Nonlinear mixed effects modelling approach in investigating amitriptyline pharmacokinetics

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OBJECTIVE

Amitriptyline (AMT) is a tricyclic agent, indicated for relief of the symptoms of depression. It can be expected influence of variability factors on pharmacokinetics of AMT, and consequently on blood level and effect. The aim of the study was to investigate pharmacokinetic characteristics of AMT and influence of different variability factors in patients with depression.

METHODS

Pharmacokinetic analysis was performed by nonlinear mixed effects modelling using *NONMEM*® software (version 7 level 2) and Perl speaks NONMEM® (version 3.5.3). Model building steps were managed using additionally *PSN*® (version 3.5.3), *Xpose*®, R®, *Pirana*®. Parameters estimation was performed by FOCE with interaction. Influence of AMT dose, demographic characteristic and co-therapy on AMT CL/F was investigated.

PATIENTS

Characteristics of patients	Mean ± Sd (%)
Male	28.6%
Age (years)	45.8 ± 8.75
Weight (kg)	69.9 ± 15.0
Characteristics of therapy	**Mean ± Sd (%)**
AMT dose (mg/day)	91.1 ± 31.3
Lithium	21.4%
Fluvoxamine	25.0%

RESULTS

Structural model was developed as a one-compartment model with first-order absorption and elimination implemented in ADVAN2/TRANS2 subroutine. The interindividual variability was evaluated by an exponential model while residual variability was best described by proportional model. Among tested covariates (gender, AMT dose and co-therapy with lithium and fluvoxamine), only influence of weight on CL/F was significant ($p<0.01$):

$$CL/F(l/h) = 70.4(l/h) \cdot \frac{WT(kg)^{0.355}}{70(kg)}$$

Inclusion of covariate into the base model decreased interindividual coefficient of variability for CL/F, and in the final model it was 8%. Acceptable model performances were confirmed by adequate diagnostic plots and internal validation.

Parameters for final model	Mean value	CI
Original data		
θ_{ka} (h^{-1})	0.633	0.497 - 0.769
θ_V (l)	1300	1216 - 1384
θ_{CL} (l/h)	70.4	66.4 - 74.4
$\theta_{CL,WT}$	0.355	0.184 - 0.526
Wp	0.290	0.266 - 0.315
Bootstrap replicates		
θ_{ka} (h^{-1})	0.647	0.488 - 0.778
θ_V (l)	1307	1214 - 1386
θ_{CL} (l/h)	70.5	66.3 - 74.5
$\theta_{CL,WT}$	0.353	0.164 - 0.546
Wp	0.289	0.267 - 0.313

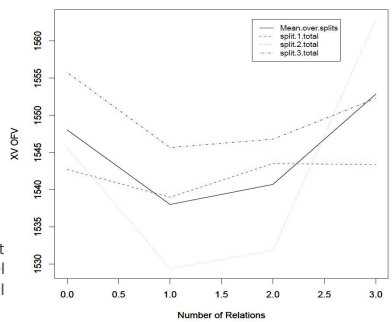

Figure 1. Linearized scm combined with cross-validation

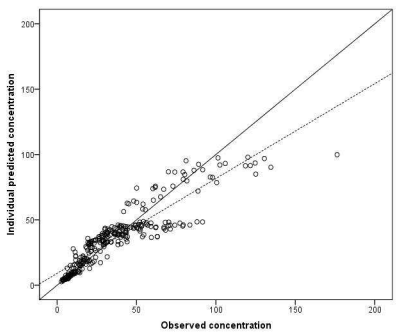

Figure 2. Individual predicted concentration of AMT (mg/l) vs. observed concentration (mg/l)

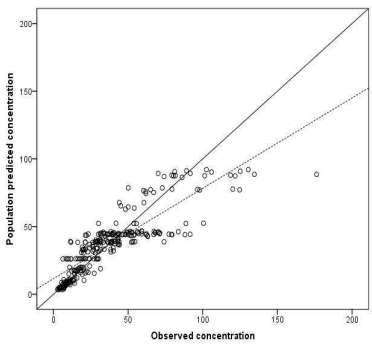

Figure 3. Population predicted concentration of AMT (mg/l) vs. observed concentration (mg/l)

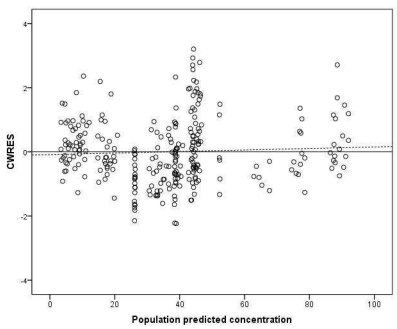

Figure 4. CWRES vs population predicted concentration (mg/l)

CONCLUSION

The final population AMT model describes and quantifies influence of weight on AMT elimination in patients with depression.
The results can be used for estimation of CL/F and individualization of dosing regimen.

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