relationship for acyclovir in the treatment of neonatal herpes simplex virus disease

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ABSTRACT

Background: Neonatal herpes simplex virus (HSV) disease has been treated with high-dose (20 mg/kg/dose) acyclovir since 1991.
Aims: Determine the safety of acyclovir in infants with neonatal HSV treated with high-dose acyclovir; examine the association between acyclovir dose and exposure with adverse events (AEs).
Study design: We obtained demographic information and acyclovir dosing via medical records. Acyclovir exposure was calculated using an established pharmacokinetic model.
Subjects: Infants <120 days of age with neonatal HSV discharged from four academic children's hospitals.
Outcome measures: We identified clinical and laboratory adverse events (AEs).
Results and conclusions: We identified 49 infants with neonatal HSV treated with acyclovir; 42 infants had complete 21-day dosing information. Median mean daily dose was 59 mg/kg/day. Clinical AEs were common among all gestational and postnatal age groups. Rash was the most common clinical AE (37 %). Mild laboratory AEs occurred in 2–37 % of infants. The median maximum doses (mg/kg/day) were higher among infants with hypokalemia, elevated blood urea nitrogen, and thrombocytosis. For all other laboratory AEs, the median maximum doses for infants without events were higher or equal to the median maximum dose of infants with the AE. The odds of experiencing any clinical or laboratory AE did not differ by predicted acyclovir exposure for either area under the curve (AUC) or maximum concentration (Cmax) (odds ratio [OR] = 1.00 [0.98, 1.03] and OR = 1.01 [0.93, 1.12], respectively). Although AEs were common with high-dose acyclovir exposure, severe AEs were rare. Acyclovir exposure was not associated with AEs.

1. Introduction

Neonatal herpes simplex virus (HSV) disease is a serious infection that causes significant morbidity and mortality [1]. Neonatal HSV disease has three clinical presentations: 1) localized infection of the skin, eyes, or mucous membranes; 2) central nervous system (CNS) infection; and 3) disseminated disease with or without CNS involvement [2,3]. Prognosis varies depending on the presentation, timing of antiviral initiation, and duration of antiviral therapy [4,5]. Acyclovir has been the treatment of choice for neonatal HSV disease since 1991 [6]. Until 2019, the dose approved by the United States Food and Drug Administration (FDA) for this indication was 30 mg/kg/day divided every 8 h

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[6,7]. However, prospective data demonstrated that higher dosing (60 mg/kg/day divided every 8 h) is associated with lower mortality compared with 30 mg/kg/day [1]. For this reason, high-dose acyclovir (60 mg/kg/day) has been recommended for the treatment of neonatal HSV disease by The American Academy of Pediatrics (AAP) since 2001 [8]. Some centers have used even higher doses (1500 mg/m^2/day divided every 8 h), with resultant equivalent weight-based dosing exceeding 100 mg/kg/day [9].

Acyclovir has been associated with adverse events (AEs) including renal toxicity, neutropenia, and, rarely, neurotoxicity [10–12]. The FDA label notes that 5–10 % of patients exposed to acyclovir during clinical trials experienced creatinine or blood urea nitrogen elevations, 2 % developed rash, 1 % developed encephalopathic abnormalities, and <1 % developed neutropenia [7]. Some, but not all, of these patients had HSV disease at the time of acyclovir exposure [10]. The frequency of AEs in infants with HSV disease treated with high-dose acyclovir has been reported in prior cohorts, but none have examined the association of acyclovir exposure with safety nor considered doses >60 mg/kg/day [1]. We sought to evaluate the safety of acyclovir in infants with neonatal HSV disease treated with high-dose acyclovir and to examine the association between acyclovir dose and exposure with AEs.

2. Materials and methods

2.1. Study population

We identified infants <120 days of age with neonatal HSV disease discharged between 2002 and 2014 from one of the following four children's hospitals: Duke University Medical Center, Children's Hospital of Orange County, The University of North Carolina Children's Hospital, and Cincinnati Children's Hospital. We considered infants to have confirmed neonatal HSV disease if they had a positive culture or polymerase chain reaction (PCR) obtained from the blood, cerebrospinal fluid, skin, mouth, nasopharynx, conjunctivae, urine, or rectum. In order to avoid false positives related to identification of transient virus, for sites other than the blood and cerebrospinal fluid, only tests obtained ≥24 h after the infant's birth were considered. Infants were considered to have suspected neonatal HSV disease if they had a clinical diagnosis of HSV without virologic confirmation. Except for infants who died while receiving acyclovir, those who received <21 days of intravenous acyclovir therapy were excluded.

