

SAFETY OF HIGH-DOSE ACYCLOVIR IN INFANTS

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A project of the Best Pharmaceuticals for Children Act

Disclosures

- Nothing to disclose

Efficacy

- Acyclovir is commonly used in hospitalized infants for neonatal Herpes simplex virus (HSV)¹
- Dose approved by the FDA is 10 mg/kg/dose every 8 hours
- 20 mg/kg/dose every 8 hours is more effective² and is recommended³



Pediatric Trials Network
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¹Hseih 2014

²Kimberlin 2001

³Kimberlin 2013

Safety – 20 mg/kg/dose

- Renal toxicity
 - 4/64 (6%) patients in prospective trial¹
 - 3/29 (10%) patients in retrospective trial²
- Neutropenia
 - 12/64 (19%) patients in prospective trial¹
 - 0/29 (0%) patients in retrospective trial²

¹Kimberlin 2001

²Kendrick 2014

Methods

- Observational cohort study
- 348 NICUs managed by the Pediatrix Medical Group
- 2002-2012
- All infants who received ≥ 14 days of IV acyclovir dosed ≥ 50 mg/kg/day
- Diagnosis of neonatal HSV disease
- ≤ 120 days of age

Methods – Clinical Adverse Events

- New AE occurring on a day of acyclovir exposure
- Reported as the percentage of infants with each AE

Adverse Events	Serious Adverse Events
Hypotension	Renal failure
Rash	Neutropenia
	Seizures

Methods – Laboratory Adverse Events

- Laboratory abnormality occurring on a day of acyclovir exposure
- Classified as AEs or SAEs based on prespecified cutoff values
- Reported as the percentage of infants with each AE

Results

- 340 infants meeting inclusion criteria

	Median (IQR)
Gestational age, weeks	34 (31, 38)
Birth weight, g	2218 (1520, 3058)
Postnatal age, days	6 (2, 11)
Source of HSV Diagnosis	
Skin, eye, mucous membrane	125 (37%)
Blood	12 (4%)
CSF	30 (9%)
Clinical diagnosis	173 (51%)

Clinical Adverse Events

		N=340
Adverse Events		
	Hypotension requiring pressors	56 (16%)
	Rash	9 (3%)
Serious Adverse Events		
	Renal failure requiring dialysis	0 (0%)
	Neutropenia requiring granulocyte colony stimulating factor	8 (2%)
	Seizure	36 (11%)

Laboratory Adverse Events

	Adverse Event		Serious Adverse Event	
Serum Electrolytes				
Hyperkalemia	> 6.5 mmol/L	80 (24%)	> 8.0 mmol/L	13 (4%)
Hypokalemia	< 3 mmol/L	11 (3%)	< 2.0 mmol/L	2 (0.6%)
Renal dysfunction				
Elevated BUN	> 60 mg/dL	4 (1%)	> 100 mg/dL	1 (0.3%)
Elevated creatinine	> 1.7 mg/dL	17 (5%)	> 3.0 mg/dL	4 (1%)
Hematologic Abnormalities				
Neutropenia	< 500/mm ³	11 (3%)	< 100/mm ³	1 (0.3%)
Leukopenia	< 5000/mm ³	41 (12%)	< 2000/mm ³	2 (0.6%)

Limitations

- No control group for comparison
- Lab collection occurred at discretion of treating physician
- Unable to distinguish whether some laboratory events were due to acyclovir versus HSV infection
- Timing of acyclovir doses was not available

Conclusions

- AEs associated with high dose acyclovir exposure were common
- SAEs were rare
- Renal dysfunction occurred in 5%
- Neutropenia occurred in 3%
- Many of the observed events may be due to underlying HSV disease rather than drug exposure
- High-dose acyclovir should be used when neonatal HSV is suspected

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