Treatment of Nocturnal Seizures: Are We still in the Dark?

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Disclosure

Ovation/Lundbeck: Principal Investigator, Industry-supported multicenter trial: Safety and Efficacy of Clobazam in Subjects with Lennox-Gastaut Syndrome
Learning Objectives

• To understand the principles of chronopharmacology

• To review published experience in chronotherapy of epilepsy
1. Targeting pharmacological treatment towards nocturnal events:

**Chronopharmacology:**
- chronopharmacokinetics
- chronopharmacodynamics / chronotoxicity
- chronotherapy

2. Specific treatment of seizures/epilepsy syndromes with nocturnal predilection:
- Frontal lobe epilepsy
- Benign rolandic epilepsy
- Panayiotopoulos syndrome
- ESES
Chronopharmacokinetics
CIRCADIAN EFFECT ON CARBAMAZEPINE KINETICS IN RAT

- PK of single 100 mg/kg oral dose given at:

- 10:00  Longest T max
- 16:00  Highest C max;  $T_{\frac{1}{2}}$  15.15 h
- 22:00  $T_{\frac{1}{2}}$  10.48 h
- 04:00

- Conclusion: 1. Absorption faster PM than AM
  2. Elimination faster at night

- Possible mechanisms involved:
  absorption, $V_d$, protein binding, hepatic blood flow, hepatic enzyme activity
**CHRONOPHARMACOKINETICS OF VALPROIC ACID FOLLOWING CONSTANT-RATE ADMINISTRATION IN MICE**

Ohdo S et al. Chronobiol Int 1991;8:35-43

- **Constant-rate administration (s.c.):**
  
  Light phase: VPA levels higher, clearance lower

- **50 mg/kg i.v:**
  
  17:00 h  Mean VPA levels higher
  
  01:00 h  Clearance higher, $V_d$ larger, AUC smaller

  $T\frac{1}{2}$ unchanged

  $Cl = V_d \times K_{el} = V_d \times \ln2 / T\frac{1}{2}$

- **Conclusion:** Clearance of VPA was higher at night due to a larger $V_d$ (decrease in protein binding?)
CHRONOPHARMACOKINETICS OF AEDS IN HUMANS

- Clobazam\(^1\) and diazepam\(^2\):
  - \(C_{\text{max}}\): AM > PM; T\(_{\text{max}}\): PM > AM
  - AUC, T\(_{1/2}\) \(\beta\): no difference

- PHT\(^3\) administration at 20:00 h vs. 08:00 h:
  - T\(_{\text{max}}\) 4 h vs. 10 h; elimination faster;
    less toxic levels; less adverse effects

- PHT\(^4\) 300 mg at 08:00 h and 20:00 h in 10 healthy
  male volunteers: no evidence of difference in
  absorption or elimination

Methods

A. 103 patients with diurnal GTC or SGTC seizures and subtherapeutic trough levels of PHT (<10) or CBZ (<4)
(Subtherapeutic Group = STG)

Randomized to:

STG 1 (N=51): dose increment, but no change in schedule
STG 2 (N=52) no dose increment, but 2/3 – 100% of daily dose at 8 PM

Monthly F/U for 1 at least one year, treating physician blinded to allocation
Results

- STG 1: 16/51 had therapeutic trough levels after 4 weeks;
- STG 2: 47/52 had therapeutic trough levels after 4 weeks (p<0.01)
- STG 2:
  - more good responders (no seizure for 1 year) (40/52 vs. 18/51, p<0.01)
  - no poor responders (<50% reduction)
Conclusions

- Administration of most or all of the dose of PHT and CBZ at 8 PM can:
  
  1. Improve the response of diurnally active epilepsy
  2. Achieve therapeutic levels in patients with subtherapeutic levels
  3. Reduce toxicity in patients with toxic levels
**Methods**

- 17 patients (median 11.9, 3.5 – 21 y/o) with predominantly nocturnal or early-morning seizures were switched to a higher evening drug dose without change in the total daily dose.

- Mean number of previous AEDs 2.7, mean number of current AEDs 1.7.

- Seizure frequency assessed over 12-month baseline and on differential dosing regimen.

- Extent of pharmacokinetic impact of differential dosing was assessed by pharmacokinetic modeling.
Results

- Median / mean follow-up on higher evening dose: 3 / 5.3 months
- Median / mean evening dose as % of daily dose: 66.6 / 65.9%
- Median / mean seizure frequency over 12-month baseline: 12 / 65.6 per month
- Median / mean seizure frequency on higher evening dose: 0 / 2.6 per month (p < 0.001)
- Mean reduction in seizure frequency: 78.5%
Monthly seizure frequency (Median and 25-75th percentile)
Equation used for pharmacokinetic modeling
Drug level as a function of time after dosing

\[ C_t = C_0 \ e^{-t \ km} + \ \frac{f \ D}{V_d} \ \left( \frac{k_{abs}}{k_{abs} - k_{el}} \right) \ \left( e^{-t \ km} - e^{-t \ k_{abs}} \right) \]
**PHARMACOKINETIC MODELING**
**REGULAR LEV**