We used medical records to obtain demographic information including gestational age at birth, age at the time of HSV diagnosis, and mode of delivery. We recorded all doses of acyclovir along with dosing weights, as well as date and time of administration. New medical diagnoses that occurred while receiving acyclovir were recorded. Laboratory test results were recorded from 3 days prior to the first dose of acyclovir to 3 days after the last dose of acyclovir. Labs of interest included were: serum sodium, potassium, glucose, blood urea nitrogen, and creatinine concentrations; white blood cell, absolute neutrophil, and platelet counts; and serum alkaline aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations.

2.2. Definitions

Disseminated HSV disease was defined as thrombocytopenia, ALT elevation, or AST elevation at diagnosis or a positive blood PCR result. CNS disease was defined as seizures during the study period or a positive cerebrospinal fluid HSV PCR without a corresponding positive blood HSV PCR. Skin, eye, mucus membrane disease was considered to be present if an HSV PCR obtained from a cutaneous lesion from the skin or from a mucus membrane was positive and criteria for disseminated or CNS disease were not met. All AEs were defined a priori as meeting AE criteria on a day with acyclovir exposure [13]. Clinical AEs evaluated were death, rash, hypotension, seizure, and renal failure. Hypotension was defined as exposure to dopamine, dobutamine, epinephrine, norepinephrine, or milrinone. Clinical AEs that occurred prior to the onset of acyclovir exposure were not included even if they continued during acyclovir exposure. We considered seizures to be present when diagnosed by a clinician; electroencephalogram confirmation was not required. Renal failure was defined as a diagnosis of acute or chronic renal failure recorded in the medical record. We categorized laboratory AEs as AEs or severe AEs based on a priori definitions (see Appendix, Supplemental Digital Content 1). Laboratory abnormalities that began prior to acyclovir exposure and continued after acyclovir was started were not considered to be AEs. Small-for-gestational-age status was defined as previously described [14].

2.3. Statistical analysis

We described the demographic characteristics of infants who received acyclovir using counts, proportions, and medians with ranges. We determined the number and proportion of infants with each clinical AE, as well as the number and proportion of infants and infant-days with each laboratory AE and severe AE. For each infant, we calculated the mean and maximum daily doses of acyclovir and used these values to calculate the median mean and median maximum daily doses, respectively. We compared the median maximum daily doses for infants with and without each AE using nonparametric Wilcoxon rank-sum tests. We determined the number of AEs occurring at each maximum daily dose. We compared characteristics for infants who received mean daily acyclovir doses of ≤80 mg/kg/day to those who received >80 mg/kg/day using two sample *t*-tests. We determined the number and proportion of infants with a post-baseline grade 3 or grade 4 AST elevation, ALT elevation, creatinine elevation, leukocytosis, leukopenia, thrombocytosis, and thrombocytopenia based on the Division of AIDS AE severity definitions for each dosing category: maximum daily IV acyclovir dose of <60 mg/kg/day, 60–80 mg/kg/day, and >804mg/kg/day during the treatment period.

Using established exposure estimation methods which consider the dose, dosing interval, and empirical Bayesian estimates of clearance and volume of each infant, we calculated the estimated acyclovir maximum concentration (Cmax) and area under the concentration-time curve at 24 h (AUC) for each infant using a one-compartment pharmacokinetic model [15]. We calculated the median participant-level mean Cmax and AUC exposure values for infants who received a maximum daily acyclovir dose of <60 mg/kg/day, 60–80 mg/kg/day, and >80 mg/kg/day. We determined the odds of leukopenia and any clinical or laboratory AE for infants with different acyclovir exposures using separate unadjusted logistic regression models.

This study was approved by the institutional review board at each site with a waiver of informed consent.

