Antiepileptic Medications and the Neonatal Brain

Section on Perinatal Pediatrics Program: Day 3
Medication Considerations in Neonatal Patients

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Faculty Disclosure Information

In the past 12 months, I have no relevant financial relationships with the manufacturers of any commercial products and/or providers of commercial services discussed in this CME activity.

I will be discussing off-label uses of antiepileptic drugs for neonatal seizures in my presentation. I will be presenting existing data but not endorsing use of any of these products.
Overview

What I will NOT talk about:
- Definition of neonatal seizures
- Whether or not seizures should be treated
- Whether seizure activity itself is harmful to the neonatal brain

What I will discuss:
- Developmental aspects of drug-brain interactions
- Commonly used AEDS
- Newer AEDs
The Questions:

How effective are currently used AEDs in controlling neonatal seizures?

What are the possible side effects of currently used AEDs?

Are there newer drugs that might be more effective and safer?
Your brain on drugs
Your brain on drugs

Depressed  Normal  On Drugs
Schematic depiction of maturational changes in glutamate and GABA receptor function in the developing brain

Nat. Rev. Neurol. doi:10.1038/nrneurol.2009.80
Treatment strategies

There are no standards of care that are evidence based

- Most experts recommend treatment of both clinical and subclinical seizures
- Rapid administration of loading doses of AEDs are recommended at diagnosis
- Optimal duration of treatment is unknown

- Pharmacokinetics in neonates are not well described

- Off-label AEDs are widely used despite lack of safety and efficacy information

Frequency of treatment: 94%

Choice of anticonvulsant:
- First line: phenobarbital (82%), lorazepam (9%), phenytoin (2%), others (1%)
- Second line: 46% of infants received a second drug
  - Lorazepam (50%), phenytoin (39%), phenobarbital (20%), other (7%)

Number of drugs used:
- 1 AED (59%), 2 AEDs (32%), 3 AEDs (7%), 4 AEDs (1%)

Discontinuation of AEDs:
- 75% of infants were discharged on treatment
## Frequently used AEDs for neonatal seizures

<table>
<thead>
<tr>
<th>DRUG</th>
<th>LOADING DOSE</th>
<th>MAINTENANCE DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>20-40 mg/kg iv</td>
<td>5 mg/kg/d</td>
</tr>
<tr>
<td>Phenytoin/phosphenytoin</td>
<td>20 mg/kg iv</td>
<td>5 mg/kg/d</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.05 mg/kg iv</td>
<td>0.15 mg/kg/h</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.05 – 0.1 mg/kg iv</td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.01 mg/kg</td>
<td>0.1-0.5 mg/kg/d</td>
</tr>
</tbody>
</table>

Phenobarbital/Phenytoin

Phenobarbital is the first line AED in clinical practice
- Only about 50% of patients achieve seizure control with phenobarbital
- As many as 30% of patients do not achieve seizure control with the addition of a second line drug

In a randomized crossover study
- Phenobarbital controlled seizures in 43%; phenytoin controlled seizures in 45%

Phenobarbital may augment the neuroprotective effect of hypothermia in HIE
Midazolam/Lidocaine

Midazolam
• Is used for seizures refractory to phenobarbital
• Reported efficacy 0 – 100%

Lidocaine
• Small studies suggest it may be effective for refractory seizures
• Response rate 60 - 92%
• Concern about arrhythmias during continuous infusion
Why do we need new drugs for neonatal seizures?

- Many neonatal seizures are difficult to control with phenobarbital, phenytoin or midazolam – up to 25% of neonatal seizures do not respond to these drugs.

- There are concerns regarding potential neurotoxic effects of these AEDs in developing brain.
  - May cause fetal malformations
  - May result in neurodevelopmental delay
  - Mechanisms of neurotoxicity are unclear
AEDs and apoptotic neurodegeneration

Animal studies suggest that suppression of synaptic neurotransmission via blockade of glutamate receptors or activation of GABA<sub>A</sub> receptors may trigger neurodegeneration in immature rodent brain.

- Bittigau et al. (2002, 2003) injected rats with phenytoin, phenobarbital, diazepam and other AEDs on P7 and analyzed their brains 24 hours later.
  - Phenytoin produced widespread neurodegeneration resembling apoptosis as did phenobarbital and diazepam in a dose-dependent manner.
  - Treatment with AEDs caused a persistent reduction in brain weight of 8-15%.

Many of these studies were done in normal animals, not those with seizures, thus the relative risk of seizures themselves vs AEDs was not assessed. However these findings spurred development of effective and potentially less toxic drugs.
Off-label use of AEDs for neonatal seizures

In the neonatal population, there is a paucity of data for MANY medications, including antiepileptic drugs.

“Off-label” use is therefore extremely common in infants.