<table>
<thead>
<tr>
<th>$T^{\frac{1}{2}}_{\text{abs}}$ (hrs)</th>
<th>$T^{\frac{1}{2}}_{\text{el}}$ (hrs)</th>
<th>Dose 8 AM (mg/kg)</th>
<th>Dose 8 PM (mg/kg)</th>
<th>$C_{\text{max}}$ (mg/L)</th>
<th>$C_{\text{min}}$ (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>7</td>
<td>15</td>
<td>15</td>
<td>30.2</td>
<td>11.8</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>25.2</td>
<td>9.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>35.2</td>
<td>13.9</td>
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</tbody>
</table>

**Differential vs. equal dosing:**
- Nocturnal $C_{\text{max}}$ increase: $+16.6\%$
- Nocturnal $C_{\text{min}}$ increase: $+17.8\%$
PHARMACOKINETIC MODELING
REGULAR CBZ

<table>
<thead>
<tr>
<th>$T_{\frac{1}{2}}$ abs (hrs)</th>
<th>$T_{\frac{1}{2}}$ el (hrs)</th>
<th>Dose 8 AM (mg/kg)</th>
<th>Dose 8 PM (mg/kg)</th>
<th>C max (mg/L)</th>
<th>C min (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>13</td>
<td>10</td>
<td>10</td>
<td>12.8</td>
<td>7.7</td>
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<tr>
<td>6.7</td>
<td></td>
<td></td>
<td></td>
<td>11.6</td>
<td>6.9</td>
</tr>
<tr>
<td>13.3</td>
<td></td>
<td></td>
<td></td>
<td>14.0</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Differential vs. equal dosing:

Nocturnal C max increase: + 9.4 %
Nocturnal C min increase: +10.4 %
Level fluctuations with equal and differential dosing
### PHARMACOKINETIC MODELING

#### CBZ XR

<table>
<thead>
<tr>
<th>T½ abs (hrs)</th>
<th>T½ el (hrs)</th>
<th>Dose 8 AM (mg/kg)</th>
<th>Dose 8 PM (mg/kg)</th>
<th>C max (mg/L)</th>
<th>C min (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4</td>
<td>13</td>
<td>10</td>
<td>10</td>
<td>11.0</td>
<td>8.6</td>
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<td>10.4</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>13.3</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Differential vs. equal dosing:

- Nocturnal C max increase: + 6.4%
- Nocturnal C min increase: +10.5%
### SUMMARY

Effect of 1:2 differential dosing on nocturnal peak and trough levels

<table>
<thead>
<tr>
<th>Type of Elimination</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; Increase</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid absorption and elimination</td>
<td>+16.6%</td>
<td>+17.8%</td>
</tr>
<tr>
<td>Rapid absorption, slower elim.</td>
<td>+9.4%</td>
<td>+10.4%</td>
</tr>
<tr>
<td>Extended release, slower elim.</td>
<td>+6.4%</td>
<td>+10.5%</td>
</tr>
<tr>
<td>Slow elimination (T&lt;sub&gt;1/2&lt;/sub&gt; el 70 hrs)</td>
<td>+1.8%</td>
<td>+2.1%</td>
</tr>
</tbody>
</table>
1. The PK impact of higher evening dose is modest
2. The PK impact of higher evening dose is lower for drugs with longer elimination half lives
3. Use of XR preparations lowers the PK impact of higher evening dose on the C max but not on C min
4. Positive response may not have been due to higher nocturnal peaks
5. Higher PM dose may compensate for adverse chronopharmacokinetics or for adverse chronopharmacodynamics
SPECIFIC TREATMENT OF SEIZURES/EPILEPSY SYNDROMES WITH NOCTURNAL PREDILECTION
NICOTINE AS AN ANTIEPILEPTIC AGENT IN ADNFLE: AN N-OF-ONE STUDY
Willoughby et al. Epilepsia 2003;44:1238-40

- 33 y/o woman with known mutation causing ADNFLE
- Open study: Nicoderm CQ, 7 mg once daily for 2 weeks alternating with no treatment
- Double-blind study: nicotine patch versus placebo patch, each for 3 periods of 2 weeks, randomized in double-blind manner

Results:
- Open study: 0.01 (SD 0.0) seizures per day (294 days) vs. 1.65 (SD 2.36) (97 days) (p < 0.0001)
- Double-blind study: 0.0 (SD 0.0) seizures per day vs. 0.56 (SD 1.14) (p < 0.0001)
12 y/o girl with ADNFLE, > 20 seizures per night

ACZ 500 mg HS added to CBZ, patient became seizure free

Proband’s father: ACZ added to CBZ, VPA and PRM, seizure reduction

Proband’s brother: ACZ added to CBZ, PHT and PRM, seizure free, off PHT and PRM. Seizure recurrence after ACZ reduction for renal calculi
Conclusions
Impact on Clinical Care and Practice

1. Chronotherapy is an emerging therapeutic approach that can be targeted successfully against nocturnal seizures

2. Certain nocturnal seizures can respond to specific medications