3. Results

We identified 49 infants with confirmed (n = 48) or suspected (n = 1) neonatal HSV disease treated with intravenous acyclovir. Most, 33/49 (67 %), infants in the cohort were between 35 and 42 weeks gestational age at the start of acyclovir therapy (Table 1). The median gestational age at birth was 38 weeks (range 24–41), and the median birth weight was 2990 g (590–4054). The median postnatal age was 8 days. Three infants were >28 days of age; these infants were 29, 55 and 90 days of age. Twenty-one (43 %) infants were born via cesarean section.

Most (40/49, 82 %) infections were diagnosed by HSV DNA PCR; 11/49 (22 %) had a positive HSV viral culture and 2/49 (4 %) had a positive HSV direct immunofluorescence assay. Of the 48 with a positive virologic test, 16 (33 %) were HSV type 1, 28 (58 %) were HSV type 2, and 5 (10 %) were unspecified. One infant was positive for both HSV type 1 and HSV type 2. Thirty-three infants had a test for HSV performed on the cerebrospinal fluid; 19/33 (58 %) infants had a positive result. Eighteen (37 %) infants had a positive test from the blood. Ninety percent (44/49) of infants had a positive test from the skin or a mucus membrane.

Table 1
Demographics.

Demographics	Overall N = 49 (%)	Disseminated N = 27 (%)	CNS N = 11 (%)	SEM N = 10 (%)
Birth weight (g), median (range)	2990 (590, 4054)	3297 (822, 3999)	1820 (590, 4054)	2895 (845, 3705)
Gestational age (weeks)				
23–29	6 (12)	2 (7)	2 (18)	2 (20)
30–34	10 (20)	5 (19)	3 (27)	2 (20)
≥35	33 (67)	20 (74)	6 (55)	6 (60)
Postnatal age (days), median (range)	8 (0, 90)	7 (0, 29)	8 (1, 90)	8 (0, 19)
Male	25 (51)	16 (59)	5 (46)	4 (40)
Race				
White	21 (43)	13 (48)	4 (36)	3 (30)
Black	15 (31)	8 (30)	4 (36)	3 (30)
Other	1 (2)	0 (0)	0 (0)	1 (10)
Unknown	12 (25)	6 (22)	3 (27)	3 (30)
Ethnicity				
Hispanic	3 (6)	2 (7)	0 (0)	1 (10)
Not Hispanic	34 (69)	20 (74)	8 (73)	5 (50)
Unknown	12 (25)	5 (19)	3 (27)	4 (40)
Cesarean section	21 (43)	13 (48)	3 (27)	5 (50)
Maximum daily acyclovir dose				
<60 mg/kg/day	7 (14)	7 (26)	0 (0)	0 (0)
60–80 mg/kg/day	21 (43)	12 (44)	4 (36)	5 (50)
>80 mg/kg/day	21 (43)	8 (30)	7 (64)	5 (50)
Herpes simplex virus type	N = 48 (%)	N = 27 (%)	N = 11 (%)	N = 10 (%)
Type 1	16 (33)[a]	7 (25)[a]	4 (36)	5 (50)
Type 2	28 (58)[a]	18 (64)[a]	7 (64)	3 (30)
Unspecified	5 (10)	3 (11)	0 (0)	2 (20)
Site of positive diagnostic test[a,b]				
Blood	18 (38)	18 (67)	0 (0)	0 (0)
Cerebrospinal fluid	19 (40)	9 (33)	10 (91)	0 (0)
Conjunctivae	3 (6)	2 (7)	0 (0)	1 (10)
Mouth	4 (8)	3 (11)	0 (0)	1 (10)
Naso/oropharynx	8 (17)	6 (22)	0 (0)	2 (20)
Rectum	9 (19)	4 (15)	2 (18)	3 (30)
Skin or mucous membrane lesions	20 (42)	8 (30)	3 (27)	9 (90)

CNS: central nervous system, HSV: herpes simplex virus, SEM: skin, eyes, or mucous membranes.
[a] 1 infant had both HSV Type 1 and HSV Type 2.
[b] Each infant could have >1 positive test.

