The Pharmacokinetics of Antiepileptics Drugs in Neonates with Hypoxic Ischemic Encephalopathy

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Objectives

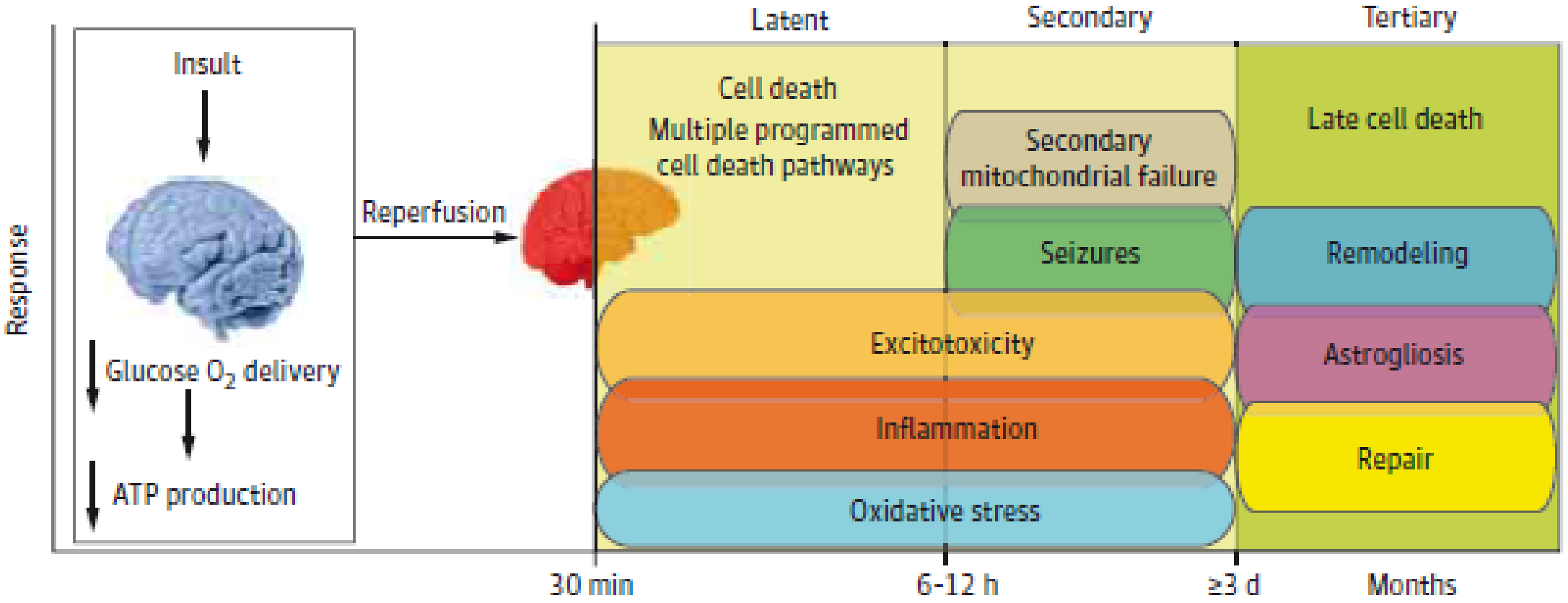
- Describe seizures in hypoxic ischemic encephalopathy
- Review the pharmacology of anti-epileptic drugs (AEDs) used in neonates
- Discuss literature for AEDs in neonatal hypoxic ischemic encephalopathy

Seizures in HIE

- HIE remains one of the most common underlying etiologies for neonatal seizures[1]
  - Incidence is 22-64% using routine EEG or aEEG
- Seizures correlate with biomarkers of brain injury
- Majority are subclinical—punctuates need for EEG
- Limited data regarding occurrence during therapeutic hypothermia (TH)
  - Much of earlier literature predates routine use of TH
  - Questions remain on relationship between hypothermia and incidence/timing of seizures in neonates with HIE
  - No reliable clinical markers predict which babies undergoing TH will seize[2]

1. Wusthoff et al. J Child Neurol 2011
2. Boylan et al. Sem in Fet Neonatal Medicine 2015

Figure 1. Schematic Overview of the Pathophysiological Features of Hypoxic-Ischemic Encephalopathy



Escobar M et al 2011

Seizures in HIE undergoing Hypothermia

- It appears overall incidence of seizures remains unchanged with the introduction of hypothermia
  - Seizure profile has been altered
  - Lower overall seizure burden, shorter individual seizure durations, seizures that are harder to detect
- Seizure burden in neonates with moderate HIE who undergo hypothermia is lower than normothermic neonates
- Seizure burden in neonates with severe HIE treated with hypothermia do not differ between normothermic and hypothermic neonates

Boylan et al. Seminars in Fetal & Neonatal Medicine 2015

Seizures in HIE and Neurodevelopment

- Long-term outcome in generally poor when both conditions are present[1]
- Debate exists over whether seizures themselves cause additional damage to the neonatal brain or if they represent a manifestation of existing brain injury
- Animal data suggest addition of seizures can have further detrimental effects
- Some neonatal data suggest worsening neurodevelopmental outcomes with seizures in the setting of birth asphyxia independent of HIE severity[2]

1. Kwon et al. J Child Neurol 2011
2. Glass et al. J Pediatr 2009

Seizures in the Neonatal Period

- Neonatal brain is more susceptible to seizures
  - Early development of excitatory neurotransmitters
  - Delayed inhibitory function of GABA
  - Excess of excitatory glutamatergic neurons with more excitable subunits than the adult brain
- $GABA_A$ receptors are expressed in lower levels and contain less alpha1 subunits where

