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ORIGINAL RESEARCH ARTICLE

Standard-Dose Versus High-Dose Acyclovir in Children Treated Empirically for Encephalitis: A Retrospective Cohort Study of Its Use and Safety

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Abstract
Background Intravenous acyclovir is the treatment of choice for herpes simplex virus encephalitis. In 2006, the American Academy of Pediatrics updated its dosing recommendations for children aged 3 months to 12 years to receive high-dose acyclovir (60 mg/kg/day). The association between acyclovir dose and toxicity is unclear.
Objective The purpose of our study was to review our institution's experience with standard- and high-dose acyclovir for the empiric treatment of encephalitis.
Study Design, Setting and Patients This retrospective cohort study included patients aged 1 month to 18 years who received acyclovir as empiric treatment for encephalitis between 2005 and 2009 at a tertiary care children's hospital. We excluded patients with baseline renal impairment and those without serum creatinine measurements prior to and during treatment.
Main Outcome Measure The main outcome measure of this study was to compare the occurrence of renal injury or failure between children who received the standard- versus high-dose regimen.
Results Sixty-one patients were included ($n = 32$ standard-dose; $n = 29$ high-dose). There was no statistical difference in change in serum creatinine from baseline between children who received standard- versus high-dose acyclovir (0 vs. 5.1 %; $p = 0.79$). One child in the standard-dose group and three children in the high-dose group developed renal injury or failure during treatment (3.1 vs. 10.3 %; $p = 0.34$). Children with renal injury or failure were older, had a longer length of stay, and longer duration of therapy than children without.
Conclusions The incidence of renal injury or failure was similar between children who received standard-dose and high-dose acyclovir.

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1 Introduction

Acyclovir is an antiviral agent used for the treatment of infections caused by many of the herpes viruses including herpes simplex virus (HSV) and varicella zoster virus (VZV). Intravenous acyclovir is the treatment of choice for HSV encephalitis based on two studies in children and adults that demonstrated a significant reduction in morbidity and mortality from HSV encephalitis when

comparing acyclovir with vidarabine [1, 2]. HSV encephalitis accounts for 10–20 % of viral encephalitis infections, with an estimated incidence between 1 in 250,000 and 1 in 500,000 individuals per year in the United States [3]. Approximately one-third of cases of HSV encephalitis occur in patients 6 months to 20 years of age [3]. In practice, children with encephalitis are treated empirically with acyclovir while awaiting results of the cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for HSV.

In neonates and infants aged up to 3 months, the recommended dose of acyclovir is 60 mg/kg/day for a total of 14–21 days [4]. This recommendation is based on a study by Kimberlin et al. [5] that compared acyclovir 45 and 60 mg/kg/day for 21 days with historic controls who received 30 mg/kg/day for 10 days for the treatment of disseminated HSV and HSV encephalitis. Mortality from disseminated HSV was significantly lower in the group who received acyclovir 60 mg/kg/day than in the historical control group (31 vs. 61 %; $p < 0.05$). The difference in mortality from HSV encephalitis was not significant (NS) between these groups (6 vs. 19 %; $p =$ NS), possibly owing to the small number of neonates with encephalitis. To our knowledge, no studies have compared high-dose acyclovir (60 mg/kg/day) with standard-dose acyclovir (30 mg/kg/day) for the treatment of HSV encephalitis outside of the neonatal period. Nonetheless, the recommended dose of acyclovir by the American Academy of Pediatrics is as follows: ≥3 months to 12 years 60 mg/kg/day for 14–21 days; ≥12 years 30 mg/kg/day for 14–21 days [4].

Since the updated dosing recommendations for HSV encephalitis were published in 2006 [6] and endorsed again in 2012 [4], high-dose acyclovir has been used at our institution in children 12 years of age and younger. The recommendation, however, has not been consistently implemented and it has been our observation that many children continue to receive standard-dose acyclovir. This may be due, in part, to observed cases of renal injury at our institution. A recent retrospective review of children treated with acyclovir for suspected HSV encephalitis found that 38 out of 51 children initially received incorrect doses compared with published guidelines [7].