Ultimately, 27/49 (55 %) infants were considered to have disseminated HSV disease, 11/49 (22 %) CNS disease, and 10/49 (20 %) skin, eyes, or mucous membranes disease. One infant had a clinical diagnosis of HSV disease and was excluded from stratification.

The median mean daily dose of acyclovir was 59 mg/kg/day (range 20–431). Infants born at 23–29 weeks gestational age had a higher median mean daily dose (75 mg/kg/day [20–134]) than those born at later gestational ages (58 mg/kg/day [28–431], P = 0.68). Daily doses varied widely by study site, with median maximum daily doses ranging from 60 mg/kg/day (20–62) to 104 mg/kg/day (60–441). The median duration of inpatient acyclovir treatment was 22 days (1–82). The median AUC and Cmax were 35.2 mg*hr/L (25th, 75th percentiles: 26.2, 54.1) and 8.2 μg/mL (6.9, 11.5), respectively.

Some infants, 14/49 (29 %), received very high doses of acyclovir with a mean daily dose of >80 mg/kg/day. These infants tended to be younger than those who received ≤80 mg/kg/day, with a mean postnatal age of 7 days versus 13 days (P = 0.03). The mean gestational age was 36 weeks for both dose groups (P = 0.90). The infant who received the highest mean daily dose weighed 3400 g and received a daily dose of 441 mg/kg/day.

Clinical AEs were common among all gestational and postnatal age groups (Table 2). Rash was the most common clinical AE, occurring in 18/49 (37 %) infants. A new diagnosis of renal failure occurred in 3 (6 %) infants, all of whom had a gestational age of 35–42 weeks and postnatal age of <14 days. These infants had creatinine levels of 1.07 mg/dL, 2.03 mg/dL, and 1.92 mg/dL on the day of the renal failure event, and none of the infants received dialysis. For 2 of these infants, the creatinine normalized while still receiving acyclovir therapy. The third infant still had an elevated creatinine at the completion of acyclovir therapy. For each clinical AE with >1 event, the median maximum dose (mg/kg/day) for infants without the event was greater than or equal to the median maximum dose for infants with the event.

Nine (18 %) infants died while receiving acyclovir: 4/16 (25 %) infants <35 weeks gestational age and 5/33 (15 %) infants ≥35 weeks gestational age. Infants who survived had a higher median maximum daily dose of acyclovir than those who died (82 mg/kg/day [59–441] and 60 mg/kg/day [20–60], respectively [P < 0.01]). No infants receiving mean daily dose >80 mg/kg/day of acyclovir died.

One or more laboratory AEs occurred in 37 % of infants (Table 3). Elevated ALT was the most common laboratory abnormality. The median maximum daily doses (mg/kg/day) were higher among infants with hypokalemia, elevated blood urea nitrogen, and thrombocytosis than among infants without these laboratory AEs, but these differences were not statistically significant. For all other laboratory AEs and SAEs, the median maximum daily doses for infants without events were greater than or equal to the median maximum daily doses for infants with the AE or SAE.

The daily frequency of AEs did not increase as the mean daily dose of acyclovir increased above 60 mg/kg/day (Fig. 1, Table 4). The 21infants who received >80 mg/kg/day maximum daily dosage during the treatment period had the highest predicted acyclovir exposures, with a median mean AUC of 45.3 mg*hr/L (25th, 75th percentiles: 35.8, 68.4) and median mean Cmax of 11.8 μg/mL (9.9, 19.5). The odds of experiencing any clinical or laboratory AE did not differ by predicted acyclovir exposure for either AUC or Cmax (odds ratio [OR] = 1.00 [0.98, 1.03] and OR = 1.01 [0.93, 1.12], respectively). The odds of leukopenia also did not differ by predicted acyclovir AUC or Cmax exposure (OR = 0.98 [95 % confidence interval: 0.95, 1.00] and OR = 0.92 [0.78, 1.02], respectively).

Table 2
Maximum daily acyclovir doses for infants with and without clinical adverse events.