Seizures in the Neonatal Period

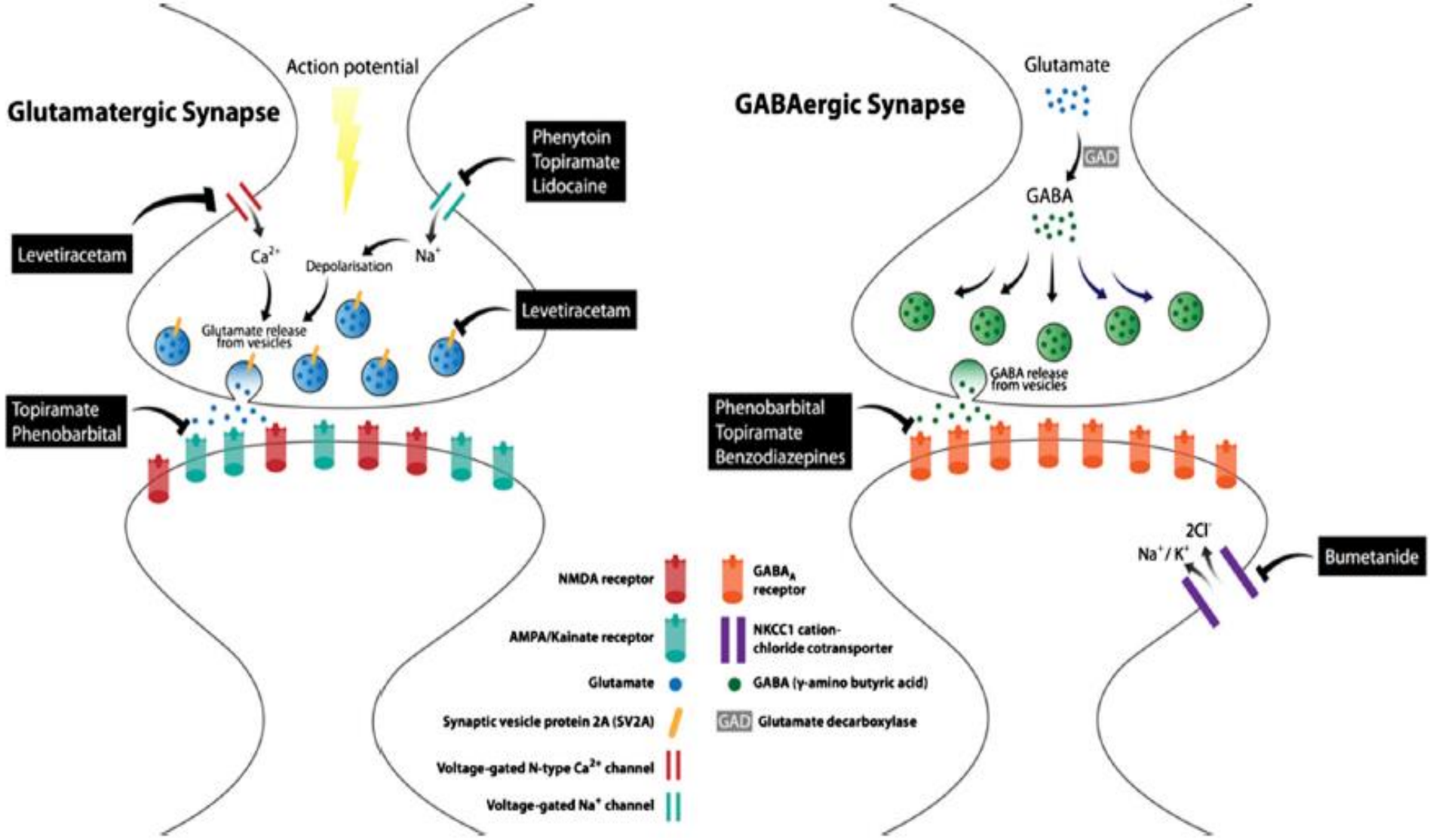
- Binding of GABA agonists/modulators to $GABA_A$ receptors trigger either influx or efflux of chloride ions depending on the neuronal equilibrium potential for chloride
- Neonatal brain contains more influx transporters (NKCC1) copmared to efflux transporters (KCC2)
  - Overall result: chloride accumulation in intracellular chloride
  - Birth ischemia and hypoxic ischemia also increase NKCC1
- Activation of $GABA_A$ receptors in neonatal brain causes chloride efflux and neuronal depolarization
  - In adult brain, $GABA_A$ receptor binding causes influx of chloride into cells, decreasing excitability
  - In neonatal brain, leads to cessation of outward seizure manifestations, persist electrical seizure activity

Antiepileptics in Hypothermia

- Systematic review has shown that use of AEDs following perinatal asphyxia in the absence of confirmed seizures is of little benefit with no improvement in survival or neurodevelopmental outcome
- Hypothermia is known to alter the pharmacokinetics of many medications
- Data describing PK of AEDs in therapeutic hypothermia are still emerging

Therapeutic Hypothermia and Pharmacokinetics

- Physiologic changes that affect many organ systems
- Renal impact
  - Can alter clearance
- Hepatic impact
  - Altered cytochrome P450 enzyme activity in animal models
  - Evidence of altered enzyme activity in humans
    - Morphine in neonates undergoing hypothermia
  - Can alter metabolism (impact dependent on type of metabolism)



Donovan M et al. Drugs 2016

Treatment for Neonatal Seizures

- Goals of therapy:
  - Cessation or minimization of seizure activity
  - Minimal to no risk of long-term neurotoxicity
- AED efficacy most commonly defined as 80% reduction in seizure severity or complete seizure cessation
- Some combinations of AEDs may cause increased neuronal apoptosis

Phenobarbital

- Place in therapy:
  - First-line AED in neonatal seizures due to extensive history of its use
- Mechanism:
  - Increases $GABA_A$-mediated inhibition
  - Limited efficacy since $GABA_A$ more likely to be excitatory in neonates
- Monitoring: serum concentrations
- Concerns:
  - Increased neuronal apoptosis, impaired neurodevelopment
  - Electroclinical uncoupling/dissociation
  - Clinically-relevant drug interactions

Population PK of Phenobarbital in Neonatal HIE treated with Hypothermia

- Retrospective evaluation of 39 neonates
  - TH: 20, normothermic: 19
- No difference in PK/levels between the two groups
  - Body weight, postnatal age were the only predictors of clearance
  - Clearance of PB increases proportionately with increasing body weight
- Dosing recommendation: use same initial dosing as non-HIE neonates, adjust maintenance dose based on levels

Shelhaas RA et al. Pediatr Crit Care Med 2013

Effect of Co-Medication on PK Parameters of Phenobarbital in Asphyxiated Newborns

