Population pharmacokinetics of Lamotrigine in epileptic patients with data from therapeutic drug monitoring

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**OBJECTIVE**

This study aims to develop a population pharmacokinetic (PK) model of lamotrigine (LTG) in epileptic patients, estimating the statistical distribution of compartmental model parameters and identifying covariates that could explain part of their variability. The implementation of population models in Bayesian algorithms, widely used in the Therapeutic Drug Monitoring (TDM) would facilitate the optimization of treatments with LTG.

**METHODS**

### Design and setting

155 sparse serum concentration data from TDM collected in 85 patients.

### Serum sampling and drug analysis

- At the end of interval and at the steady-state
- HPLC with UV detection
  - CV \(\text{interday} = 5.20\%\)
  - CV \(\text{intraday} = 8.40\%\)

**Pharmacokinetic analysis**

**PK model:** One-compartment (parameter estimated: Clearance)

**Covariates:** Age, gender, TBW, BSA, and concurrent valproic acid and/or inducers (Carbamazepine, phenobarbital or phenytoin) therapy.

**Preliminary analysis:** Graphical and GAM implemented in Xpose

**Software:** NONMEM program, version V; double precision, I, L1, (ADVAN2, TRANS2); FOCE

**Statistical model:** \(\hat{\gamma} = \beta \exp(\eta)\) and \(C_{ij} = C_{ij} \exp(\epsilon_i)\)

**Hypothesis testing:** LLD=3.8 (p<0.05); SE fixed parameters <30%; decrease of the interindividual and residual variabilities.

**RESULTS**

### Table 1: Demographic and clinical data of the patient population

<table>
<thead>
<tr>
<th>Gender</th>
<th>TBW (kg)</th>
<th>BSA (m²)</th>
<th>Concurrent Valproic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>28</td>
<td>1.8</td>
<td>Yes</td>
</tr>
<tr>
<td>Female</td>
<td>32</td>
<td>1.5</td>
<td>No</td>
</tr>
</tbody>
</table>

### Table 2: Population pharmacokinetic parameters of LTG estimated from the final model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/h)</td>
<td>0.022 ± 0.01</td>
</tr>
<tr>
<td>Vp (L)</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>F</td>
<td>0.8 ± 0.1</td>
</tr>
</tbody>
</table>

### Figure 1: Scatterplot from final and model:

- A) Observed serum LTG concentrations (OBS) vs. population predicted concentrations (PRED);
- B) CP vs. individual predicted concentrations (PRED); C) Weighted residuals (WRES) vs. CP.

### Figure 2: Prediction and residuals

- Final model vs. observed concentrations (RES vs. PRED).

### Figure 3: Pharmacokinetic parameters

- Parameters estimated from final model.

### Figure 4: Pharmacokinetic parameters

- Final model vs. observed concentrations.

**CONCLUSIONS**

1. TBW and AGE were the main physiological covariates that explain part of the interindividual variability of clearance in the model.
2. The association with VPA, a very well known enzyme inhibitor, produces a LTG delayed elimination and, only in adult population, IND have shown a significant influence, increasing the LTG clearance. This covariate was not well represented (2\% in children).
3. In the final model, the initial variability in CL was reduced by 39\% and 42\% for children and adults, respectively.
4. The PK population model proposed could be used to estimate LTG appropriate dosage guidelines. Moreover their simple structure will allow an easy implementation in clinical PK software and their application in dosage individualization by Bayesian approach.

**REFERENCES**


Francis S. The clinical pharmacokinetics of the new antiepileptic drugs. Epilepsia 1989; 40 Suppl. 2: 54.


