OBJECTIVE: To compare the efficacy of fosphenytoin and phenobarbital as first-line anti-epileptic drug (AED) for neonatal seizures treatment and to assess neurodevelopmental outcomes at 18 months of age.

METHODS: A single center retrospective cohort review of all neonates admitted to a Level III NICU during the study period with clinical and electroencephalographic (EEG) diagnosis of seizures. Data collection included maternal antenatal complications as well as neonatal baseline characteristics and clinical outcomes, including details pertaining to seizure diagnosis and management. The primary outcome variable was long-term neurodevelopmental status determination by a pediatric neurologist and/or developmental-behavioral specialist at 18 months of age.

RESULTS: Infants in both groups had similar baseline characteristics for neonatal variables (gestational age, birth weight, gender, mode of delivery and 5-minute APGAR score) as well as maternal antenatal complications. For outcome variables there was no difference in EEG/neuroimaging findings, time to seizure control, recurrence of seizures, need for a second-line AED, and discharge home on AED. However, we did find significantly fewer infants in the fosphenytoin group vs phenobarbital group (4.8% vs 30%, p=0.02) with moderate to severe neurodevelopmental delay at 18-month assessments.

CONCLUSIONS: Fosphenytoin as well as phenobarbital are equally efficacious as first-line AED in neonatal seizure control but neonates treated with fosphenytoin have significantly better neurodevelopmental outcomes at 18 months of age. Further multicenter studies are recommended to confirm our findings.
Abstract

• OBJECTIVE: To compare the efficacy of fosphenytoin and phenobarbital as first-line anti-epileptic drug (AED) for neonatal seizures treatment and to assess neurodevelopmental outcomes at 18 months of age.
• METHODS
• RESULTS
• CONCLUSIONS

Introduction

Neonatal seizures are common in both term and preterm infants, ranging with a risk of seizures being highest in the neonatal period (1.8 to 3.5/1000 live births in the United States). They are often indicative of an underlying pathological process such as hypoxic ischemic encephalopathy, intracranial hemorrhage, stroke or sepsis. Neonatal seizures are associated with high morbidity and mortality. While outcome is strongly influenced by etiology, there is evidence that uncontrolled seizures can exacerbate brain injury and have a negative impact on neurodevelopment. The question of which therapy to initiate is highly disputed, as some AEDs may have negative effects on the developing brain.

Currently the most commonly used first line treatment in new onset neonatal seizures is phenobarbital in most clinical settings, despite known negative impact on the developing neonatal brain. Phenobarbital binds to the GABA receptor, improving the effect of GABA by extending the duration of chloride channel openings and allows increased flow of chloride ions across the membrane. This causes neuronal hyperpolarization and is in fact excitatory in nature in neonates. When neuronal activity is abnormally suppressed, the timing and sequence of synaptic connections can be disrupted and it causes nerve cells to receive signals to self-destruct resulting in apoptosis. Fosphenytoin, a phosphate ester prodrg, is equally efficacious with no known neurocognitive side effects, though cardiac side effects are well known.

Methods

A single center retrospective cohort review of all neonates admitted to a Level III NICU during the study period with clinical and electroencephalographic (EEG) diagnosis of seizures. The primary outcome variable was long-term neurodevelopmental status at 18 months of age.
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Introduction

• Neonatal seizures are common in both term and preterm infants, often indicative of an underlying pathological process and associated with high morbidity and mortality.

• While neurodevelopmental outcome is strongly influenced by etiology, uncontrolled seizures themselves can exacerbate brain injury.

• The question of which therapy to initiate as first line is highly disputed, as some Anti-epileptic drugs (AEDs) may themselves have negative impact on the developing brain.

Methods

A single center retrospective cohort review of all neonates admitted to a Level III NICU during the study period with clinical and electroencephalographic (EEG) diagnosis of seizures. Data collection included maternal antenatal complications as well as neonatal baseline characteristics and clinical outcomes, including details pertaining to seizure diagnosis and management. The primary outcome variable was long-term neurodevelopmental status determination by a pediatric neurologist and/or developmental-behavioral specialist at 18 months of age.

Results

Infants in both groups had similar baseline characteristics. There was no difference in most outcome variables.

However, we did find significantly fewer infants in the fosphenytoin group vs phenobarbital group with moderate to severe neurodevelopmental delay at 18-month assessments.

Conclusions

Fosphenytoin as well as phenobarbital are equally efficacious as first-line AED in neonatal seizure control but neonates treated with fosphenytoin have significantly better neurodevelopmental outcomes at 18 months of age.

References
Results

• Infants in both groups had similar baseline characteristics for neonatal variables (gestational age, birth weight, gender, mode of delivery and 5-minute APGAR score) as well as maternal antenatal complications as shown in Table 1.

• For outcome variables there was no difference in EEG, neuroimaging findings, recurrence of seizures, need for a second-line AED, time to seizure control and discharge home on AED as shown in Table 2 and Figure 1.

• However, we did find significantly fewer infants in the fosphenytoin group vs phenobarbital group (4.8% vs 30%, p=0.02) with moderate to severe neurodevelopmental delay at 18-month assessments as demonstrated in Figure 2.
Efficacy of Fosphenytoin as First-line Anti-epileptic for Neonatal Seizures as Compared to Phenobarbital

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Figure 1. Though 52% of neonates treated with phenobarbital had recurrent seizures while only 26% of neonates treated with fosphenytoin had recurrent seizures, this was not statistically significant. There was also no statistical significance between both drugs in the need for a second anti-epileptic drug (AED) or if the neonate was discharged home on an AED.

Table 1. Infants in both groups had similar baseline characteristics for neonatal variables as well as maternal antenatal complications.

Table 2. There was no difference in EEG, neuroimaging findings, recurrence of seizures, or time to seizure control.

Clinical Characteristics for First line Anti-Epileptic Drugs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fosphenytoin</th>
<th>Phenobarbital</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (grams)</td>
<td>3144.3 (630.6)</td>
<td>3298.5 (631.6)</td>
<td>0.31</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>5 – minute APGAR score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2 (18.2)</td>
<td>3 (20)</td>
<td>0.76</td>
</tr>
<tr>
<td>Birth asphyxia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Moderate</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Minimal</td>
<td>2 (18.2)</td>
<td>10 (40.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIE</td>
<td>3 (20)</td>
<td>9 (40.9)</td>
<td>0.44</td>
</tr>
<tr>
<td>Other</td>
<td>9 (26.5)</td>
<td>9 (26.5)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
| Table 2. There was no difference in EEG, neuroimaging findings, recurrence of seizures, or time to seizure control.

Comparative effectiveness of Fosphenytoin and phenobarbital

- Normal to Mild Delay
- Moderate to Severe Delay

Figure 2. At neurodevelopmental or neurology follow ups at 18 months, 30% of infants treated with phenobarbital had a moderate to severe delay while 5% of infants treated with fosphenytoin had a moderate to severe developmental delay.
Conclusion

- Fosphenytoin as well as phenobarbital are equally efficacious as first-line AED in neonatal seizure control but neonates treated with fosphenytoin have significantly better neurodevelopmental outcomes at 18 months of age.

- Further multicenter studies are recommended to confirm our findings.
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References

Anticonvulsants for neonates with seizures (Cochrane Review). 2009
Conde, JR Castro; et al, Midazolam in Neonatal Seizures with no response to phenobarbital. Neurology 2005: 64; 876-879
Tekgul, Hasan; et al, The Current Etiologic Profile and Neurodevelopmental Outcome of Seizures in Term Newborn Infants: Pediatrics 206; 117; 1270-1280
Vezzani A. Epilepsy and Inflammation in the Brain: Overview and Pathophysiology. Epilepsy Currents. 2014; 14: 3-7
Drugs of abuse that cause developing neurons to commit suicide. Nuri B. Farber John W. Olney

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