Antiepileptic drugs and cardiovascular disease
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Disclosures

Commercial Interest

UCB

Eisai, Sunovion, Pfizer, Upsher-Smith

Financial Relationship

Speaking, advisory board

Consultant (via the Epilepsy Study Consortium)
Learning Objective

• To recognize the effects of particular antiepileptic drugs on various surrogate markers of vascular risk
# Vascular disease in epilepsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Study size</th>
<th>Standardized ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neligan et al. (2011)</td>
<td>19,114 person-years</td>
<td>IHD mortality: 1.5*</td>
<td>1.1 - 2.0</td>
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<tr>
<td></td>
<td></td>
<td>Stroke mortality: 2.9*</td>
<td>2.1 - 3.9</td>
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<tr>
<td>Olesen et al. (2011)</td>
<td>~213,000 person-years† (epilepsy patients without prior history of stroke)</td>
<td>CVD mortality: 1.64*</td>
<td>1.57 - 1.72</td>
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<td></td>
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<td>MI morbidity: 1.09*</td>
<td>1.00 - 1.19</td>
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<td></td>
<td></td>
<td>Stroke morbidity: 2.22*</td>
<td>2.09 - 2.36</td>
</tr>
<tr>
<td>Mu et al. (2011)</td>
<td>~7,000 person-years†</td>
<td>Cardiac disease mortality: 1.6</td>
<td>0.5 - 5.22</td>
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<tr>
<td></td>
<td></td>
<td>CVD mortality: 1.14</td>
<td>0.36 - 3.61</td>
</tr>
<tr>
<td>Ding et al. (2006)</td>
<td>~5,000 person-years†</td>
<td>MI mortality: 10.7*</td>
<td>5.6 - 95.3</td>
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<tr>
<td>Gaitatzis et al. (2004)</td>
<td>~23,000 person-years†</td>
<td>IHD mortality: 1.34*</td>
<td>1.19 – 1.5</td>
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<td></td>
<td></td>
<td>IHD mortality, age &lt; 65: 1.63*</td>
<td>1.34 – 1.98</td>
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<td></td>
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<td>CVD morbidity: 6.96*</td>
<td>6.4 – 7.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CVD morbidity, age &lt;65: 14.19*</td>
<td>12.0 – 16.7</td>
</tr>
<tr>
<td>Nilsson et al. (1997)</td>
<td>53,250 person-years</td>
<td>IHD mortality: 2.5*</td>
<td>2.3 - 2.7</td>
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<tr>
<td></td>
<td></td>
<td>CVD mortality: 5.3*</td>
<td>4.9 – 5.8</td>
</tr>
<tr>
<td>Annegers et al. (1984)</td>
<td>“Approached 10,000 person-years”</td>
<td>IHD mortality: 1.2</td>
<td>0.9 – 1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHD mortality, age 25 - 44: 5.7*</td>
<td>1.8 – 13.3</td>
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<tr>
<td></td>
<td></td>
<td>IHD mortality, age 45 - 64: 2.5*</td>
<td>1.4 – 4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHD morbidity: 1.63*</td>
<td>1.2 – 2.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHD, idiopathic epilepsy only: 1.49*</td>
<td>1.0 – 2.15</td>
</tr>
</tbody>
</table>
CYP450 enzymes and cholesterol synthesis

Nebert and Russell, Lancet 2002
CYP51A1 and cholesterol synthesis

Selected portions of the cholesterol synthetic pathway
Good

• More than 10 cross-sectional studies of adults & children found elevated total cholesterol in CBZ-treated patients relative to controls or VPA-treated patients (LoPinto & Mintzer, Curr Treat Opt Neurol 2010)

• Half dozen studies of PB show elevated cholesterol too

• Much less cross-sectional data with PHT - suggestive but not significant

• Limited by cross-sectional design -- cannot definitively ascribe changes to the drug
• Half-dozen studies measured lipids before and after CBZ treatment, documenting increases in total cholesterol of 20-25 mg/dL

• Unclear that this is specific to CBZ

• No data on PHT, newer AEDs

Bramswig et al, Epilepsia 2003
Effects of Antiepileptic Drugs on Lipids, Homocysteine, and C-Reactive Protein

Scott Mintzer, MD,1 Christopher T. Skidmore, MD,1 Caitlin J. Abidin, BS,1 Megan C. Morales, BS,1 Inna Chervoneva, PhD,2 David M. Capuzzi, MD, PhD,3 and Michael R. Sperling, MD1

Objective: The widely prescribed anticonvulsants phenytoin and carbamazepine are potent inducers of cytochrome P450 enzymes, which are involved in cholesterol synthesis. We sought to determine whether these drugs have an effect on cholesterol and other serological markers of vascular risk.

Methods: We recruited 34 epilepsy patients taking carbamazepine or phenytoin in monotherapy whose physicians had elected to change treatment to one of the noninducing anticonvulsants lamotrigine or levetiracetam. Fasting blood samples were obtained both before and 6 weeks after the switch to measure serum lipid fractions, lipoprotein(a), C-reactive protein, and homocysteine. A comparator group of 16 healthy subjects underwent the same serial studies.

