Intravenous Acyclovir and Renal Dysfunction in Children: A Matched Case Control Study

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Objectives A cluster of children receiving intravenous (IV) acyclovir for meningoencephalitis developed acute renal failure in April-May 2008, which prompted a retrospective case-control study to determine the rate of and risk factors for acute nephrotoxicity during IV acyclovir treatment in children.

Study design The percentage decrease in glomerular filtration rate in children receiving IV acyclovir who had ≥1 creatinine measurement after acyclovir initiation from October 2006 to January 2009 was classified as renal risk, injury, or failure according to modified Pediatric Risk Injury, Failure, Loss, End-Stage Renal Disease criteria. Univariate and multivariate matched analyses were conducted to identify risk factors contributing to nephrotoxicity.

Results In the selected study group, renal dysfunction was seen in 131 of 373 (35%) treatment courses studied: 81 of 373 (22%) risk, 36 of 373 (9.7%) injury, and 14 of 373 (3.8%) failure. Most renal dysfunction occurred within 48 hours of the initiation of acyclovir. Renal function returned to the normal range but not to baseline in most cases during the follow-up period. Risk factors for renal dysfunction included acyclovir dose >15 mg/kg (OR 3.81, 95% CI 1.55-9.37) for risk; cumulative exposure greater than calculated cumulative exposure based on 500 mg/m^2/dose (OR 6.00, 95% CI 1.95-18.46) for injury; and age >8 years (OR 21.5, 95% CI 2.2, >1000) and ceftriaxone coadministration (OR 19.3, 95% CI 1.8, >1000) for failure.

Conclusions Nephrotoxicity associated with IV acyclovir is common and necessitates renal function monitoring. Risk factors include greater dose, older age, and concomitant ceftriaxone administration. Outside the neonatal period, renal dysfunction may be minimized by dosing IV acyclovir below thresholds associated with nephrotoxicity (ie, ≤500 mg/m^2/dose or ≤15 mg/kg/dose), particularly in older patients. *(J Pediatr 2015;166:1462-8)*.

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Acyclovir is used commonly in children for the empiric treatment of meningoencephalitis and neonatal sepsis and for treatment of suspected or proven herpes simplex virus (HSV) and varicella zoster virus (VZV) infections. Recommended dosing regimens vary depending on the offending virus (HSV or VZV) and clinical indication. Dosing acyclovir at 20 mg/kg by intravenous (IV) every 8 hours is recommended for neonatal HSV infections. The Food and Drug Administration–approved dose for HSV encephalitis in children 3 months of age to 12 years is also 20 mg/kg every 8 hours, but many experts recommend 30-45 mg/kg/day for this age group. For children 12 years of age and older, 10 mg/kg every 8 hours is recommended for HSV encephalitis, with consideration by some sources of dosing based on ideal body weight.[1] For VZV infections, recommended doses include 10 mg/kg IV every 8 hours or 500 mg/m^2 every 8 hours.[1-3]

Studies in animals and humans demonstrate that acyclovir can cause nephrotoxicity characterized by intrarenal obstructive nephropathy secondary to drug crystal formation in the collecting ducts.[4,5] Interstitial nephritis and tubular necrosis also can result in renal insufficiency, and it is hypothesized that direct tubular injury causes rapid increases in serum creatinine (sCr) levels within 12 hours of initiation of treatment.[6,7]

From April-May 2008, we observed 4 cases of acute renal failure in patients with meningoencephalitis receiving 20 mg/kg/dose of IV acyclovir every 8 hours. In all cases, patients concomitantly received vancomycin, ceftriaxone, and IV contrast for imaging studies and developed acute nephrotoxicity within 24-72 hours of initi-

BMI	Body mass index
eGFR	Estimated glomerular filtration rate
HSV	Herpes simplex virus
IV	Intravenous
sCr	Serum creatinine
VZV	Varicella zoster virus
$\Delta dose_{500}$	Difference between total cumulative acyclovir dose before attaining worst renal dysfunction category and a calculated (potential) cumulative exposure based on receipt of 500 mg/m^2/dose

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The authors declare no conflicts of interest.

0022-3476/$ - see front matter. Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.jpeds.2015.01.023

ating acyclovir therapy. These observations prompted our study of the rate of and potentiating risk factors for acute renal failure in children receiving IV acyclovir.

Methods

We conducted a retrospective case-control study of patients admitted to Children's Hospital Colorado from October 2006 to January 2009 who received treatment doses of IV acyclovir. Approval was obtained from the Colorado Multiple Institutional Review Board. Patients with ≥1 sCr measurement after initiation of IV acyclovir were included. Hematology/oncology patients and those receiving oral acyclovir were excluded.