- Prospective open-label study in term asphyxiated newborns (GA ≥37 wk) with HIE and treated with phenobarbital
- Standardized phenobarbital dosing
  - Load: 10-20 mg/kg/dose over 15 min
    - Maintenance 2.5-4 mg/kg IV twice daily
  - Repeat loading dose up to 40 mg/kg total
  - Non-responders:
    - Phenytoin (15-20 mg/kg IV, 2.5-4 mg/kg IV twice daily maintenance)
    - Midazolam 0.05-0.3 mg/kg continuous infusion
- Phenobarbital levels asses at 2-3, 24, 48, 72, and 96 hr after load

Sima M. et al Physiol Res 2015

Effect of Co-Medication on PK Parameters of Phenobarbital in Asphyxiated Newborns

- Co-medications considered in analysis:
  - Vasoactives: dopamine, dobutamine, norepinephrine
  - AEDs: phenytoin, midazolam
  - Analgesics: sufentanil, tramadol
  - Diuretics: furosemide
- Possible dose-dependent and dose-independent interactions between PB and other medications evaluated
  - Dose-dependent: cumulative doses of co-medication within acute phase of treatment used (normalized to kg of body weight)
  - Dose-independent: any dosing/exposure to co-medication

Effect of Co-Medication on PK Parameters of Phenobarbital in Asphyxiated Newborns

- Possible mechanistic pathways for PK interactions
  - Alteration of renal blood flow after vasoactive medications
    - Changes in clearance
  - Changes in body water content induced by diuretics
    - Changes in volume of distribution
  - Alterations in elimination due to alterations in liver drug metabolism
    - Changes in half-life, clearance

Effect of Co-Medication on PK Parameters of Phenobarbital in Asphyxiated Newborns

- 37 full term newborns enrolled

Patient Demographics	Number
Male, n (%)	22 (59%)
Hypothermia, n (%)	24 (65%)
Normothermia, n (%)	13 (35%)
Gestational age (wk)	39.32 ± 1.36
Body weight (kg)	3.24 ± 0.65
PB loading dose	5.04 to 34.29 mg/kg
PB maintenance dose	1.07 to 20.31 mg/kg/day

Effect of Co-Medication on PK Parameters of Phenobarbital in Asphyxiated Newborns

Table 1. Proportion of patients using specific co-medication.

	Any co-medication	**Any vasopressor**	**Dopamine**	**Dobutamine**	**Norepinephrine**
n/N	37/37	32/37	31/37	30/37	4/37
(%)	(100.00)	(86.49)	(83.78)	(81.08)	(10.81)
	Phenytoin	**Sufentanil**	**Midazolam**	**Tramadol**	**Furosemide**
n/N	11/37	27/37	26/37	14/37	26/37
(%)	(29.73)	(72.97)	(70.27)	(37.84)	(70.27)

Effect of Co-Medication on PK Parameters of Phenobarbital in Asphyxiated Newborns

	Vd (L/kg)	Cl (L/hr/kg)	T ½ (h)
All patients	0.48	0.0034	93.7
Any vasoactive drug Yes No	0.47 0.48	0.0034 0.0043	93.02 93.7
Norepinephrine Yes No	0.44 0.48	0.0052 0.0034	62.8 92.4
Phenytoin Yes No	0.45 0.48	0.0034 0.0035	128.3 92.4
Furosemide Yes No	0.48 0.45	0.0034 0.0035	92.4 93.7

Phenytoin

- Mechanism:
  - Reduces excitatory neurotransmission by blocking voltage-gated sodium channels
- Place in therapy: 2nd line to phenobarbital
- Efficacy only 50% when used in combination with phenobarbital
- Monitoring: serum concentrations (free and total)
- Concerns:
  - Potential detrimental effect on developing neurons

Phenytoin in Hypothermia

- Data specifically describing use of phenytoin for neonatal HIE patients undergoing hypothermia are lacking
- Hypothermia reduces elimination via reduced cytochrome P450 2C metabolism
- Pediatric therapeutic hypothermia data suggests that phenytoin clearance is significantly decreased
  - Increased drug levels for extended period of time after cooling
  - Trends towards higher free levels during rewarming
- Close monitoring of serum concentrations warranted

Empey PE et al. Crit Care Med 2013

Lidocaine

- Mechanism:
  - Inhibits voltage-gated sodium channels, preventing depolarization
- Place in therapy:
  - Second or third-line agent
- Dosing formulation: IV only (continuous)
- Efficacy up to 78%
- Monitoring:
  - Serum concentrations (>9 mg/L results in toxicity)

Lidocaine

- Safety Concerns:
  - Cardiotoxicity—proarrhythmias and bradycardia
  - Seen in some normothermic infants receiving lidocaine
- Clearance:
  - “High clearance” –strongly dependent on hepatic blood flow
  - Decreased during hypothermia secondary to decreased cardiac output, stroke volume

Lidocaine PK-PD in Hypothermia

- Cardiotoxicity mechanism
  - Serum concentration
  - Heart rate
- TH could theoretically decrease risk of toxicity compared to normothermic HIE infants
  - Heart rate reduced by hypothermia itself

Lidocaine in Asphyxiated Newborn with Hypothermia

- Severe perinatal asphyxia followed by encephalopathy qualifying for TH
  - TH started within 6 hours of birth and maintained x 72 hours
- Comparison group-historical controls (normothermic asphyxiated neonates with seizures)

Table 1 Characteristics of the study groups*

	Hypothermia	Normothermia†	p Value
Number of patients	22	26	–
Gender (number of male/female infants)	13/9	16/10	–
Gestational age (weeks)	39.8 (36.0–42.1)	39.4 (34.1–42.7)	0.61
Body weight (kg)	3.46 (2.06–4.29)	3.40 (2.05–4.36)	0.89

*Values are expressed as mean (range).
†Normothermia reference group for pharmacokinetic modelling.