	N = 49 (%)	Disseminated N = 27 (%)	CNS N = 11 (%)	SEM N = 10 (%)	Dose for infants with AE median (range)	Dose for infants without AE median (range)	P-value*
Rash	18 (37)	7 (26)	5 (45)	6 (60)	51 (20–121)	61 (20–441)	0.11
Hypotension	12 (24)	10 (37)	1 (9)	1 (10)	50 (20–182)	80 (20–441)	<0.01
Death	9 (18)	8 (30)	0 (0)	1 (10)	60 (20–60)	82 (59–441)	<0.01
Seizure	7 (14)	4 (15)	3 (27)	0 (0)	60 (19–127)	78 (20–441)	0.42
Renal failure	3 (6)	3 (11)	0 (0)	0 (0)	60 (60–61)	80 (20–441)	0.19

Participants with event: maximum daily IV dose up to the day of the event.
Participants without event: maximum daily IV dose while on acyclovir.
AE: adverse event, CNS: central nervous system, SEM: skin, eyes, or mucous membranes.
* P-value for Wilcoxon rank-sum test comparison of the median dose for infants with and without the adverse event.

Table 3
Maximum daily acyclovir doses for infants with and without laboratory adverse events.

	N = 49 (%)	Disseminated N = 27 (%)	CNS N = 11 (%)	SEM N = 10 (%)	Daily dose for infants with AE median (range)	Daily dose for infants without AE median (range)	P-value
Hyperglycemia	17 (35)	12 (44)	2 (18)	3 (30)	61 (20–221)	80 (20–441)	0.33
Hypoglycemia	1 (2)	1 (4)	0 (0)	0 (0)	60	78 (20–441)	0.60
Hypernatremia	2 (4)	2 (7)	0 (0)	0 (0)	60	77 (20–441)	0.12
Hyponatremia	6 (12)	4 (15)	2 (18)	0 (0)	60 (40–182)	80 (20–441)	0.08
Hyperkalemia	7 (14)	5 (19)	1 (9)	1 (10)	40 (19–441)	80 (20–318)	0.08
Hypokalemia	9 (18)	6 (22)	2 (18)	1 (10)	96 (60–221)	64 (20–441)	0.15
Elevated BUN	4 (8)	3 (11)	0 (0)	1 (10)	96 (60–221)	65 (20–441)	0.24
Elevated creatinine	10 (20)	7 (26)	0 (0)	3 (30)	60 (58–221)	80 (20–441)	0.38
Elevated ALT	21 (43)	20 (74)	0 (0)	1 (10)	60 (19–102)	80 (20–441)	<0.01
Elevated AST	21 (43)	20 (74)	0 (0)	1 (10)	60 (20–102)	80 (20–441)	<0.01
Leukocytosis	1 (2)	0 (0)	1 (9)	0 (0)	51	71 (20–441)	0.15
Leukopenia	14 (29)	12 (44)	1 (9)	1 (10)	60 (40–96)	80 (20–441)	<0.01
Neutropenia	0 (0)	0 (0)	0 (0)	0 (0)		77 (20, 441)	
Thrombocytosis	5 (10)	0 (0)	3 (27)	2 (20)	110 (60–151)	71 (20–441)	0.27
Thrombocytopenia	21 (43)	18 (67)	1 (9)	2 (20)	60 (19–169)	80 (40–441)	<0.01

Participants with event: maximum daily IV dose up to the day of the event.
Participants without event: maximum daily IV dose while on acyclovir.
AE: adverse event, ALT: aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CNS: central nervous system, SEM: skin, eyes, or mucous membranes.

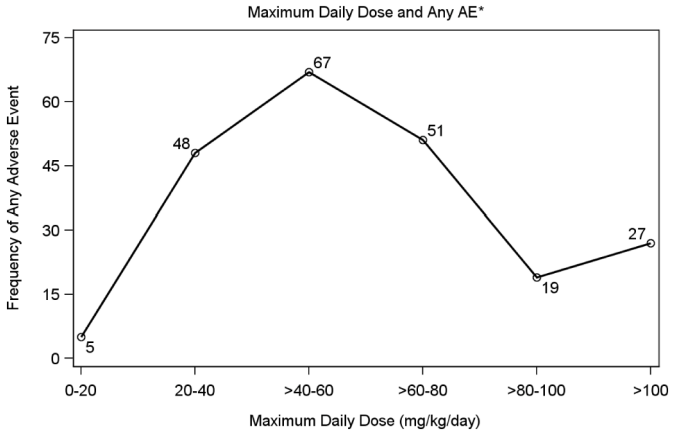

Fig. 1. Adverse events by maximum daily dose.
Daily frequency of clinical or laboratory adverse events by maximum daily dose (mg/kg/day).
AE, adverse event.