We designed a study to describe our institution's experience with standard- and high-dose acyclovir for empiric treatment of encephalitis in children. The primary objective was to compare the occurrence of renal injury or failure between children who receive the standard- versus high-dose regimen. Secondary safety objectives were to characterize risk factors for renal injury or failure and to describe other adverse events that occur in children receiving acyclovir. Secondary efficacy objectives were to describe the occurrence of HSV encephalitis and to describe mortality in children receiving acyclovir for empiric treatment.

2 Materials and Methods

2.1 Study Design

Following research ethics board approval, a retrospective chart review of all patients who received acyclovir as empiric treatment for encephalitis at British Columbia's Children's Hospital (BCCH) was performed. Patients who received acyclovir between January 1, 2005 and April 30, 2009 were identified via the pharmacy database.

2.2 Patients

Patients aged 1 month to 18 years who received at least one dose of intravenous acyclovir for the empiric treatment of encephalitis were included in this study. Exclusion criteria were as follows: patients admitted to one of the hospital's two oncology wards, those who received acyclovir for an indication other than encephalitis, and immunocompromised patients who received acyclovir as herpes virus prophylaxis. Patients with a baseline estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 or those without a serum creatinine (SCr) measurement both prior to and during treatment with acyclovir were also excluded.

2.3 Data

The patients' health records were used to gather demographic information, hospital ward, medical problems, diagnosis of HSV, blood and CSF cultures and PCR, computed tomography (CT), magnetic resonance imaging (MRI), acyclovir dose and duration, concomitant medications, intravenous fluids, oral fluid intake, urine output, liver enzymes, white blood cell (WBC) and neutrophil counts, SCr and urea. SCr is typically measured three times per week in patients receiving acyclovir at our institution. When height was available, eGFR was calculated using the Schwartz equation [8, 9]: eGFR = [$k \times$ height (cm)/SCr (mg/dL)]; $k = 0.45$ for infants ≤1 year of age, $k = 0.55$ children >1 year of age and adolescent girls, $k = 0.7$ for adolescent boys ≥12 years of age.

Patients who received 30 and 60 mg/kg/day of acyclovir were grouped as standard-dose and high-dose acyclovir, respectively. To address patients whose dose of acyclovir changed during the course of therapy, patients were categorized into standard- versus high-dose groups based on the total mg/kg dose received during the first 48 hours of therapy. That is, patients whose total dose (over the first 48 h) was <90 mg/kg were included in the standard-dose and those with ≥90 mg/kg were included in the high-dose acyclovir group. This method was used instead of mean or median dose to avoid confounding by patients whose renal

function changed during therapy and required renal dose adjustment of acyclovir.

The pRIFLE criteria (acronym indicating pediatric Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease) [10] was used to define renal injury (eGFR decrease of 50 % from baseline or urine output <0.5 mL/kg/h for 16 h) and renal failure (eGFR decrease of 75 % from baseline or eGFR <35 mL/min/1.73 m^2 or urine output <0.3 mL/kg/h for 24 h or anuric for 12 h). If data were incomplete for height and we were therefore unable to calculate eGFR, change in SCr was used to determine renal injury and failure. In this case, a SCr doubling and tripling from baseline were considered renal injury and renal failure, respectively, instead of eGFR decrease of 50 and 75 % from baseline. This definition corresponds to the renal injury and failure definitions in the RIFLE criteria for adults [11]. Post hoc, we examined the data for renal risk as defined by the pRIFLE and RIFLE criteria (eGFR decrease of 25 % from baseline and SCr increase by 1.5 times baseline or urine output <0.5 mL/kg/h for 6 h) [10, 11].