Results: In the epilepsy patients, switch from either phenytoin or carbamazepine produced significant declines in total cholesterol (−24.8mg/dl), atherogenic (non-high-density lipoprotein) cholesterol (−19.9mg/dl), triglycerides (−47.1mg/dl) (all p < 0.0001), and C-reactive protein (−31.4%; p = 0.027). Patients who stopped taking carbamazepine also had a 31.2% decline in lipoprotein(a) level (p = 0.0004), whereas those taken off phenytoin had a decrease in homocysteine level (−1.7μmol/L; p = 0.005). All of these changes were significant when compared with those seen in healthy subjects (p < 0.05). Results were similar whether patients were switched to lamotrigine or levetiracetam.

Interpretations: Switching epilepsy patients from the enzyme-inducers carbamazepine or phenytoin to the noninducing drugs levetiracetam or lamotrigine produces rapid and clinically significant amelioration in several serological markers of vascular risk. These findings suggest that phenytoin and carbamazepine may substantially increase the risk for cardiovascular and cerebrovascular disease.

Ann Neurol 2009;65:448–456

Antiepileptic drugs (AEDs) are utilized extensively in the general population. A recent large survey of ambulatory practice data demonstrated that an AED was mentioned at more than 13% of outpatient healthcare visits in the United States in 2003 to 2004, a proportion that approaches that of penicillins or corticosteroids.1

Although many new AEDs have been introduced over the past 15 years, the consensus first choice for known to figure prominently in numerous important aspects of metabolism.4 In addition to their well-established effects on drug metabolism, both steroid metabolism and vitamin D metabolism are altered by treatment with enzyme inducers.5–7

Another area of metabolism that is worthy of study is that of the potential effects of AEDs on vascular risk. Epidemiological studies suggest that patients with epilepsy have a greater prevalence of cardiovascular and
Methods

- Epilepsy patients on monotherapy with phenytoin (PHT) or carbamazepine (CBZ) being switched to lamotrigine (LTG) or levetiracetam (LEV)

- Fasting blood draws were obtained for a lipid panel, Lp(a), CRP, homocysteine, and B vitamins (folate, B6, B12) while still on PHT or CBZ monotherapy

- The same tests were performed again after switch to LEV or LTG, 6 weeks after the last dose of the old (inducing) drug

- Patients taking lipid-lowering agents excluded; those taking vitamins excluded from B vitamin and homocysteine analyses
Cholesterol in patients converted from CBZ or PHT to non-inducers (LEV or LTG)

Mintzer et al. Ann Neurol 2009
<table>
<thead>
<tr>
<th>Measure (mg/dL)</th>
<th>Pt group (N)</th>
<th>On inducer (mean ± SD)</th>
<th>On non-inducer (mean ± SD)</th>
<th>p-value (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>All (n =38)</td>
<td>217 ± 43</td>
<td>191 ± 38</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Non-HDL chol.</td>
<td>All (n =38)</td>
<td>155 ± 42</td>
<td>135 ± 36</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>All (n =38)</td>
<td>62 ± 21</td>
<td>56 ± 16</td>
<td>p=0.002</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>All (n =38)</td>
<td>142 ± 126</td>
<td>90 ± 47</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>All (n =37)</td>
<td>4.2 ± 5.2</td>
<td>2.4 ± 4.1</td>
<td>p=0.003</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>CBZ only (n=20)</td>
<td>33 ± 25</td>
<td>23 ± 18</td>
<td>p=0.004</td>
</tr>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>PHT only (n=13)</td>
<td>13.5 ± 6.4</td>
<td>10.5 ± 3.9</td>
<td>p=0.02</td>
</tr>
</tbody>
</table>

All changes p<0.05 relative to changes in normal subjects (not shown)
Conversion from inducing AEDs to topiramate: CRP

Mintzer et al., Epilepsy Research 2012
Estimated vascular risk at draw 1 relative to draw 2

Drug-treated patients
36 ± 47%

Normal subjects
3 ± 23%

P < 0.005
Carotid intimal thickness

- Combined thickness of intimal and medial layers of the carotid, by ultrasound, shown to be a very potent surrogate marker for both CVA and MI risk
- Considered a marker of systemic atherogenesis
- 3 separate groups have found increased carotid IMT in AED-treated epilepsy patients relative to controls
- One found CBZ-treated patients with ↑ IMT than untreated patients (Hamed et al., Epilepsy Res 2007)
Carotid IMT and duration of AED Rx

Chuang et al., Epilepsia 2012
pharmacoepidemiology

- Olesen et al. (Pharmacoepidemiol Drug Saf 2011) - looked at vascular dz rates by individual AED in national Danish database

- Unfortunately used CBZ as the baseline for comparison

- Found ↓ rates of MI (28%) and CVA (14%) in VPA-treated pts, ↓ rate of CV death (15%) in LTG-treated pts (relative to CBZ-treated patients)

- Also found ↑ rate of CVA (21%) in OXC-treated pts, and ↑ rate of CV death (8-10%) in OXC- and PB-treated pts
Impact on Clinical Care and Practice

• Patients with epilepsy have higher rates of vascular disease

• Enzyme-inducing AEDs exert deleterious effects on multiple surrogate markers of vascular risks -- it is possible that they increase the risk of MI and other vascular conditions

• At minimum, patients taking these drugs need to be screened for vascular risk (e.g. lipid panel, cardiac & carotid imaging) -- and perhaps we should consider prescribing changes