Van den Broek et al. Arch Dis Child Fetal Neonatal Ed 2013

Lidocaine in Asphyxiated Newborn with Hypothermia

- Intervention:
  - Lidocaine started when seizures persisted on aEEG despite phenobarbital and midazolam therapy
- Empirically decreased dosing for predicted decrease in clearance
  - 2 mg/kg over 10 min, 4 mg/kg/hr x 6 hours, 2 mg/kg/hr 6-12 hours
- Monitoring:
  - Levels obtained daily

Lidocaine in Asphyxiated Newborn with Hypothermia

- Efficacy:
  - >80% reduction in seizure burden within 4 hours of starting infusion
- Safety:
  - Assessed using cardiac monitoring
  - Clinical monitoring of arrhythmias based on observation of sudden deviations in heart frequency

Lidocaine in Asphyxiated Newborn with Hypothermia

- 22 asphyxiated term neonates undergoing hypothermia who received lidocaine for seizures
  - Serum concentrations: 83
- Efficacy:
  - 20/22 (91%) of neonates responded to addition of lidocaine
  - 2 neonates who did not respond had severe structural brain damage on MRI
- Safety:
  - No effect of lidocaine plasma concentrations on heart rate
  - No arrhythmias were observed

Lidocaine in Asphyxiated Newborn with Hypothermia

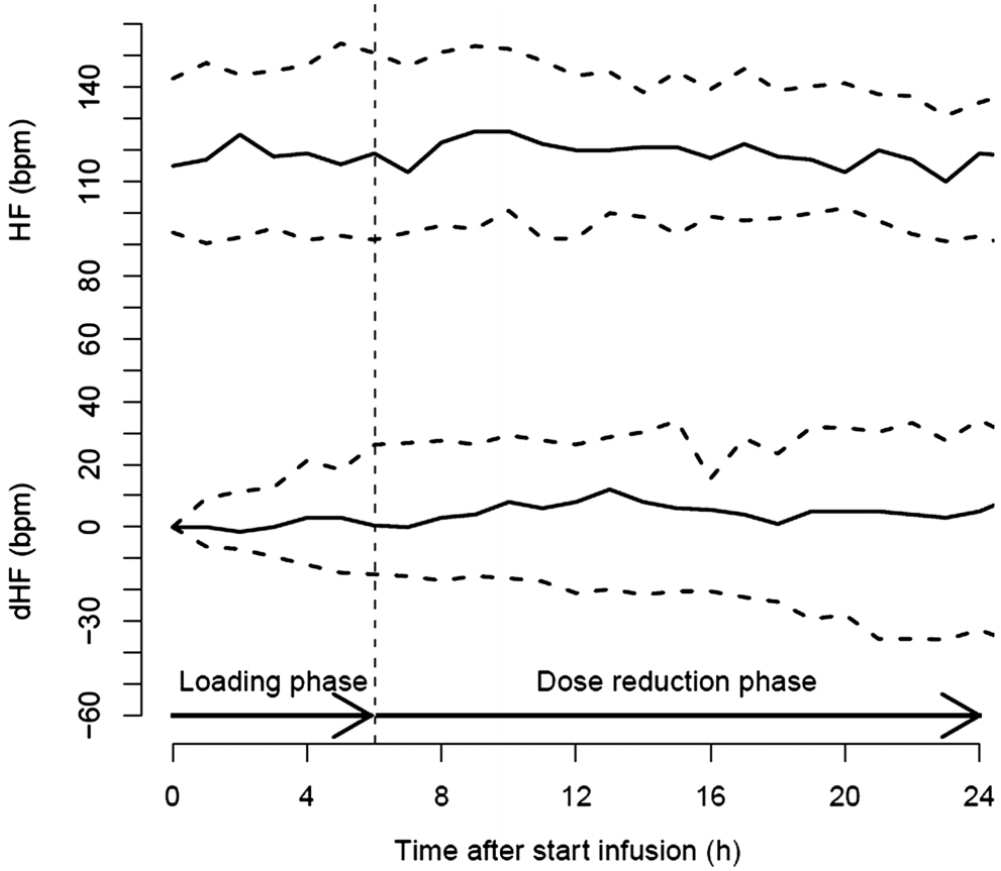
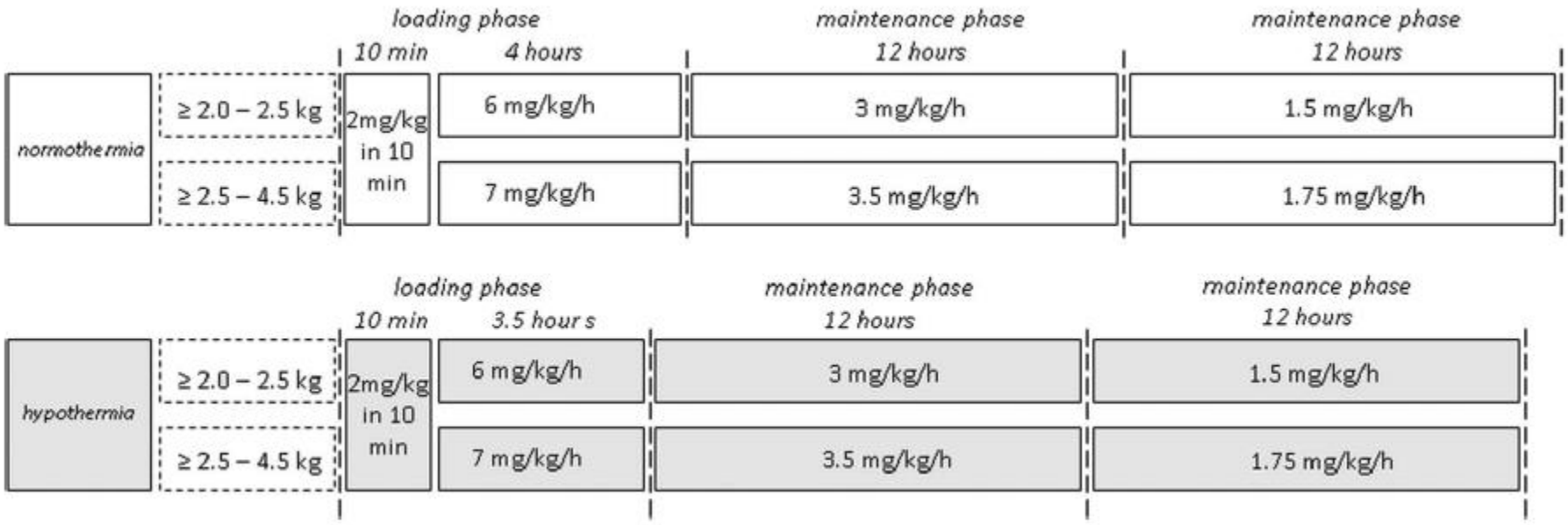


Figure 2 Relationships between lidocaine and heart rate.