The Schwartz equation was used to calculate baseline estimated glomerular filtration rate (eGFR) before the administration of acyclovir, based on sCr level and height adjusted for body surface area.[8] For patients lacking a baseline sCr measurement, the normal mean sCr for age was used.[8] In patients for whom height was not documented, height was derived from weight-for-length curves using the same percentile as the patient's weight for age. Subsequent eGFRs were determined on the basis of each sCr measurement after acyclovir was started, and the percentage decrease in eGFR from baseline was calculated. For patients with a baseline sCr before the initiation of acyclovir and follow-up sCr values available, the final percentage change in eGFR was calculated using the last available sCr for each treatment course. Patients developing renal dysfunction >1 week after the end of acyclovir administration were excluded, given the possibility of other causes of nephrotoxicity. Acute kidney injury was graded according to changes in estimated creatinine clearance as defined by the Pediatric Risk Injury, Failure, Loss, End-Stage Renal Disease classification system.[9] Decreases in eGFR of 25%-49% defined risk; 50%-74% defined injury, and ≥75% defined failure. The first eGFR decrease that fulfilled the criterion for the patient's worst category of dysfunction attained during acyclovir treatment was included for analysis.

Cases were defined as patients who developed renal dysfunction (risk, injury, or failure). For each case, we identified all possible controls without renal dysfunction that had received at least the same number of IV acyclovir doses as the case at the time of the patient's worst category of renal dysfunction. We used random sampling among this pool to identify matched controls. Controls were used only once for matching within each renal dysfunction stratum (risk, injury, failure); however, because the pool of controls was constant, the same control could be matched to cases in different renal dysfunction groups. On the basis of the frequency of various levels of renal dysfunction, we matched controls in the following case: control ratios: risk, 1:2; injury, 1:4; and failure, 1:5.

Statistical Analyses

The primary outcome was the rate of renal risk, injury, and failure among IV acyclovir recipients. Secondary outcome measures were admission to the intensive care unit, dialysis requirements, and length of hospitalization. Risk factors analyzed included age, sex, race, weight, body mass index (BMI), acyclovir dose and duration, and concomitant nephrotoxic antimicrobials and contrast agents.

Descriptive statistics were used to report demographic and clinical characteristics. For aggregate comparisons of cases and controls for each of the risk, injury, and failure groups, a Mantel-Haenszel χ^2 test was computed for categorical variables. For continuous variables with normal distributions, mean values for case and control groups were compared with the independent samples t test, and for those with nonnormal distributions, median values were compared using the Mann-Whitney U test (SPSS, Inc, v.19; IBM, Armonk, New York). P values <.05 were considered significant.

Matched univariate analyses for the risk, injury, and failure groups were performed with dichotomous variables. For continuous variables, distributions for cases and controls were graphed. For those distributions that were sufficiently disparate, receiver operating characteristic curves were generated to model sensitivity and specificity for each variable in distinguishing cases from controls (**Figure 1**; available at www.jpeds.com). Values that optimized sensitivity and specificity were chosen as cut points and used for subsequent dichotomous comparisons in matched analyses.

To assess the relationship between acyclovir dosing and nephrotoxicity (risk, injury, and failure groups), we performed 2 evaluations. Initially, univariate matched analyses were conducted by comparing acyclovir doses of ≤15 mg/kg/dose vs >15 mg/kg/dose and ≤500 mg/m^2/dose vs >500 mg/m^2/dose, for each outcome. The second method compared the total cumulative amount of acyclovir administered to each subject before attaining his/her worst renal dysfunction category to a calculated (potential) cumulative exposure based on receipt of 500 mg/m^2/dose. Differences between the 2 exposures ($\Delta dose_{500}$) >0 reflect actual cumulative exposures that are greater than expected based on a 500 mg/m^2/dose. For controls, the actual exposure was truncated at the same number of acyclovir doses as its matching case to calculate the $\Delta dose_{500}$.

For comparing outcomes in cases and controls, matched univariate analyses were performed using Epi Info V3.5.3 (Centers for Disease Control and Prevention, Atlanta, Georgia), yielding ORs and 95% CIs. Variables with a $P \leq .2$ were included in subsequent multivariate conditional logistic regression analyses for the risk and injury groups to derive ORs and 95% CIs for model predictors. The PHREG procedure (SAS version 9.3; SAS Institute Inc, Cary, North Carolina) was performed with the model parameters that were identified as significant in the univariate analyses. A stratum was used for each matched set, and FORWARD selection was prespecified.[10] For interrelated variables (eg, body surface area, weight, age, and dosing variables), only the most significant dose variable was used in the model. Because patients who received antibiotic therapy in conjunction with acyclovir generally received either ceftriaxone or cefotaxime, only ceftriaxone was used in multivariate analyses. For the failure group, a multivariate analysis for sparse data, the Conditional