2.4 Statistical Methods

Descriptive statistics were used to describe patient demographic information and to characterize the non-renal adverse events and the concomitant nephrotoxic drugs. Diagnosis of HSV between groups was compared using the Fisher's exact test. The mean changes in eGFR from baseline in the standard-dose and high-dose acyclovir groups were compared using the Wilcoxon rank sum test. The change in eGFR from baseline was calculated from the patient's baseline SCr and the highest SCr during treatment with acyclovir (%change in GFR = [lowest eGFR − baseline eGFR]/baseline eGFR × 100 %). When SCr was only available, we expressed the highest SCr on treatment as a percentage of the baseline SCr (% baseline SCr = highest SCr/baseline SCr × 100 %). Subgroup analysis of patients based on age categories (1 month to <12 years and ≥12 years to 18 years) was performed for this outcome. The combined proportion of patients with renal injury and renal failure in the standard-dose and high-dose acyclovir groups was compared using the Fisher's exact test.

Descriptive statistics were used to characterize factors associated with renal injury or failure. Assuming $\alpha = 0.05$ and $\beta = 0.2$, a sample size of 21 patients per group was required to show a mean difference of 12 % change in eGFR or SCr from baseline between groups; the 12 % value was based on results of two retrospective reviews [12, 13]. Missing data were reported; all calculations and statistical analyses were performed on available data only.

3 Results

A total of 104 children were screened for inclusion in the study. Forty-three children were excluded: nine received acyclovir for another indication, one did not receive any doses, 32 did not have SCr measurements both prior to and during treatment, and one had a baseline eGFR <50 mL/min/1.73 m^2. Demographic information is shown in Table 1. Children who received high-dose acyclovir were younger than those who received standard-dose acyclovir. There were also more admissions to critical care in the high-dose group. The most common presenting signs overall were seizure, fever, and headache.

Table 1 Characteristics of children receiving empiric acyclovir for presumed encephalitis

	Standard dose ($n = 32$)	High dose ($n = 29$)
Age (months), median; range	53.5; 6–202	36; 1.8–192
1 month–<12 years; *n* (%)	26 (81.2)	27 (93.1)
12–18 years; *n* (%)	6 (18.8)	2 (6.9)
Male; *n* (%)	22 (68.8)	10 (34.5)
Weight (kg), median; range	18.1; 4.6–81.6	15.0; 2.8–62.0
Admitting diagnosis; *n* (%)		
Meningitis	6 (18.8)	2 (6.9)
Encephalitis	12 (37.5)	9 (31.0)
Seizure	5 (15.6)	5 (17.2)
Status epilepticus	6 (18.8)	7 (24.1)
Other	4 (12.5)	6 (20.7)
Length of stay (days), median; range	6.5; 3–41	7.0; 4–30
Admission to critical care; *n* (%)	14 (43.8)	20 (69.0)
Initial signs and symptoms; *n* (%)		
Altered level of consciousness	5 (15.6)	12 (41.1)
Behavioral disturbance	2 (6.3)	3 (10.3)
Fever	20 (62.5)	15 (51.7)
Headache	9 (28.1)	7 (24.1)
Motor deficit	5 (15.6)	0 (0)
Photophobia	0 (0)	2 (6.9)
Seizure	23 (71.9)	18 (62.1)
Neck stiffness	3 (9.4)	2 (6.9)
Vomiting	6 (18.8)	4 (13.8)
Other	2 (6.3)	6 (20.7)
Oral intake (mL/day), median; range	352; 28–1,072	314; 52–740
Intravenous hydration (mL/day), median; range	1,006; 148–3,064	978; 129–2,363
Acyclovir dose (mg/kg/day), median; range	30; 21.2–50.4	57.5; 31.4–60.0
Acyclovir duration (days), median; range	3; 1–20.7	3; 0.67–22.0