Table 4
Participants with Grade 3 and 4 post-baseline laboratory toxicities by maximum daily dose category.

	<60 mg/kg/day N = 7 (%)	60–80 mg/kg/day N = 21 (%)	>80 mg/kg/day N = 21 (%)
Elevated ALT	2 (29)	7 (33)	5 (24)
Elevated AST	3 (43)	10 (48)	3 (14)
Elevated direct bilirubin	2 (29)	7 (33)	5 (24)
Elevated creatinine	3 (43)	3 (14)	5 (24)
Leukocytosis	0 (0)	0 (0)	0 (0)
Leukopenia	0 (0)	0 (0)	0 (0)
Thrombocytosis	0 (0)	0 (0)	0 (0)
Thrombocytopenia	3 (43)	6 (29)	4 (19)

Note: All reported lab values are included. Baseline biochemistry is the closest lab value prior to the first IV acyclovir dosing.
ALT, aminotransferase; AST, aspartate aminotransferase.

4. Discussion

This study provides safety and predicted exposure data for 49 infants treated with high-dose acyclovir for neonatal HSV disease. We found that clinical and laboratory AEs were common, but usually not severe. For most AEs, there did not appear to be a relationship between the dose or exposure of acyclovir and the incidence of AEs. Survival was more common in infants who received very high mean daily doses of acyclovir (>80 mg/kg/day) rather than 30 mg/kg/day or the AAP-recommended dose of 60 mg/kg/day.

The FDA-approved package insert for intravenous acyclovir notes that nephrotoxicity and neurotoxicity can occur with high doses or when there are underlying electrolyte abnormalities or renal insufficiency [7]. Leukopenia, skin rash, and liver enzyme abnormalities have also rarely been attributed to acyclovir toxicity [16,17]. Nephrotoxicity occurs when acyclovir crystals precipitate in the renal tubules, resulting in a crystal nephropathy [18]. The risk of acyclovir-related renal toxicity is increased by dehydration, underlying renal dysfunction, and concomitant use of other nephrotoxic medications [10,19]. Prior reports found that nephrotoxicity occurred in 6–10 % of infants and children treated with high-dose acyclovir [1,20]. In our cohort of infants with neonatal HSV disease, 20 % had a serum creatinine level > 1.7 mg/dL. Infants without elevated creatinine concentrations had a higher median maximum daily dose than those with elevated creatinine concentrations, suggesting that nephrotoxicity is not entirely dose-dependent. It is likely that the virus itself or the resultant clinical syndrome also had important contributions to nephrotoxicity. Most of these infants were born prematurely, which may have made them more susceptible to nephrotoxic insults. Electrolyte abnormalities occurred in 53 % of infants in our study.

Cases of acyclovir-associated neurotoxicity have been reported in children [21–23]. However, it is difficult to attribute neurologic symptoms to acyclovir because they may occur as a result of direct infection of the CNS with HSV or as a sequela of underlying critical illness. This is especially true for infants in whom meningoencephalitis is a common presentation of HSV infection [24]. Because acyclovir is not typically given to infants in the absence of HSV infection, we are unable to easily separate the effects of the medication from the effects of the infection. The dose-response analysis that we performed found that infants without seizure had a higher median maximum daily dose than infants who had a seizure. This suggests that there is not a dose-dependent relationship between acyclovir exposure and neurotoxicity. Idiosyncratic acyclovir-associated neurotoxicity may still occur.