Time-course of the heart rate (HF, upper) and the heart rate change from baseline (dHF, lower) during lidocaine infusion under hypothermia. Lines represent the median and the minimum and maximum observed values.

Lidocaine Proposed Dosing Algorithm



After loading infusion:

- 5.9% of the simulated newborns had a concentration >9 mg/L
- 2.2% of simulated newborns with concentrations >10 mg/L
- 2.5% had a plasma concentration below 4 mg/l

Midazolam (Benzodiazepines)

- Place in therapy: 2nd or 3rd line
- Mechanism:
  - Increase inhibitor neurotransmission via $GABA_A$ receptor
- Efficacy 50% as second-line agent, 73-100% as third-line agent
- Dosing formulation: IV (intermittent, continuous), PO
- Monitoring: none
- Concerns:
  - Higher doses can cause cardiac depression
  - Serum concentrations can build up with decreased hepatic function
  - Benzodiazepines may cause neurodevelopmental impairment, smaller hippocampal region in brain

Levetiracetam

- Place in therapy: 2nd or 3rd line
- Mechanism:
  - Thought to work via stabilization of synaptic vesicles to prevent release of neuroexcitatory transmitters
- Dosing formulation: IV or PO (1:1 conversion)
- Monitoring: serum concentrations available, no clear data to support
- Efficacy 35-64% in first 24 hours, 52-100% within 72 hours
- Concerns:
  - Relatively safe, does not cause neuronal apoptosis
  - Somnolence, irritability seen in pediatric patients

Levetiracetam For the Treatment of Seizures in Neonatal HIE

- Study objective: determine the safety and efficacy of levetiracetam in treatment of neonatal seizures due to HIE
- Single-center retrospective cohort at Cincinnati Children's
  - Neonates treated with hypothermia for HIE between August 2008-April 2015
  - GA>35 weeks
  - Clinical recognized encephalopathy or seizures
  - One of the following: fetal distress at delivery, resuscitation, 5 min APGAR<6, metabolic acidosis (pH<7.1 or base deficit>10)

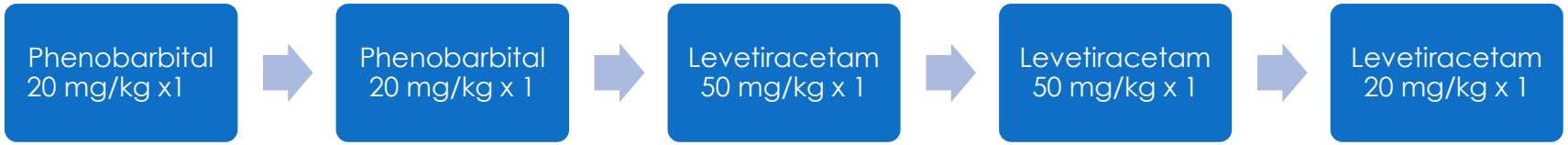
Venkatesan C. et al. J of child neurol 2017

Levetiracetam For the Treatment of Seizures in Neonatal HIE

- Additional criteria applied for cooling
- Physiologic criteria:
  - Cord blood gas or any postnatal gas at ≤ 1 hour of life with a pH ≤ 7.0 or a base deficit of ≥ 16
  - If no blood gas available or blood gas had pH 7.01-7.15 and/or base deficit 10-15.9 AND history of acute perinatal event AND 10 min AGPAR <10 OR need for continuous ventilation initiated at birth and continued for at least 10 min
- Neurologic criteria:
  - Presence of moderate/severe encephalopathy OR seizures
- TH eligibility: criteria recognized, initiated within 6 hours of birth

Levetiracetam For the Treatment of Seizures in Neonatal HIE

- EEG monitoring
  - Continuous prolonged video EEG completed in most neonates
    - 4/32 (12%) levetiracetam patients had treatment initiated at outside hospitals with incomplete records upon transfer or inability to monitor via continuous EEG
- Neonatal seizure protocol



  - If seizures persist: pyridoxine challenge, midazolam continuous infusion, Fosphenytoin, or other AEDs
  - Once loading dose initiated of an AED, patients placed on maintenance doses

Levetiracetam For the Treatment of Seizures in Neonatal HIE

Table 1. Demographic and Clinical Information About Patient Population.

Infant characteristics	
Total infants, n	127
Male, n (%)	75 (59%)
Median gestational age, wk (range)	39.1 (35-42.4)
Birth weight, g (mean ± SD)	3296 ± 659
Median head circumference, cm (range)	34.5 (28.5 – 38)
Cesarian section, n (%)	69 (54%)
Median Apgar score, 1 min	1
Median Apgar score, 5 min	4
Maternal characteristics	
Maternal age, y, mean ± SD	27.6 ± 6.1
First child, n (%)	64 (50%)
Hypertension, n (%)	24 (19%)
Gestational diabetes, n (%)	15 (12%)
Complication, n (%)	
Meconium-stained fluid	49 (39%)
Placental abruption	25 (20%)
Chorioamnionitis	14 (11%)

Cooled: 87
Not cooled: 40

Levetiracetam For the Treatment of Seizures in Neonatal HIE

Table 2. Antiepileptic Drug Response All Infants.[a]

Total infants	127
Infants with seizures	83 (65%)
Infants with seizures receiving PHB first	80 (96%)
Cessation occurred after:	
PHB only	51 (61%)
LEV only	2 (2.5%)
PHB then LEV	23 (28%)
PHB, other AED, then LEV	2 (2.5%)
AEDs beyond LEV	5 (6%)

Abbreviations: AED, antiepileptic drug; LEV, levetiracetam; PHB, phenobarbital.

[a]Values are n (%) unless otherwise noted.

Levetiracetam For the Treatment of Seizures in Neonatal HIE

Table 3. Antiepileptic Drug Response: Comparison of Cooled and Uncooled Infants.

	Cooled	Uncooled
Total	87	40
Seizures	55 (63%)	28 (70%)
Cessation after		
PHB only	37 (67%)	14 (50%)
LEV only	2 (4%)	0 (0%)
PHB and LEV only	12 (21%)	11 (39%)
PHB, other AED, LEV	2 (4%)	0 (0%)
AEDs beyond LEV	2 (4%)	3 (11%)

Abbreviations: AED, antiepileptic drug; LEV, levetiracetam; PHB, phenobarbital.