Table 2 Safety outcomes

	Standard dose ($n = 32$) (%)	High dose ($n = 29$) (%)	p Value
Baseline SCr (μmol/L), median; range	36; 17–98	29; 18–94	
Highest SCr on treatment (μmol/L), median; range	40; 11–420	34; 11–302	
% Baseline SCr, median; range	100; 61.1–608.7	105.1; 57.9–402.67	0.79
1 month–<12 years	100; 61.1–192	103.6; 57.9–359.3	0.87
12–18 years	124.5; 79.1–608.7	254.6; 106.4–402.7	0.66
Urine output (mL/kg/h), median; range	1.9; 0.7–4.5	2.2; 1.0–4.4	
Renal outcomes; *n* (%)			
Renal risk	3 (9.4)	1 (3.4)	
Renal injury	0 (0)	1 (3.4)	0.48
Renal failure	1 (3.1)	2 (6.9)	0.60
Renal injury or failure	1 (3.1)	3 (10.3)	0.34
Concomitant nephrotoxic drugs; *n* (%)			
Aminoglycosides	2 (6.3)	0 (0)	
Cephalosporins	28 (87.5)	29 (100)	
Furosemide	4 (12.5)	5 (17.2)	
Mannitol	1 (3.1)	1 (3.4)	
NSAIDs	8 (25.0)	4 (13.8)	
Penicillins	3 (9.4)	1 (3.4)	
Vancomycin	20 (62.5)	20 (69)	
Other	1 (3.1)	2 (6.9)	
Other adverse events; *n* (%)			
Leukopenia	2 (6.3)	0 (0)	
Neutropenia	1 (3.1)	0 (0)	
Elevated liver enzymes	2 (6.3)	2 (6.9)	
Rash	4 (12.5)	2 (6.9)	
Other	1 (3.1)	3 (10.3)	

NSAIDs non-steroidal anti-inflammatory drugs, *SCr* serum creatinine

Data were incomplete for height, with only 5 % of children having a documented height in their medical record. Therefore, we were unable to calculate eGFR and report instead SCr. Data for safety outcomes are shown in Table 2. The median change in SCr from baseline was numerically higher in the high-dose group as opposed to the standard-dose group, but this did not reach statistical significance. One child in the standard-dose group and three children in the high-dose group developed renal injury or failure during treatment with acyclovir; however, renal injury or failure resolved during or following completion of acyclovir therapy in all children. Renal injury occurred after a median of 1 day of treatment (range 1–2 days). Acyclovir was discontinued in two of the children with renal failure. Acyclovir dose was reduced in the remaining two children. In the child with renal injury, concomitant non-steroidal anti-inflammatory drug (NSAID) therapy was discontinued. All children were supported with IV fluids and none required dialysis or renal replacement therapy.

When comparing children with and without adverse renal outcomes, the children with renal injury or failure were older (median 162 vs. 44 months [range 69–193 vs. 2–202 months]) and had a longer length of stay (median 24.5 vs. 7 days [range 8–26 vs. 3–41 days]). Children with adverse renal outcomes also had a longer duration of acyclovir therapy (median 11 vs. 3 days [range 1–22 days for both groups]). The daily dose of acyclovir, the volume of intravenous hydration, and the number of concomitant nephrotoxins was similar between children with and without adverse renal outcomes. The most common potentially nephrotoxic drugs were cephalosporins and vancomycin (Table 2).

Other adverse events were variably reported. A complete blood count (CBC) was available prior to and during treatment for 30 children (94 %) in the standard-dose group and 23 children (79 %) in the high-dose group. Liver enzymes were available prior to and during treatment for 19 children (59 %) in the standard-dose group and 16 children (55 %) in the high-dose group. Leukopenia, neutropenia, and elevated liver enzymes were uncommon adverse events (Table 2). Other adverse events included six children (9.8 %) with rash, one child (1.6 %) with phlebitis, and two children (3.3 %) with altered level of consciousness.

All children had CSF PCR testing for HSV; one child in each group had a positive HSV PCR. Of these children, one received acyclovir for 22 days and the other for 10 days, prior to transfer to a community hospital for a planned duration of 21 days. This is in contrast to the median treatment duration of 2.7 days (range 1–21 days) in children with a negative HSV PCR. Neuroimaging with CT or MRI was performed in 18 (56 %) and 17 (54 %) children in the standard-dose group, respectively, and 21 (72 %) and 8 (25 %) children in the high-dose group. Only one child in the high-dose group had a CT that was suggestive of HSV encephalitis. The most common discharge diagnosis was seizure disorder, febrile seizure, or status epilepticus, followed by presumed viral encephalitis. Two children, both in the high-dose acyclovir group, died during the study period. One child died secondary to cardiac arrest and the other secondary to status epilepticus; neither child had any evidence of HSV encephalitis.

