

Effect of Valproic Acid Daily Dose on Phenobarbital Clearance - Nonlinear Mixed Effects Modelling Approach



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BACKGROUND AND OBJECTIVE

Phenobarbital (PB) is antiepileptic drug approved for partial and generalized seizures.

The aim of the study was to explore impact of valproic acid (VPA) daily dose on PB oral clearance (CL/F) in adult patients with epilepsy.

METHODS

- Data were collected from 136 epileptic patients during routine therapeutic drug monitoring (usually 1-2 samples per patient)
- 25% of patients were co-treated with VPA
- Nonlinear mixed effects modelling was performed for the pharmacokinetic analysis by NONMEM® software (version 7.2)
- Model building steps were managed using additionally PSN® (version 3.5.3), Xpose®, R®, Pirana®
- FOCEI was used for parameter estimation
- Structural model - ADVAN2 TRANS2
- Interindividual variability - exponential model
- Residual variability - proportional model
- Vd and ka were fixed at 0.6 l/kg and 3 h⁻¹ [1]
- Bootstrap resampling technique and adequate diagnostic plots was used for model evaluation

Characteristic of patients	Number Mean	Percentage Sd
Male	69	50.74%
Age (years)	42.04	13.00
Weight (kg)	73.04	14.20
Height (cm)	171.8	8.921
Serum creatinine (μmol/l)	83.24	16.43
AST (U/l)	27.15	13.31
ALT (U/l)	32.62	19.07

Characteristic of therapy	Mean ± Sd
PB (mg/day)	130.2 ± 58.37
Steady state PB concentrations (mg/l)	19.26 ± 9.003
VPA (mg/day)	1109 ± 433.9

RESULTS

Inclusion of DVPA (VPA daily dose) in the base model	ΔOFV
$TVCL = \theta_{CL} * EXP(\theta_{CL,DVPA} * DVPA/1000)$	15.114
$TVCL = \theta_{CL} * (1 + \theta_{CL,DVPA} * DVPA/1000)$	15.552
$TVCL = \theta_{CL} * (1 + DVPA/1000)^{\theta_{CL,DVPA}}$	14.190

Parameters of final model		Mean value	Standard error
θ_{CL} (l/h)	Typical value of PB CL/F	0.291	0.0152
$\theta_{CL,DVPA}$	Effect of VPA daily dose	-0.201	0.0495
$\omega_{CL,F}^2$	Variance for CL/F	0.172	0.0219
Wp	Proportional error	0.148	0.0178

- Concomitant treatment with usual VPA dose of 1000 mg/day resulted in PB CL/F average decrease of 20%.
- The stability and good predictability of the model was confirmed by bootstrap resampling technique and adequate diagnostic plots.

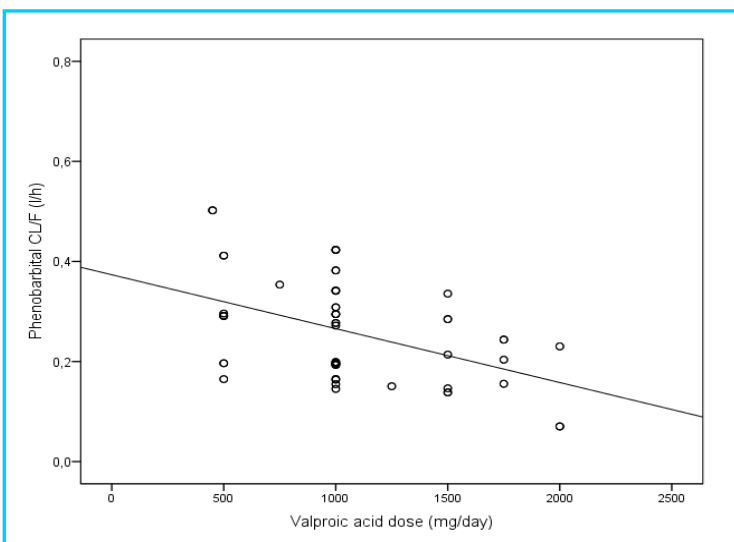


Figure 1. Phenobarbital (PB) oral clearance (CL/F) vs. valproic acid (VPA) daily dose

CONCLUSION

The final population PK model describes and quantifies influence of VPA daily dose on PB elimination. The results can be used for estimation of PB CL/F and individualization of PB dosing regimen, especially useful for patients co-treated with VPA.

References

[1] Johannessen Landmark C, Johannessen SI, Tomson T. Host factors affecting antiepileptic drug delivery-pharmacokinetic variability. *Adv Drug Deliv Rev.* 2012;64 (10):896-910.

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