High-Dose Intravenous Acyclovir for Paediatric Meningoencephalitis – An Increased Risk of Acute Kidney Injury?

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Introduction

Acyclovir is widely used to treat children with Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV) infections. For HSV/VZV meningoencephalitis, the U.S. Food and Drug Administration recommends intravenous (IV) acyclovir 20mg/kg/dose (high-dose) 8 hourly for children ≥3 months old whereas American Academy of Paediatrics recommends 15mg/kg/dose 8 hourly for children 3 months to 12 years old due to reports of nephrotoxicity, especially in those ≥12 years old with concomitant ceftriaxone.

Aim of Study

To determine the incidence of acute kidney injury (AKI) in those receiving high-dose IV acyclovir for meningoencephalitis in KK Women's and Children's Hospital, Singapore (KKH).

Methodology

A retrospective cohort study of all paediatric patients admitted to KKH from 1st March 2016 to 31st March 2017 (CIRB 2017/2507)

Inclusion & Exclusion Criteria
- Included patients aged 0 to 18 years old and received at least one dose of high dose IV acyclovir for treatment of meningoencephalitis
- Excluded if patient had pre-existing chronic kidney disease or received IV or oral acyclovir for HSV prophylaxis

Data collection
- Patient demographics
- Clinical data

AKI staging
- Estimated Glomerular Filtration Rate (eGFR) determined using the Schwartz equation
- Patients developing renal impairment more than 1 week after the end of treatment were excluded (Table 1)

Statistical analyses
- Descriptive statistics
- Data analysis was done using REDCap and Microsoft Office Excel 2010

Results and Discussion

Of 214 children on IV acyclovir, 45 had other indications and 30 received low-dose acyclovir for meningoencephalitis; hence, 139 children were included (mean age: 5.28±4.8 years).

- Seventy six percent of the children were aged 3 months to 12 years old and 51.8% were Chinese.
- The median duration of IV acyclovir was 2 days [interquartile range:2-3 days] and all patients were adequately hydrated.

Table 1. Incidence of AKI according to pRIFLE and KDIGO criteria

	Definition	N = 139
pRIFLE criteria; n (%)		
No renal injury[a]	eGFR decrease < 25%	137 (98.6)
Renal risk	eGFR decrease ≥ 25%	0 (0.0)
Renal injury	eGFR decrease ≥ 50%	1 (0.7)
Renal failure	eGFR decrease ≥ 75% or eGFR < 35mL/min/1.73m^2	1 (0.7)
Renal loss	Persistent failure > 4 weeks	0 (0.0)
End-stage	Persistent failure > 3 months	0 (0.0)
KDIGO criteria; n (%)		
Stage 1	Increase 1.5 – 1.9x baseline or increase of ≥ 26.5 µmol/L	1 (0.7)
Stage 2	Increase 2 – 2.9x baseline	0 (0.0)
Stage 3	Increase > 3x baseline or Initiation of renal replacement therapy or eGFR < 35 mL/min/1.73m2 (< 18y)	1 (0.7)

[a] Patients were assumed to have no renal injury if they did not have a repeated serum creatinine measurement

- Two children (1.4%) aged 12 and 15 years old developed AKI
  - Occurred after an average of 3.5 days from acyclovir initiation
  - Both did not receive any concurrent nephrotoxic drugs but were co-treated with IV ceftriaxone
  - Both were managed supportively with hydration in the general ward and their serum creatinine normalised
- Lower percentage of AKI (1.4%) than the 13.1% occurrence reported with high-dose acyclovir by Rao et. Al,
  - Likely because our patients were well-hydrated and patients with chronic kidney disease were excluded
  - Reduces risk of intra-tubular crystallization of acyclovir in kidneys
- Microbial resolution based on cerebrospinal fluid (CSF) or blood HSV/VZV polymerase chain reaction (PCR) could not be determined to assess the efficacy of high dose IV acyclovir
- One hundred and thirty three children (95.7%) improved clinically and were discharge well and stable.

Table 2. Other adverse events reported

Non-renal adverse events	N = 139 (%)
Leukopenia	6 (4.3)
Neutropenia	4 (2.9)
Thrombocytopenia	6 (4.3)
Elevated liver enzymes	9 (6.5)
Rash	0
Phlebitis	0

- Most did not develop any adverse events
- Some of the non-renal adverse events may be complications of their viral infections, instead of being entirely attributed to IV acyclovir.

Conclusion

- In our study, incidence of AKI secondary to high-dose IV acyclovir for paediatric meningoencephalitis was 1.4%, lower than 13.1% reported in two studies, where the median onset of AKI was 1-14 days.
- Based on our study findings, considering the possibility of increased risk of treatment failure for dosing <20mg/kg/dose, high-dose IV acyclovir could be considered for treatment of HSV/VZV meningoencephalitis in ≤12 years old. However, hydration and close monitoring of renal function would be prudent when high-dose IV acyclovir is used.

References
1. Elion GB. Mechanism of action and selectivity of acyclovir. The American journal of medicine. 1982;73(1a):7-13.
2. Rao S, Abzug MJ, Carosone-Link P, et al. Intravenous Acyclovir and Renal Dysfunction in Children: A Matched Case Control Study. The Journal of Pediatrics. 2015;166(6):1462-1468.e1464.
3. Kendrick JG, Ensom MH, Steer A, White CT, Kwan E, Carr RR. Standard-dose versus high-dose acyclovir in children treated empirically for encephalitis: a retrospective cohort study of its use and safety. Paediatric drugs. 2014;16(3):229-234.