Population Modelling of the Absolute Bioavailability and Pharmacokinetics of Phenobarbitone in Infants with Seizures

Anders Lanner
Uppsala University; Merck Sharpe & Dohme Ltd (Sweden)

Bruce Charles*
School of Pharmacy, Australian Centre for Paediatric Pharmacokinetics, University of Queensland, Brisbane, (Australia)

Xiao (Lucy) Xiaonian
Sino-German Research Institute, Nanchang (PR China)

Tim Donovan
Grantley Stable Neonatal Unit, Royal Women’s Hospital, Brisbane (Australia)
Neonatal Seizures

- Seizures arise from an electrophysiological imbalance in brain; Neuro-excitatory activity exceeds neuro-inhibitory activity
- Seizures occur more often in the neonatal period than at any other time in life
- Incidence of 1-2 per 1000 term live births
- Higher risk (6%-13%) in premature infants
- Diagnosis by clinical observation, confirmed in majority of cases by EEG
Neonatal Seizures - Concerns

- Seizures are a neurologic condition requiring immediate medical attention
- Repetitive/prolonged neonatal seizures can increase susceptibility of developing brain to subsequent seizure-induced brain injury in adolescence/adulthood (changed neuronal connectivity, not cell death)
- Overzealous a/c medication may contribute to brain injury in continuing seizures
Neonatal Seizures - Treatment

- Phenobarbitone (PB) is a mainstay of treatment; PB doses adjusted to a putative target therapeutic range of 15-25 mg/L
- Low PB levels: Breakthrough seizures; Asphyxia during seizures → hypoxemia
- High PB levels: Delay development in otherwise non-seizure children (brain injury 2° to hypoperfusion)
- Weaned of PB after 1-3 months seizure-free
Drug Absorption in Infants, Neonates

• Infants, neonates – Rate of and extent of drug absorption may vary from older children and adults because of several factors including:
  - Gastric and duodenal pH
  - Gastro-intestinal emptying/motility
  - Pancreatic and bile secretions
  - Intestinal absorptive surface area
  - Intestinal mucosal barrier function

• Very little data on PK of phenobarb in neonates and infants, while bioavailability of PB is unknown
Study Aims

• To determine clearance, volume of distribution, oral bioavailability of phenobarbitone in neonates and infants
• Assess the influence of various patient characteristics on the PK typical values
• Estimate the interindividual variability about PK parameters, and the residual variability in the population model
Patient Characteristics

Patients (M, F) 113 (73,40)
Weight (kg) 3 (0.59-5.8)
Gestation age (weeks) 37 (23-42)
Postnatal age (days) 13 (1-108)
Samples (i.v., p.o) 310 (183,127)
Samples per individual 2 (1-9)
PB conc. (mg/L) 30 (3-93)
Samples per Individual

![Bar graph showing distribution of samples per individual. The x-axis represents the number of samples per individual, ranging from 1 to 9, and the y-axis represents the count (N), ranging from 0 to 35. The graph indicates that most individuals have between 1 and 4 samples, with a few having 5 to 8 samples, and very few having 9 samples.]
Sample Times – I.V. and Oral

Post-dose sampling times (I.V. and Oral)
Methods

- Retrospective TDM serum phenobarb data
- NONMEM 5 (v.1.1), G77 compiler
- ADVAN2 TRANS2
- Covariate screening (P=0.01, ΔOFV -6.7)
- FOCE with INTERACTION (\(\eta\) and \(\varepsilon\))
- Variability; BLOCK (CL, V, F1)

\[
P_{k_j} = P_{kTV} \cdot e^{\eta_{j,k}} \\
C_{OBS,ij} = C_{PRED,ij} + \varepsilon_{ij}
\]
## Examples of Covariate Screening

<table>
<thead>
<tr>
<th></th>
<th>$\Delta$OFV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clearance (CL)</strong></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>-50</td>
</tr>
<tr>
<td>Age</td>
<td>-18</td>
</tr>
<tr>
<td>Gestational age</td>
<td>-10</td>
</tr>
<tr>
<td>Sex</td>
<td>194</td>
</tr>
<tr>
<td>Infection</td>
<td>5</td>
</tr>
<tr>
<td>Weight + Age</td>
<td>-83</td>
</tr>
</tbody>
</table>

| **Volume (V)**   |             |
| Weight           | -53         |
| Age              | 14          |
| Infection        | 470         |

- CL (Weight), V (Weight) $\Delta$OFV $-97$ (Final)
- CL (Weight + Age), V (Weight) $\Delta$OFV $-141$
Population Model

Structural Model

Ka (/h) = 2.0 fixed

CL (L/h) = 0.0122 + 0.00328 \((Wt-3270)/1000\)

V (L) = 1.9 + 0.592 \((Wt-3270)/1000\)

F (%) = 0.61

Derived

t_{1/2} (h) = 108
Population Model

Variance Model

Interindividual variability (CV%)

- $CL = 38.0$
- $V = 33.9$
- $F = 33.6$

Residual variability (mg/L)

- $\sigma = 6.0$ (40%-20% at 15-30 mg/L)
Model Diagnostics

![Observed vs Predicted](image)

![Weighted Residuals vs Predicted](image)
Weight, Age and Clearance

\[ CL (L/h) = 0.0122 + 0.00328 \cdot \frac{(Wt - 3270)}{1000} \]
Weight, Age and Volume

\[ V (L) = 1.9 + 0.592 \cdot \frac{(Wt - 3270)}{1000} \]
Weight and Half Life

![Graph showing the relationship between weight (g) and half life (h).]
## Phenobarbitone PK – Infant vs Adult

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Infant*</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (mL/h/kg)</td>
<td>3.7</td>
<td>3.0 - 4.3</td>
</tr>
<tr>
<td>Volume (mL/kg)</td>
<td>581</td>
<td>540 - 700</td>
</tr>
<tr>
<td>Half life (h)</td>
<td>108</td>
<td>96 - 100</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>61</td>
<td>90 - 100</td>
</tr>
</tbody>
</table>

*At median wt (3270 g), this study
Summary and Conclusions

• CL, V of phenobarbitone increase linearly with weight from birth to 3.5 mo.
• CL per kg, V per kg is constant from birth to 3 mo; CL, V, $t_{1/2}$ similar to adults
• Current practice of LD and MD per kg is OK
• Oral bioavailability is 61%; Implications for switching i.v. $\leftarrow\rightarrow$ p.o.?
• Considerable interindividual variability in PK
• 20%-40% unexplained variability in TR
Some Significant Facts About Australia!

- World’s driest continent
- World’s shortest Prime Minister
- World’s most beautiful women (and men)
- World’s best weather, beaches, bla...bla...
  and
- The Australian Centre for Paediatric Pharmacokinetics (ACPP)
ACPP - Mater Children’s Hospital, Brisbane

Come down and see us sometime!!

8th World Congress on Clinical Pharmacology & Therapeutics, Brisbane, 1st - 6th August, 2004

7th PAGANZ-PAWS meeting, Brisbane, Feb., 2005