Levetiracetam For the Treatment of Seizures in Neonatal HIE

Neonates-Levetiracetam	N = 32
Prolonged (>24 hr) continuous EEG, n (%)	28 (88)
Seizure cessation after initiation, n (%)	27 (84)
LEV used as 2nd line agent to phenobarbital*	23 (72)
Mean dosing time between PB and LEV	6 hr (1-15 hours)
Time to seizure cessation (LEV 2nd line to PB)	72 hr of seizure onset
LEV used 3rd line, n (%)*	2 (6)
LEV used 1st line, n (%)*	2 (6)

*Seizure cessation occurred after initiation, no additional AEDs required

Levetiracetam For the Treatment of Seizures in Neonatal HIE

- 5 (16%) failed levetiracetam initiation
  - N = 1: LEV 50 mg/kg x 3→PB 20 mg/kg→TOP 5 mg/kg
  - N = 1: PB→LEV→FOS→TOP→midazolam drip
  - N = 3: PB→LEV→FOS
- Cessation of seizures generally occurred 48 hours after first PB dose

Levetiracetam For the Treatment of Seizures in Neonatal HIE

Dosing information	
Total loading dose (mg/kg)	63 (range: 20-150 mg/kg)
Initial loading dose (mg/kg)	50 mg/kg
Maintenance dose (mg/kg/day)	65 (range: 30-100)
Maintenance dose at discharge (mg/kg/day)	58 (range: 5-100)
Maintenance dose divided BID, n (%)	17 (56)
Discharged home on LEV, n (%)	20 (63)
Age at discontinuation	4.4 months (range: 21 days-8.7 months)
Duration of follow-up	32 months (range: 2-64)

Topiramate

- Mechanism:
  - Reduces frequency of action potential firing by altering GABA neurotransmission, blocking voltage-gated sodium channels, weakly blocking glutamate receptors
- Place in therapy: emerging 3rd line option
- Effectiveness: 67%
- Dosing formulation: PO only (may give rectally)
- Monitoring: None
- Concerns:
  - Appears well-tolerated
  - Potentially neuroprotective, reduces brain injury in HIE models (glutamate blockade)
  - Potentially additive neuronal apoptosis when co-administered with phenobarbital

Topirimate Neuroprotection Data

- Neuronal cultures:
  - Consistently attenuates cell damage induced by oxygen-glucose deprivation or excitotoxic glutamate concentrations
- Animal models of transient global cerebral ischemia
  - Reduced severity of tissue damage when used alone or in combination with hypothermia
  - Neuroprotective doses: 5-200 mg/kg, usually single dose
- Animal models of neonatal periventricular leukomalacia
  - Exerts neuroprotective effects

Safety and Efficacy of Topirimate in Neonates with HIE (NeoNATI)

- Study objective: evaluate the safety of TOP 10 mg/kg (higher dose than previous study of 5 mg/kg) and its long-term effect on neurologic functions
- Multicenter randomized controlled pilot trial of newborns treated with whole body hypothermia within 6 hours from birth
  - GA $\geq$ 36 weeks and BW $\geq$ 1.8 kg AND one of the following
  - 10 min A PGAR $\leq$ 5
  - Persisting need for resuscitation, including intubation or mask ventilation 10 min after birth
  - Acidosis (pH <7.0 and/or base deficit $\geq$ 16
  - Moderate to severe encephalopathy

Filippi et al. J Matern Fetal Neonatal Med 2017

Safety and Efficacy of Topirimate in Neonates with HIE (NeoNATI)

- Fluid management:
  - 60-70 mL/kg/day, increased by 10-20 mL/kg/day based on changes in body weight and serum electrolyte levels
  - Minimal enteral nutrition allowed with human milk from first day of life
- Seizure management:
  - 1st line phenobarbital
  - 2nd line midazolam
- Hypotension (MAP<40mmHg):
  - Saline boluses→dopamine, dobutamine, norepinephrine
- Analgesia: fentanyl

Safety and Efficacy of Topirimate in Neonates with HIE (NeoNATI)

- Topamax 10 mg/kg/day started from beginning of hypothermia
  - Daily x 3 days for total of 3 doses
- Plasma concentrations
  - T0: Before beginning drug/hypothermia
  - T1 and every 4 hours for first 34 hours (trough prior to 2nd dose, peak)
  - T40, 48, trough prior to 3rd dose, peak
  - Additional levels obtained at 12, 24, 48 hours after discontinuation of therapy

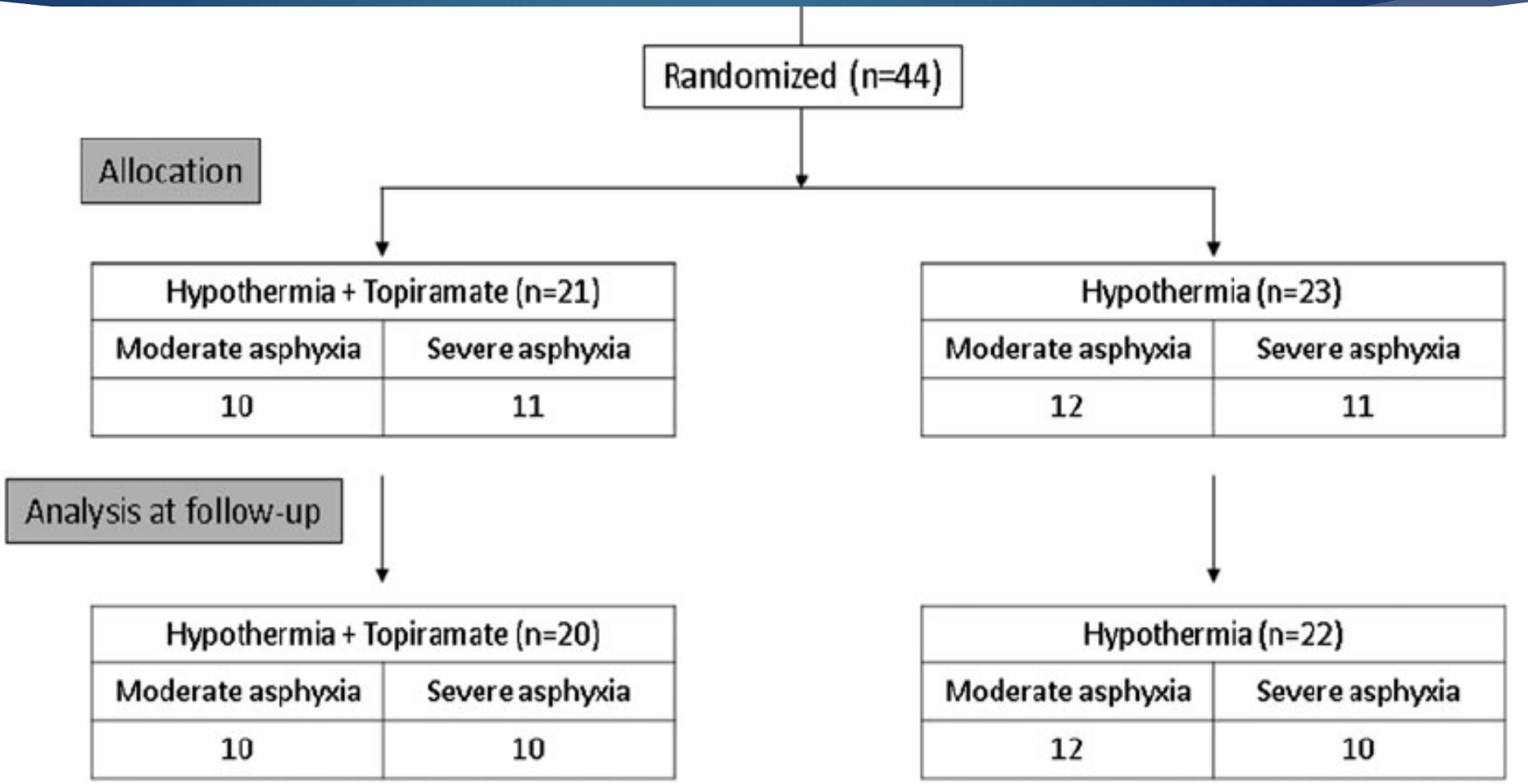
Safety and Efficacy of Topirimate in Neonates with HIE (NeoNATI)

