The Use of Indirect Response Model to Assess Interaction Between Drugs: acenocoumarol and amoxicillin + clavulanic acid

X Delavenne¹, T Basset ², P Girard ³, H Decousus ¹,4, P Mismetti ¹,4, S Laporte ¹

¹(1) Dept. of clinical pharmacology, EA3065; University Hospital of Saint-Etienne, France; (2) Lab. of pharmacology and toxicology, University Hospital of Saint-Etienne, France; (3) EA3738, Faculty of medicine Lyon sud, Oullins, France; (4) Dept of Internal medicine and therapeutics, EA3065, University Hospital of Saint-Etienne, France

Introduction

• Acenocoumarol is an oral anticoagulant frequently prescribed with antibiotic association amoxicillin plus clavulanic acid (AM+AC)
• Literature data: 7 cases reports and 1 case control trial reporting an increase in anticoagulation level
• Aim of this study: to investigate the influence of AM+AC on PK-PD of acenocoumarol

Methods

Design

• 8 healthy volunteers
• Single dose of 8 mg of acenocoumarol on day 1 and 8
• 1g of amoxicillin + 250 mg of clavulanic acid from day 3 to 9

Blood samples and dosage

• 11 blood samples at day 1 and at day 8.
• Acenocoumarol PK dosage: HPLC, Lichrosorb SRP 18 Chrompack
• Acenocoumarol PD marker: prothrombin time ratio (PTr), chronometric method, Diagnostica Stago

PK/PD analysis

• 1st step: structural identification of PK model by meta-analysis
• 2nd step: an indirect PK/PD model was build conditional on the individual bayesian PK parameters estimations

PK results

• 2 compartment model with first-order absorption and lag-time
• inter-individual variability on CL,V2,V3, Ka, Lag
• covariates: Weight on V2 and AM+AC on CL

PD results

• The final model included 4 parameters with 2 hyperbolic functions: SYNTH, C50, E₀, θₕ
• Hill coefficient over parameterized the model
• No covariate directly influenced PTr

PK and PD parameter estimates

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pop value</th>
<th>Inter-individual variability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/h)</td>
<td>4.68</td>
<td>9.09</td>
</tr>
<tr>
<td>TTT on CL</td>
<td>0.875</td>
<td>2.07</td>
</tr>
<tr>
<td>V2 (L)</td>
<td>24.5</td>
<td>1.8</td>
</tr>
<tr>
<td>WGT on V2</td>
<td>11.8</td>
<td>6.5</td>
</tr>
<tr>
<td>Ka (h⁻¹)</td>
<td>4.04</td>
<td>79</td>
</tr>
<tr>
<td>Alag (h)</td>
<td>0.404</td>
<td>14.5</td>
</tr>
<tr>
<td>Residual error on PK (%)</td>
<td>23.8</td>
<td></td>
</tr>
<tr>
<td>Residual error on PD (%)</td>
<td>27.8</td>
<td></td>
</tr>
</tbody>
</table>

References