Case reports have suggested that neutropenia can occur with prolonged or repeated acyclovir courses [16,17]. However, a study that used 30 mg/kg/day of acyclovir to treat 107 infants found that none developed a white blood cell count <2500/mL [6]. A prospective study of 60 mg/kg/day found that an absolute neutrophil count (ANC)

<1000/mm^3 occurred in 16 % of 64 treated infants [1]. A retrospective study of 89 infants with HSV disease treated with acyclovir found that an ANC <500/mm^3 occurred in 6 % of infants and on <1 % of days with acyclovir exposure [25]. No infant in our study had an ANC <500/mm^3, providing further support that the incidence of neutropenia while exposed to acyclovir is low. In all of the studies in which neutropenia occurred, the infants recovered uneventfully with continuation of acyclovir therapy or after completion of the treatment course [1].

The AAP recommendation that 60 mg/kg/day be used for neonatal HSV disease was based on a clinical trial that compared 66 infants treated with high-dose acyclovir to an earlier clinical trial cohort of 107 infants treated with the 30 mg/kg/day [1,7,8]. The effect on mortality was particularly striking for infants with disseminated disease: 61 % of those treated with 30 mg/kg/day divided every 8 h for 10 days died compared to 31 % of those treated with 60 mg/kg/day divided every 8 h for 21 days [1]. In our cohort, only 18 % of infants died, suggesting further improvements in survival over time. No infants treated with >80 mg/kg/day of acyclovir died, even though several of these infants were preterm and would have been expected to have an increased risk for adverse outcomes, including death.

In a recent population pharmacokinetic study, investigators found that infants 36–41 weeks postmenstrual age required acyclovir doses of 20 mg/kg/dose every 6 h to achieve sufficient serum concentrations to reach an effective acyclovir concentration in the CNS [15]. We observed that high exposures of acyclovir were not associated with increased frequency of laboratory or clinical AEs, and 21 infants in our cohort received maximum daily doses >80 mg/kg/day during the treatment period. In our study, infants born at <29 weeks gestational age had a higher median mean daily dose than older infants. This was primarily driven by one center where clinicians used a dosing strategy of 500 mg/ m^2/dose rather than 20 mg/kg/dose [9]. For young children and infants, body-surface-area-based dosing can result in dramatically higher doses than weight-based dosing [26]. This is clearly seen in our cohort, with infants dosed according to body surface area receiving as much as 7 times the 30 mg/kg/day dosing of acyclovir. Even at these high doses, serious AEs were uncommon.

5. Limitations

Our study is limited by the retrospective nature of the analysis. Laboratory assessments were obtained at the discretion of the treating physician rather than systematically. Similarly, diagnostic evaluations for clinical AEs were conducted at the discretion of the treating physician. It is possible that our findings represent some AEs that were due to HSV disease itself, other disease processes, or concomitant medications and were not caused by acyclovir exposure.

6. Conclusion

Although AEs were common with high-dose acyclovir use, severe AEs were rare. Acyclovir exposure was not associated with the incidence of AEs. Very high doses of acyclovir (>80 mg/kg/day) were not associated with increased AEs but larger prospective studies are needed to verify this finding.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2022.105616.

References

[1] D.W. Kimberlin, C.Y. Lin, R.F. Jacobs, et al., Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections, Pediatrics 108 (2001) 230–238.

[2] S.G. Pinninti, D.W. Kimberlin, Neonatal herpes simplex virus infections, Pediatr. Clin. N. Am. 60 (2013) 351–365.

[3] F. Xu, M.R. Sternberg, B.J. Kottiri, et al., Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States, JAMA 296 (2006) 964–973.

[4] D.W. Kimberlin, C.Y. Lin, R.F. Jacobs, et al., Natural history of neonatal herpes simplex virus infections in the acyclovir era, Pediatrics 108 (2001) 223–229.

[5] S.S. Shah, P.L. Aronson, Z. Mohamad, S.A. Lorch, Delayed acyclovir therapy and death among neonates with herpes simplex virus infection, Pediatrics 128 (2011) 1153–1160.

[6] R. Whitley, A. Arvin, C. Prober, et al., A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. Infectious diseases collaborative antiviral study group, N. Engl. J. Med. 324 (1991) 444–449.

[7] Fresenius Kabi, APP Pharmaceuticals, LLC. Acyclovir Sodium Injection: For Intravenous Infusion Only. 2012. Fresenius Kabi web site. https://www.fresenius-kabi.com/en-ca/documents/Acyclovir-PM-ENG-v1.1-Clean.pdf. (Accessed 21 October 2021).