- Safety assessment
  - Respiratory and hemodynamic paramaters
  - Before starting hypothermia, q6h x 72 hours then after rewarming
  - CBC, glucose, electrolytes, LFTs, renal function, cardiac enzymes, CRP, coagulation studies x 96 hours
- Outcome measures
  - Primary: combined frequency of mortality and severe neurodevelopmental delay (18-24 months)
  - Secondary: epilepsy, blindness, hearing loss, neurodevelopmental delay (composite motor or cognitive score <85, any degree of CP, visual, or hearing impairment)

Safety and Efficacy of Topirimate in Neonates with HIE (NeoNATI)

- Neuroimaging follow-up with standard structural brain MRI
  - End of hypothermia, within first week, and as clinically indicated
- Blinded neuroradiologist interpreted MR studies using scoring system to rate extent of injury in the basal ganglia/thalamus region (0-4) and in the watershed region (0-5)
  - Higher scores corresponded to more extensive damage
- MRI classified accorded to predominant pattern of injury
  - Normal
  - WS predominant
  - BG/T predominant

Safety and Efficacy of Topirimate in Neonates with HIE (NeoNATI)



Safety and Efficacy of Topirimate in Neonates with HIE (NeoNATI)

	All patients N=44	H-TOP N=21	H N=23	P value
Male, n (%)	21 (67.4)	13 (61.9)	14 (60.9)	0.95
GA, wk	39.2 ± 1.53	38.8 ± 1.32	40.2 ± 1.6	0.34
BW, kg	3.3 ± 0.497	3.204 ± 0.529	3.388 ± 0.469	0.22
Outborn, n (%)	43 (97.7)	20 (95.5)	23 (100)	0.3
APGAR, 1 min	1 (0-7)	1 (0-7)	1 (0-7)	0.87
APGAR, 5 min	4 (0-8)	4 (0-7)	4 (0-8)	1
Mechanical ventilation, n (%)	21 (70.5)	14 (66.7)	17 (73.9)	0.55
Tx with phenobarbital for seizures, n (%)	28 (63.6)	14 (66.6)	14 (60.9)	0.7

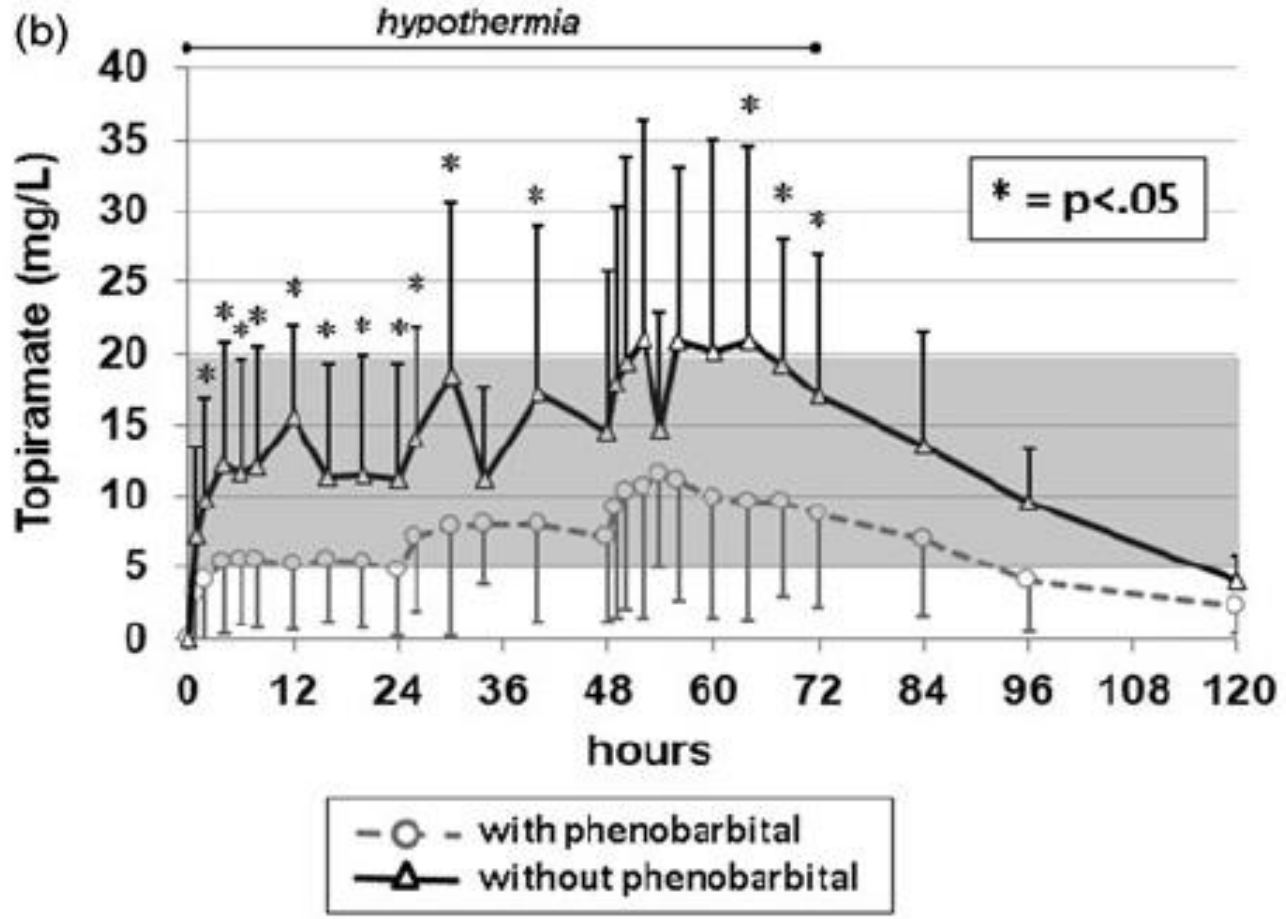
Safety and Efficacy of Topirimate in Neonates with HIE (NeoNATI)

