

Effect of Carbamazepine Daily Dose on Topiramate Clearance – Population Modelling Approach



Marija Jovanović¹, Dragoslav Sokić², Iztok Grabnar³, Tomaž Vovk³, Milica Prostran⁴, Katarina Vučićević¹, Branislava Miljković¹

¹ Department of Pharmacokinetics and Clinical Pharmacy, Faculty of Pharmacy, University of Belgrade, Serbia

² Clinic of Neurology, Clinical Centre of Serbia, Belgrade

³ Department of Biopharmaceutics and Pharmacokinetics, Faculty of Pharmacy, University of Ljubljana, Slovenia

⁴ Department of Pharmacology, Clinical Pharmacology and Toxicology, School of Medicine, University of Belgrade, Serbia.



BACKGROUND AND OBJECTIVE

Topiramate (TPM) is a broad spectrum antiepileptic drug approved for treatment of children and adults as mono- or co-therapy. Many factors can influence variability in pharmacokinetics (PK) but also in therapeutic response.

The aim of the study was to investigate influence of carbamazepine (CBZ) daily dose on TPM oral clearance (CL/F) in adult patients with epilepsy.

METHODS

BIOANALYTICAL ASSAY

➤ High-performance liquid chromatography (HPLC) with fluorescent detection for determination of total TPM concentration

POPULATION PK ANALYSIS

➤ NONMEM[®] software (version 7.2), Perl speaks NONMEM[®] (version 3.5.3), Xpose[®], R[®], Pirana[®]

➤ A one-compartment model with first order absorption and elimination

➤ The first-order conditional estimation method with interaction (FOCEI) for estimation of CL/F and V/F; k_a was fixed at the value $2h^{-1}$

➤ Interindividual variability: $CL/F = TVCL * EXP(ETA(1))$

➤ Residual variability: $Y = F + EPS(1)$

PATIENTS

Table 1. Characteristics of patients

Characteristic	Number (%)	Mean ± Sd	Range
Gender	M	41 (52.56%)	
	F	37 (47.44%)	
Age (years)		37.62 ± 10.76	19 - 67
Weight, WT (kg)		75.19 ± 15.59	46 - 113
Height (cm)		172.45 ± 10.47	150 - 198
Tobacco smoking	18 (23.08%)		

Table 2. Characteristics of TPM therapy and CBZ co-therapy

Drug	Number	Mean ± Sd	Range
TPM (mg/day)		318.91 ± 175.08	50 - 1200
SS TPM conc. (mg/l)	Trough	70 (59.32%)	6.47 ± 4.04
	1 - 6h after dose	48 (40.68%)	9.43 ± 4.64
CBZ (mg/day)	20 (25.64%)	1000 ± 401.3	300 - 1600

RESULTS

MODEL BUILDING

Table 3. Inclusion of DCBZ (carbamazepine daily dose)

	OFV	ΔOFV
Base model	258.355	
$TVCL = \theta_{CL} * EXP(\theta_{CL_DCBZ} * (DCBZ/1000))$	207.175	51.180
$TVCL = \theta_{CL} * (1 + \theta_{CL_DCBZ} * (DCBZ/1000))$	205.782	52.573
$TVCL = \theta_{CL} * (1 + (DCBZ/1000) * \theta_{CL_DCBZ})$	218.121	40.234

Table 4. Final model parameters

Parameter	Mean value	95% CI
θ_{CL}	1.53	1.45 - 1.61
θ_{CL_DCBZ}	0.476	0.335 - 0.617
ω_{CL} [CV%]	16.5	11.8 - 20.2
θ_V	0.575	0.499 - 0.651
Wp	0.134	0.083 - 0.185

➤ Mean TPM CL/F during CBZ co-therapy was higher for 60.8% than in patients not co-treated with CBZ.

➤ The stability and good predictability of the model was confirmed by bootstrap resampling technique and adequate diagnostic plots.

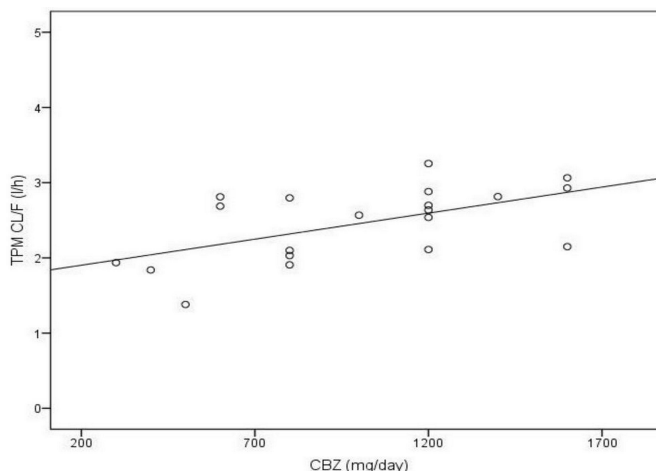


Figure 1. Topiramate (TPM) oral clearance (CL/F) vs. carbamazepine (CBZ) daily dose

CONCLUSION

Final population PK model quantifies influence of CBZ daily dose on TPM CL/F. The results from the study allow individualization of TPM dosing in routine patient care, especially useful for patients on different CBZ dosing regimens.

REFERENCES

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