Population Pharmacokinetics of Clobazam and its Active Metabolite in pediatric patients with epilepsy: Effect of weight, genotype and co-therapy

Manisha Lamba*, Richard C. Brundage, Stephen P. Wanaski, Katherine A. Tracy, Stephen D. Collins, and Angela K. Birnbaum

11th March 2008
What do we know?

- **Lennox-Gastaut Syndrome (LGS)**
  - Catastrophic childhood epilepsy with atonic seizures, developmental retardation, and behavioral disturbances

- **Clobazam (CLB)**
  - High Bioavailability (87%), Low oral clearance (2.5 L/hr)
  - Metabolized by CYP3A4 and 2C19 to the active metabolite- N-Desmethylclobazam (NCLB)
  - NCLB further metabolized by 2C19 to 4’ OH-NCLB (inactive metabolite)

Kosaki K et al., Brain & Development (2004) 26: 530-534
What do we want to know?

Population pharmacokinetics of CLB and NCLB in target patient population

• Essentially pediatric patients
Study Design and Patient Characteristics

- Phase 2, multi-center, randomized, double-blind, dose-ranging study
  - N: 60
  - Treatment length: 11 weeks
- 6 weight groups (~10 per group) randomly assigned to low or high dose treatment group
  - Low-Dose target: 0.25mg/kg (≤ 10 mg)
  - High-Dose target: 1.0 mg/kg (≤ 40 mg)
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean (Range) / Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8 (1,23)</td>
</tr>
<tr>
<td>Gender</td>
<td>Females: 40%</td>
</tr>
<tr>
<td></td>
<td>Males: 60%</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>26.6 (11.6,75.2)</td>
</tr>
<tr>
<td>CYP2C19 genotype status</td>
<td>Intermediate Metabolizers: 21%</td>
</tr>
<tr>
<td>Concomitant Drugs</td>
<td>VPA: 43%</td>
</tr>
<tr>
<td></td>
<td>LTG: 19%</td>
</tr>
<tr>
<td></td>
<td>FBM: 13%</td>
</tr>
<tr>
<td>Race</td>
<td>Non-White: 14%</td>
</tr>
<tr>
<td></td>
<td>White: 85%</td>
</tr>
</tbody>
</table>
Structural Model

- 1-compartment model with first-order absorption and elimination
- Estimation done with FOCE-I using ADVAN7 in NONMEM-VI
- Exponential between-subject variability on PK parameters
- Proportional error for residual variability

Dosing Depot

Central V2

Fixed

k_{12}

k_{20}

CL_{other}

NCLB V3

Globally unidentifiable

k_{23}

CLM

k_{30}

Size-Based Covariate Modeling

Size-Based Covariate Modeling

- Clearance standardized for body-weight of 70 kg with a power coefficient of 0.75

\[
CL_i = CL_{pstd} \times \left( \frac{W_i}{70} \right)^{0.75} \times \exp(\eta_i)
\]

where:
- \(i = CL\) in ith individual
- \(CL_{pstd}\) = Population Standardized clearance
- \(\eta_i\) = ith subject’s random deviation from \(CL_{pstd}\)

- All other covariates tested after ‘size-standardization’ of clearance

- Categorical covariates (2C19 genotype status, gender, concomitant AED drugs) tested proportionally

Exploratory Graphs of CLB CL/F: Size Issues
## Estimates of CLB

<table>
<thead>
<tr>
<th></th>
<th>NONMEM Estimate (95% CI)</th>
<th>Bootstrap Medians (95(^{th}) percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CL/F</strong> (L/hr/70kg)</td>
<td>5.99 (5.15, 6.83)</td>
<td>5.98 (5.23, 6.79)</td>
</tr>
<tr>
<td><strong>V/F</strong> (L)</td>
<td>96.8 (22.7, 171)</td>
<td>108 (50.2, 219)</td>
</tr>
<tr>
<td><strong>BSV(_{CL/F})</strong> (%)</td>
<td>47.1 (36.3, 54.8)</td>
<td>46.4 (34.2, 54.4)</td>
</tr>
<tr>
<td><strong>Residual Error (%)</strong></td>
<td>26.3 (17.2, 33.1)</td>
<td>26.5 (18.7, 34.4)</td>
</tr>
</tbody>
</table>

- After accounting for weight, random variability in CL/F from 56% to 47%
### Estimates of NCLB

<table>
<thead>
<tr>
<th></th>
<th>NONMEM Estimate (95% CI)</th>
<th>Bootstrap Medians (95th percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLM (L/hr/70kg)</strong></td>
<td>1.07 (0.884, 1.26)</td>
<td>1.09 (0.922, 1.27)</td>
</tr>
<tr>
<td><strong>Intermediate CYP2C19 metabolizers (% of CLM)</strong></td>
<td>58.9 (30.3, 87.5)</td>
<td>56.7 (36.7, 97.9)</td>
</tr>
<tr>
<td><strong>Felbamate cotherapy (% of CLM)</strong></td>
<td>33.4 (19.4, 47.4)</td>
<td>32.4 (22.6, 57.4)</td>
</tr>
<tr>
<td><strong>BSV_{CLM} (%)</strong></td>
<td>57.3 (43.1, 68.5)</td>
<td>54.8 (42.0, 67.2)</td>
</tr>
<tr>
<td><strong>Residual Error (%)</strong></td>
<td>18.8 (13.6, 22.9)</td>
<td>18.6 (14.4, 22.9)</td>
</tr>
</tbody>
</table>

- After accounting for covariates, random variability in CLM ↓ from 77% to 57.3%
- Covariance between CL/F and CLM was not significant, very less and thus dropped
Results (continued)

• After size standardization, no other covariate was statistically significant for CLB CL/F

• Between subject variability (BSV) on V/F of CLB could not be estimated

• Fraction metabolized to N-CLB ‘posterior’ un-identifiable
  – Fixed at 0.70

Levy R.H. Drug Metabolism and Disposition; Vol 11, No. 4: 286-292
Diagnostic Graphs

**CLB**

- Population Predicted CLB vs. Observed CLB
- Individual Predicted CLB vs. Observed CLB

**NCLB**

- Population Predicted NCLB vs. Observed NCLB
- Individual Predicted NCLB vs. Observed NCLB
How do we interpret the high clearance?

- Similar findings from literature:
  - Tedeschi et al. reported “CLB is more extensively metabolized in children”
  - Theis et al. reported increasing serum concentrations of CLB with age within pediatric patients

- CYP3A4 effect?
  - ‘Maturity’ of CYP3A4 with age?
  - However, very few patients above 16 years in this patient population

- Background Concomitant Drugs?
  - Each patient on at least three conmeds

What do we know now?

- Population standardized clearance of CLB in LGS patients is twice as high as adult healthy volunteers/patients
  - No age effect is discernible after adjusting for weight in this patient population
  - May have implications for dosing of children: Confirm in future study
- Population standardized clearance of NCLB is similar to adults
  - Lower CLM relative to CL/F supports its elimination rate limited disposition
- Patients on felbamate co-therapy and intermediate metabolizers of CYP2C19 have markedly reduced clearance
Acknowledgements

• University of Minnesota
  – Varun Goel, MS
  – Kyle Baron, Pharm.D

• Nick Holford, MB, ChB, FRACP