No significant difference in primary outcome

Table 2. Efficacy outcomes.

	H-TPM	H	*p*	RR (95% CI)
Mortality and severe neurodevelopmental disability, *n* (%)	7/21 (33.3)	7/23 (30.4)	.841	1.095 (0.46–2.60)
Epilepsy, *n* (%)	3/21 (14.3)	7/23 (30.4)	.211	0.469 (0.14–1.58)
Hearing loss, *n* (%)	2/18 (11.1)	2/22 (9.1)	.837	1.222 (0.19–7.83)
Blindness, *n* (%)	3/20 (15.0)	3/20 (15.0)	.280	0.660 (0.18–2.41)
Abnormal writhing general movements at 1 month	8/21 (38.1)	9/22 (40.9)	.854	0.931 (0.443–1.954)
Abnormal fidgety general movements at 3 months	8/21 (38.1)	6/22 (27.3)	.460	1.396 (0.583–3.345)
Hammersmith Infant Neurological Examination at 12 months	64.2 ± 21.4	61.7 ± 27.3	.748	–
Cognitive composite score at 18–24 months	67.7 ± 35	76.7 ± 44	.492	–
Motor composite score at 18–24 months	69.7 ± 37	69.5 ± 40	.992	–
Language composite score at 18–24 months	62.4 ± 33	66.3 ± 38	.734	–
Neurodevelopmental impairment				
Cognitive composite score <70	6/20 (30.0)	6/22 (27.3)	.849	1.100 (0.423–2.861)
Cognitive composite score <85	9/20 (45.0)	8/22 (36.4)	.580	1.237 (0.593–2.581)
Motor composite score <70	6/20 (30.0)	7/22 (31.8)	.901	0.900 (0.365–2.218)
Motor composite score <85	7/20 (35.0)	9/22 (40.9)	.702	0.855 (0.392–1.867)
Language composite score <70	7/18 (38.9)	7/21 (33.3)	.727	1.667 (0.505–2.695)
Language composite score <85	10/18 (55.6)	11/21 (52.4)	.848	1.061 (0.593–1.895)
Cerebral palsy	7/20 (35.0)	6/22 (27.3)	.599	1.167 (0.476–2.861)

Safety and Efficacy of Topirimate in Neonates with HIE (NeoNATI)



Safety and Efficacy of Topirimate in Neonates with HIE (NeoNATI)

Table 3. Visual analysis of MRI within the first week of life by score.

	H-TPM $n = 20$	H $n = 23$	p	RR (95% CI)
Basal ganglia (BG/T)				
Score 0	14 (70)	14 (60.9)	.629	1.15 (0.74–1.77)
Score 1	0	1 (4.3)	.547	0.38 (0.02–8.86)
Score 2	2 (10)	4 (17.4)	.495	0.57 (0.12–2.81)
Score 3	3 (15)	2 (8.7)	.526	1.72 (0.32–9.31)
Score 4	1 (5)	2 (8.7)	.6411	0.57 (0.06–5.88)
Watershed (WS)				
Score 0	15 (75)	14 (60.9)	.323	1.23 (0.81–1.86)
Score 1	0	0	N/A	N/A
Score 2	1 (5)	5 (21.7)	.162	0.23 (0.03–1.81)
Score 3	1 (5)	1 (4.3)	.919	1.15 (0.08–17.22)
Score 4	3 (15)	2 (8.7)	.526	1.72 (0.32–9.31)
Score 5	0	1 (4.3)	.601	0.38 (0.02–8.86)
Predominant pattern of injury				
Normal	12 (60)	12 (52.2)	.616	1.15 (0.68–1.95)
WS	4 (20)	5 (21.7)	.892	0.92 (0.28–2.96)
BG/T	4 (20)	6 (26.1)	.647	0.77 (0.25–2.34)
Moderate–severe brain injury	7 (35)	8 (34.8)	.988	1.01 (0.44–2.28)

Safety and Efficacy of Topirimate in Neonates with HIE (NeoNATI)

- No significant differences in patient co-treated with TOP and controls for most hemodynamic parameters
  - HR significantly lower at T66 and T72
- No adverse effects related to TOP were observed
- No patient was discontinued early secondary to limiting adverse effects

Summary

- HIE remains a significant etiology of neonatal seizures
  - Therapeutic hypothermia has not altered overall incidence but has caused changes in seizure burden, duration, and clinical presentation
- Developmental differences in the neonatal brain are responsible for altered responses to traditional antiepileptic drugs compared to older patient populations
- Neonatal pharmacodynamics may demonstrate need for alternative therapies such as lidocaine, levetiracetam, and topirimate
- Further studies are needed to validate potentially neuroprotective properties of certain antiepileptic agents

Questions