[8] American Academy of Pediatrics, Herpes simplex, in: D.W. Kimberlin, M.T. Brady, M.A. Jackson, S.S. Long (Eds.), Red Book: 2015 Report of the Committee on Infectious Diseases, 30 Edition, American Academy of Pediatrics, Elk Grove Village, IL, 2015, pp. 432–445.

[9] K.F. Tiffany, D.K. Benjamin, P. Palasanthiran, et al., Improved neurodevelopmental outcomes following long-term high-dose oral acyclovir therapy in infants with central nervous system and disseminated herpes simplex disease, J. Perinatol. 25 (2005) 156–161.

[10] R. Schreiber, J. Wolpin, G. Koren, Determinants of aciclovir-induced nephrotoxicity in children, Paediatr. Drugs. 10 (2008) 135–139.

[11] J. Gentry, C. Peterson, Death delusions and myoclonus: acyclovir toxicity, Am. J. Med. 128 (2015) 692–694.

[12] D.W. Kimberlin, R.J. Whitley, W. Wan, et al., Oral acyclovir suppression and neurodevelopment after neonatal herpes, N. Engl. J. Med. 365 (2011) 1284–1292.

[13] A. England, K. Wade, P.B. Smith, et al., Optimizing operational efficiencies in early phase trials: the pediatric trials network experience, Contemp. Clin. Trials. 47 (2016) 376–382.

[14] I.E. Olsen, S.A. Groveman, M.L. Lawson, et al., New intrauterine growth curves based on United States data, Pediatrics 125 (2010) e214–e224.

[15] M.R. Sampson, B.T. Bloom, R.W. Lenfestey, et al., Population pharmacokinetics of intravenous acyclovir in preterm and term infants, Pediatr. Infect. Dis. J. 33 (2014) 42–49.

[16] A.M. Tuncer, B. Evis, B. Kunak, N. Akcayoz, U. Ertem, Erythroblastopenia and leukopenia in the patient with severe herpes zoster treated with intravenous acyclovir, Turk. J. Pediatr. 31 (1989) 317–321.
[17] H.M. Feder Jr., R.K. Goyal, P.J. Krause, Acyclovir-induced neutropenia in an infant with herpes simplex encephalitis: case report, Clin. Infect. Dis. 20 (1995) 1557–1559.
[18] S.G. Yarlagadda, M.A. Perazella, Drug-induced crystal nephropathy: an update, Expert Opin. Drug Saf. 7 (2008) 147–158.
[19] S. Rao, M.J. Abzug, P. Carosone-Link, et al., Intravenous acyclovir and renal dysfunction in children: a matched case control study, J. Pediatr. 166 (1462–1468) (2015) e1–e4.
[20] J.G. Kendrick, M.H. Ensom, A. Steer, et al., Standard-dose versus high-dose acyclovir in children treated empirically for encephalitis: a retrospective cohort study of its use and safety, Paediatr. Drugs. 16 (2014) 229–234.
[21] D.K. Strong, D. Hébert, Acute acyclovir neurotoxicity in a hemodialyzed child, Pediatr. Nephrol. 11 (1997) 741–743.
[22] N. Nakamoto, T. Nakayama, S. Kudo, et al., A case report of acute encephalitis with neuro-psychiatric side-effects of acyclovir, No To Hattatsu. 30 (1998) 334–338.
[23] L. Chevret, D. Debray, C. Poulain, et al., Neurological toxicity of acyclovir: report of a case in a six-month-old liver transplant recipient, Pediatr. Transplant. 10 (2006) 632–634.
[24] S.H. James, D.W. Kimberlin, Neonatal herpes simplex virus infection: epidemiology and treatment, Clin. Perinatol. 42 (2015) 47–59, viii.
[25] J.E. Ericson, M. Gostelow, J. Autmizguine, et al., Safety of high-dose acyclovir in infants with suspected and confirmed neonatal herpes simplex virus infections, Pediatr. Infect. Dis. J. 36 (2017) 369–373.
[26] I.H. Bartelink, C.M. Rademaker, A.F. Schobben, et al., Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations, Clin. Pharmacokinet. 45 (2006) 1077–1097.