BACKGROUND AND OBJECTIVES

Controlled-release (CR) formulation of carbamazepine (CBZ) tablets, in contrast to immediate-release (IR) form, show lower peak–trough fluctuation of CBZ concentration which leads to less adverse effects, and allow more convenient twice-daily dosing regimen. The aim of the study was to investigate relative bioavailability ($F_R$) of CR relative to IR CBZ tablets.

METODS

Study design

Retrospective routine TDM data from 2003-2005 period from the Unit for Antiepileptic Drugs at the Institute of Mental Health, Belgrade, Serbia. All patients ($n=379$) were diagnosed with epilepsy. Therapy: carbamazepin (CBZ), mono- or poly-therapy CBZ was administered 2–4 times per day in the form of 200mg IR tablets (Karbamazepin; Galenika, Belgrade, Serbia, or Karbatin; Hemofarm, Vrsac, Serbia) or 400mg CR tablets (Tegretol CR400; Novartis Pharma, Basel, Switzerland). 1–2 blood samples per patient were collected. Assay: EMIT®COBAS MIRA (Hoffmann la Roche LTD). Inter- and intra- CV <10%. Total CBZ concentrations were measured. Covariates available from patients’s chart whose effect was examined as weight, age, gender, smoking status, CBZ daily dose, co-therapy (phenobarbital, valproic acid, lamotrigine, benzodiazepines).

RESULTS

Model building

Table 2 – Population pharmacokinetic analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BASE MODEL</th>
<th>FINAL MODEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_a$ ($h^{-1}$)</td>
<td>-0.077</td>
<td>0.224</td>
</tr>
<tr>
<td>V/F</td>
<td>1.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

When final NONMEM run was repeated with altered $k_a$ fixed at three times lower and three times greater values for both, IR and CR formulation, parameter estimates changed by less than 7 % compared to the final run results. Similarly, with variation of V/F at lower and upper limit of its usual literature reported range (0.8 - 2 L/kg), no more than 6 % difference in estimated parameters was observed. Alteration of $k_a$ and V/F resulted in $\delta$OBJ in the range between -0.762 and +41.745.

Table 1 – Patients’ characteristics

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>LEARNING SET</th>
<th>VALIDATION SET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of SS samples</td>
<td>423</td>
<td>72</td>
</tr>
<tr>
<td>Number of patients</td>
<td>265</td>
<td>46</td>
</tr>
<tr>
<td>Number of patients taking CR CBZ tablets</td>
<td>124 (47 %)</td>
<td>25 (54 %)</td>
</tr>
</tbody>
</table>

Pharmacokinetic analysis

NONMEM (Ver.V,level 1.1,GlobalMax LLC,USA), Visual-MM (Ver.V, RDPP,France). One compartment model with first order absorption and elimination (ADVAN2 TRANS2 PREDPP subroutine), FOCE estimation

Relative clearance was estimated ($CL/F$)

Analysis was performed by forward inclusion of covariates into the base model. $\delta$OBJ>3.844 ($p<0.05$) and backward elimination from full model: $\delta$OBJ>6.63 ($p<0.01$).

CONCLUSIONS

In the present study, no difference in bioavailable fraction between CR and IR formulations was observed ($F_R = 1$). The results from the study with sparse data are in compliance with the results in a previously reported data-rich study with well-timed blood samples during the absorption phase.

References


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