4 Discussion

Primary objectives of our study were to characterize the use of standard- and high-dose acyclovir at our institution and to compare the occurrence of renal injury or failure between children who received the standard- versus high-dose regimen. Most children who received acyclovir for empiric treatment of encephalitis were younger than 12 years of age. Two children older than 12 years received high-dose acyclovir, contrary to published dosing recommendations [4]. One of these children developed renal failure while receiving high-dose acyclovir. Children at our institution received empiric acyclovir for a median of 3 days in both dosing groups. The median change in SCr from baseline in children who received standard- and high-dose acyclovir was 0 and 5.1 %, respectively. This difference was much lower than the estimated 12 % difference we derived from two retrospective reviews [12, 13] and used for our sample size calculation. If there was indeed a statistical difference in change in SCr from baseline between the two dosing groups at our institution, it would likely be small and of questionable clinical significance. The occurrence of renal injury and renal failure was 3.1 and 10.3 % in the standard- and high-dose groups, respectively. This is lower than the 18 % occurrence of renal failure reported in a small group of children receiving acyclovir and ceftriaxone for presumed meningoencephalitis [12].

We attempted to characterize risk factors for renal injury or renal failure in children receiving acyclovir. In our study, dose did not appear to be related with adverse renal outcomes. This is in contrast to the report by Vomiero et al. [12] where they found a significant correlation between acyclovir dose and renal impairment. However, Schreiber et al. [13] did not find a correlation between acyclovir dose and decreased GFR. In our study, children who had renal injury or failure were older and received a longer duration of acyclovir than children without renal injury or failure; however, this was not statistically significant. Schreiber et al. [13] found that concomitant nephrotoxic drugs and impaired baseline GFR were significant predictors of acyclovir nephrotoxicity. Our study excluded patients with impaired baseline GFR. We did not find a difference in number of concomitant nephrotoxic drugs between children with and without renal injury or failure. It is possible that our study did not have enough power to elucidate risk factors for renal injury or failure in children receiving acyclovir.

There are some limitations to this study that are inherent to its retrospective design. Firstly, the small number of patients with confirmed HSV encephalitis at this institution (one child in each dosing group) precluded comparison of the efficacy between standard- and high-dose acyclovir in this population. Meadows et al. [14] described the incidence of HSV encephalitis diagnosis in infants receiving empiric acyclovir as 1.4 %, which was lower than our study (overall 3.3 %). Secondly, some patient information was incomplete or unavailable. For example, the children's oral intake and urine output were variably reported; this could have led to an underestimate in both parameters. Height was minimally recorded in our patients, which prevented us from calculating eGFR. We instead reported our outcomes based on SCr as opposed to eGFR. This makes comparison of absolute values between groups difficult because it does not account for age or size. Thirdly, confounding of results could have occurred due to the severity of illness or type of care provided to the patient. Lastly, our study sample was too small to do multivariate analysis which would have better allowed elucidation of risk factors for renal injury while controlling for other confounders. Given that the median treatment duration was 3 days, the incidence of renal injury or failure in our study may be lower than in children who receive acyclovir for the treatment of confirmed HSV encephalitis.

5 Conclusions

To our knowledge, this is the first report that compares the safety of standard-dose and high-dose acyclovir for encephalitis. We did not find an association between acyclovir dose and renal injury or failure, although it is possible that our study was underpowered to detect a significant association. Given that age may be associated with renal injury or failure and that one of the two children over 12 years of age who received high-dose acyclovir

went on to develop renal failure, it is advisable to continue to limit high-dose acyclovir to children younger than 12 years of age. Renal injury or failure was reversible in all of the children in this study. HSV encephalitis, although rare, can result in significant morbidity and mortality. Shorter acyclovir duration has been associated with increased risk of relapsed HSV encephalitis; however, the relationship between acyclovir dose and HSV relapse, or morbidity and mortality from HSV encephalitis is not clear [15, 16]. Given the results of our study, the continued use of high-dose acyclovir for the empiric treatment of encephalitis in children younger than 12 years of age, according to published recommendations [4], is advisable.

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