ESTIMATION OF RELATIVE BIOAVAILABILITY OF CONTROLLED - RELEASE CARBAMAZEPINE TABLETS BASED ON ROUTINE TDM DATA

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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 Karbapin; 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 well: weight, age, gender, smoking status, *CBZ* daily dose, co-therapy (phenobarbitone, valproic acid, lamotrigine, benzodiazepines).

Table 1 – Patients' characteristics

CHARACTRISTICS	LEARNING SET	VALIDATION SET
Number of *SS* samples	423	72
Number of patients	265	46
Number of patients taking *CR CBZ* tablets	124 (47 %)	25 (54 %)

Pharmacokinetic analysis

***NONMEM* (Ver.V,level 1.1,GloboMax LLC,USA), *Visual-NM* (Ver.V,RDPP,France)**

One compartment model with first order absorption and elimination (*ADVAN2, TRANS2 PREDPP subroutine*), *FOCE* estimation

***ka* and *V/F* were fixed at the literature values: $kaCR=0.077h^{-1}$, $kaIR=0.224h^{-1}$, $V/F=1.4L/kg$**

Relative clearance was estimated (*CL/F*)

Analysis was performed by forward inclusion of covariates into the base model: $\Delta OBJ>3.84$ ($p<0.05$) and backward elimination from full model: $\Delta OBJ>6.63$ ($p<0.01$).

RESULTS

Model building

Table 2 – Population pharmacokinetic analysis

kaCR=0.077h^{-1}, *kaIR*=0.224h^{-1}, *V/F*=1.4 L/kg FIX	*OBJ*	*ΔOBJ*
BASE MODEL		
Interindividual variability: *CL/F=TVCL*EXP(ETA(1))* Residual variability: *Y=F+EPS(1)*	1229.248	
FORWARD INCLUSION – Influence of CBZ formulation on F_R *ka=kaCR*(1-CR)+kaIR*CR* S2=V/(THETA(5)*(1-CR)+CR), where CR=0 for CR formulation	1204.219	25.029
BACKWARD ELIMINATION – Influence of CBZ formulation on F_R	1080.721	2.171
FINAL MODEL PARAMETERS		

Parameter	mean value	95% *CI*
θ_{CL}	5.35	4.95 - 5.75
$\omega^2_{CL/F}$ *[CV%]*	36.5	31.6 - 40.7
σ^2 *[μg/mL]*	1.18	0.98 - 1.36

When final *NONMEM* run was repeated with altered *ka*, 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 *ka* and *V/F* resulted in *ΔOBJ* in the range between -0.762 and +41.745.

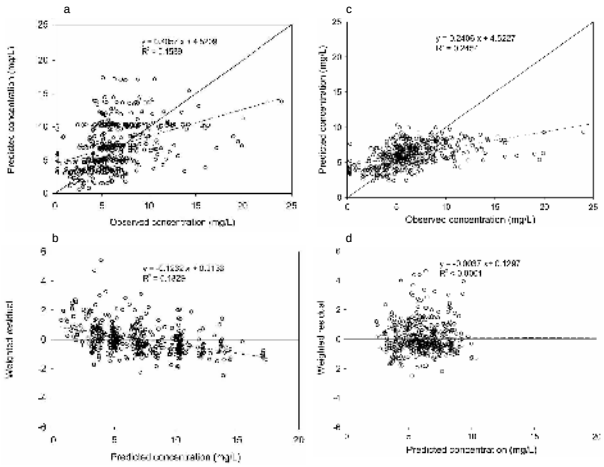

Figure 2 – Scatterplots for the base (a, b) and the final model (c, d)

Model validation

Table 3 – Validation of population model

VALIDATION PARAMETER	BASE MODEL	FINAL MODEL
mean prediction error	-0.12 (-0.88 – 0.63)	-0.17 (-0.86 - 0.53)
root mean squared prediction error	3.25 (2.14 - 4.08)	2.99 (1.71 - 3.86)

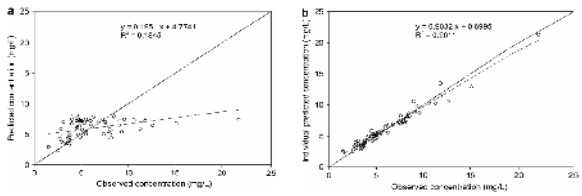

Figure 3 – Scatterplot for model validation

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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