Levetiracetam and Topiramate are now relatively commonly used in older children. Anecdotal data suggest these drugs may be efficacious in neonates. Silverstein and Ferriero surveyed Child Neurologists in 2007 regarding their use of these two drugs. (Silverstein, Ferriero. Pediatric Neurology 2008; 39:77-79)
<table>
<thead>
<tr>
<th></th>
<th>Levetiracetam</th>
<th>Topiramate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended</strong></td>
<td>47%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Order of use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>54%</td>
<td>33%</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; or subsequent</td>
<td>50%</td>
<td>53%</td>
</tr>
<tr>
<td><strong>Dose recommended</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>32%</td>
<td>60%</td>
</tr>
<tr>
<td>20 mg/kg</td>
<td>40%</td>
<td>10%</td>
</tr>
<tr>
<td>30 mg/kg</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>other</td>
<td>8% (higher)</td>
<td>30% (lower)</td>
</tr>
<tr>
<td><strong>Treatment beneficial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58%</td>
<td>70%</td>
</tr>
<tr>
<td>No</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>Uncertain</td>
<td>31%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0%</td>
<td>30%</td>
</tr>
<tr>
<td>None</td>
<td>92%</td>
<td>63%</td>
</tr>
<tr>
<td>Uncertain</td>
<td>8%</td>
<td>7%</td>
</tr>
</tbody>
</table>
Levetiracetam

Mechanism of action:
- Primarily through interaction with the synaptic vesicle protein 2A, which is implicated in the control of synaptic vesicle fusion, exocytosis, and neurotransmitter release
- Animal studies suggest it does not cause apoptosis or disrupt synaptic development and may be neuroprotective

PK data
- 2/3 eliminated unchanged in urine; 1/3 hydrolysed in blood and tissue
- Mean half life 18.5 hours on day 1; 9.1 hours on day 7

Safety data:
- Generally safe in children and adults; case studies and PK studies suggest safety in neonates
Levetiracetam - Ongoing trials

Efficacy of Intravenous Levetiracetam in Neonatal Seizures: A Phase 2 Randomized Blinded Controlled Study of the Efficacy of Intravenous Levetiracetam as First Line Treatment for Neonatal Seizures, San Diego, CA


- RCT to determine efficacy in terminating neonatal seizures when given as first-line therapy compared with phenobarbital
Levetiracetam - Ongoing trials

Efficacy of Levetiracetam for Neonatal Seizures, Cincinnati, USA

- [http://www.clinicaltrials.gov/ct2/show/record/NCT10475656](http://www.clinicaltrials.gov/ct2/show/record/NCT10475656)

- An observational study comparing Levetiracetam and phenobarbital as first line treatment

- Primary outcome: proportion of neonates who achieve seizure freedom as measured by continuous EEG for 24 hours after infusion of drug
**Topiramate**

Mechanism of action:
- Reduces the frequency of action potential during sustained depolarization
- Modulates GABA activity by enhancing activity at some types of GABA receptors without effect on NMDA receptors
- Weakly antagonizes excitatory activity of the kainate/glutamate AMPA receptor
- Has neuroprotective activity in animal studies likely due to effects at AMPA site
- Animal studies suggest no harmful effects; no increased apoptosis

PK data:
- 70% excreted unchanged in urine
- Only available in oral form

Efficacy data is limited
Topiramate – Ongoing trials

There are no ongoing trials of Topiramate as an AED; two trials are evaluating it as a neuroprotective agent in HIE:

Topiramate as an Adjuvant to Therapeutic Hypothermia for Infants with Hypoxic Ischemic Encephalopathy, California
- RCT to evaluate neuroprotective properties of oral topiramate (5 mg/kg/day)
- Primary outcome – seizure occurrence

Safety and Efficacy of Oral Topiramate in Neonates with Hypoxic Ischemic Encephalopathy Treated with Hypothermia: a Pilot Study of the Neonatal Neuroprotection of Asphyxiated Tuscan Infants, (NeoNATI) Network, Italy
- Primary outcome – neurologic outcome at 6, 12, 18 months
Bumetanide – Preclinical data

Mechanism of action:
- Inhibits the chloride co-transporter, reduces intracellular chloride
- Reduction in intracellular chloride reduces or reverses the depolarizing action of GABA and thus decreases neuronal firing
- Augments phenobarbital activity

PK data:
- Half life ~ 6 hours (up to 15 hours)
- 40% cleared by the renal system; 60% through hepatic metabolism

Safety data:
- No studies in infants
Bumetanide – Ongoing trials

Pilot study of Bumetanide for Newborn Seizures, Massachusetts, USA

- www.clinicaltrials.gov/ct2/show/NCT00830531

- Randomized, double-blind, controlled, dose escalation study of bumetanide as add-on therapy to treat refractory seizures caused by HIE, focal or multi-focal stroke, or intracranial hemorrhage not controlled by a loading dose of phenobarbital
Bumetanide – Ongoing trials

NEMO1: An open label exploratory dose finding and pharmacokinetic clinical trial of bumetanide for the treatment of Neonatal Seizure using Medication Off-patent, EU

- www.clinicaltrials.gov/ct2/show/NCT01434225

- Stage 1: to estimate the optimal dose of bumetanide for treatment of seizures not responding to in initial dose of phenobarbitone
- Stage 2: to determine the pharmacokinetics at an optimal dose level
Other potential therapeutic agents

Benzodiazepines
• Modulate GABA_A receptors; studies of different routes of administration in pediatric populations, not neonates

Xenon
• Non-competitive blocker of NMDA receptors, antiapoptotic and neuroprotective in animal studies; under investigation in neonates with HIE (“Neuroprotective Effects of Hypothermia Combined with Inhaled Xenon Following Perinatal Asphyxia”, Medical Research Council, UK)
Changes you may want to make in practice

Over the next 5 – 10 years, it is likely that new therapeutic agents will have undergone testing in well-designed clinical trials. Those with greater efficacy and fewer potential side effects than phenobarbital and phenytoin may emerge.

• Keep your eye out for them!

Different seizure etiologies may warrant different approaches to treatment.

• One size may not fit all – be selective.

Centrally-acting drugs interact with developing brain in ways that may be beneficial or harmful – and in ways different from adult brains.

• Use them at the lowest effective dose, for the shortest time to minimize unintended negative consequences.
References

For more information on this subject, see the following publications:
