Incidence of Delayed Cerebral Ischemia in Aneurysmal Subarachnoid Hemorrhage Patients Receiving Nimodipine with or without Phenytoin for Seizure Prophylaxis

Baylor University Medical Center – Dallas
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Background
Aneurysmal subarachnoid hemorrhage (aSAH) occurs in 9.7-14.5 per 100,000 (~30,000) adults in the United States annually.

Incidence of potential complications:
- Delayed cerebral ischemia (DCI): ~30%
- Seizures: ~27%
- Cerebral vasospasm: ~32.5%-97%
- Mortality: ~26%-36%

Treatment options:
- Nimodipine is shown to improve neurological outcomes
- Phenytoin is often used for short term seizure prophylaxis

Drug-drug interaction between phenytoin and nimodipine:
- Phenytoin is a CYP3A4 inducer
- Nimodipine is a CYP3A4 substrate
- Interaction may lead to sub-therapeutic nimodipine serum levels, resulting cerebral vasospasm and poor clinical outcomes
- Clinical significance of this interaction has not previously been evaluated

Baylor University Medical Center-Dallas is an urban, teaching and research institution, with a level 1 trauma and comprehensive stroke center, as well as a 16-bed neurological-ICU

Objective
To assess the efficacy of nimodipine in preventing DCI for patients with aSAH who did or did not receive phenytoin for seizure prophylaxis

Methods
Single center, retrospective chart review of 120 patients who received nimodipine with a confirmed aSAH between January 1, 2013, and August 31, 2014

Primary Endpoint
Incidence of DCI

Secondary Endpoints
Incidence of cerebral vasospasm, seizures, and mortality

Inclusion Criteria:
- Received nimodipine
- Diagnosed aSAH
- Age ≥18 years
- Transcranial doppler or cerebral angiography
- Hospitalization ≥7 days

Exclusion Criteria:
- Traumatic SAH
- Pregnancy
- History of seizures or seizure disorder
- Outpatient antiepileptic medication
- Inappropriate nimodipine dosage

Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Phenytoin N=21</th>
<th>No Phenytoin N=49</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>56 (12.9)</td>
<td>55.8 (11.7)</td>
<td>0.952</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>14 (66.7)</td>
<td>32 (65.3)</td>
<td>0.912</td>
</tr>
<tr>
<td>Stroke Hx, n(%)</td>
<td>0 (0)</td>
<td>2 (4.1)</td>
<td>0.347</td>
</tr>
<tr>
<td>LOC, n(%)</td>
<td>5 (23.8)</td>
<td>11 (22.5)</td>
<td>0.901</td>
</tr>
<tr>
<td>Statin, n(%)</td>
<td>21 (100)</td>
<td>36 (73.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Rebleeding, n(%)</td>
<td>1 (4.8)</td>
<td>1 (2)</td>
<td>0.531</td>
</tr>
<tr>
<td>Clip, n(%)</td>
<td>1 (4.8)</td>
<td>8 (16.3)</td>
<td>0.261</td>
</tr>
<tr>
<td>Coil, n(%)</td>
<td>19 (90.5)</td>
<td>32 (65.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stent, n(%)</td>
<td>1 (4.8)</td>
<td>2 (4.1)</td>
<td>1</td>
</tr>
</tbody>
</table>

Patient Selection

Results

Delayed Cerebral Ischemia

<table>
<thead>
<tr>
<th>Percent</th>
<th>Phenytoin</th>
<th>No Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>33.3%</td>
<td>16.3%</td>
</tr>
</tbody>
</table>

Cerebral Vasospasm

<table>
<thead>
<tr>
<th>Percent</th>
<th>Phenytoin</th>
<th>No Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>76.2%</td>
<td>53%</td>
</tr>
</tbody>
</table>

Seizures

<table>
<thead>
<tr>
<th>Percent</th>
<th>Phenytoin</th>
<th>Levetiracetam</th>
<th>Other</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>18.9%</td>
</tr>
</tbody>
</table>

Mortality

<table>
<thead>
<tr>
<th>Percent</th>
<th>Phenytoin</th>
<th>No Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14.3%</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

Discussion

Although the results of this study did not achieve statistical association, the higher incidence of DCI, vasospasms, and mortality is of clinical interest and may be hypothesis generating for a future controlled study

Seizure incidence fell within previously reported ranges and occurred only in patients who did NOT receive prophylaxis

Phenytoin has been associated with poor functional and cognitive outcomes

Levetiracetam may be a safer and more tolerable alternative for seizure prophylaxis

Limitations
Retrospective ● Single center ● Small sample ● MD practice variation ● Lack aSAH severity assessment ● Selectin bias

Conclusion

The incidence of DCI did not statistically differ between treatment groups; however, the increased occurrence in patients who received phenytoin raises concern. Although these results were not statistically significant, analyzing trends towards a greater incidence of unfavorable outcomes may reflect clinical significance. The possibility of a worse clinical outcome with phenytoin may support the use of an alternative antiepileptic

References

Disclosures
Sara S. Schulz, PharmD – nothing to disclose; Jennifer M. Roth, PharmD, BCPS – nothing to disclose; C. Joseph Kramer, PharmD, BCPS - nothing to disclose; Huanying Qin, MS - nothing to disclose; James West, MD - nothing to disclose; Kenneth F. Layton, MD - nothing to disclose; Dion Graybeal, MD - nothing to disclose.