Title: Time-to-seizure modeling of lacosamide used in monotherapy in patients with newly diagnosed epilepsy.
Journal: Clinical Pharmacokinetics
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Online resource 2

1. PK model for lacosamide

The population PK model for LCM has been previously developed using 4272 plasma concentration data from 906 patients with epilepsy from three Phase 3 trials (SP754, SP755 and EP0008; UCB data on file).

Briefly, a one compartment PK model with first order absorption and elimination was used as the structural model. A covariate search resulted in several significant parameter-covariate relationships as shown in the final model equations:

$$CL\ \left(\frac{L}{h}\right) = 1.92 \times \left(\frac{BW}{70}\right)^{0.75} \times 0.827^{RACEGRP} \times 1.34^{INDUC}$$

Where RACEGRP is 1 if Asian and 0 otherwise, INDUC is 1 if an enzyme inducing antiepileptic drug (AED) was co-administered or 0 otherwise (in the present analysis no AED was co-administered).

$$V\ (L) = 59.5 \times \left(\frac{BW}{70}\right)$$

$$F1 = \left(\frac{BW}{70}\right)^{0.375}$$

Originally, inter-individual variability was included on all three model parameters as an exponential relationship and was re-assessed with the new dataset.

The residual variability was described with as a combined (additive + proportional) error model.

The current dataset only supported the free estimation of one IIV component, the relative bioavailability F. IIV_CL and IIV_V were fixed to the estimates of the original model.

Goodness-of-fit plots and residual plots for the final population pharmacokinetic model of LCM are shown in Figure 1 and Figure 2, respectively. The model adequately described the data with no indication of bias or model misspecification. The distribution of conditional weighted residuals shown in Figure 3, is close to normality.

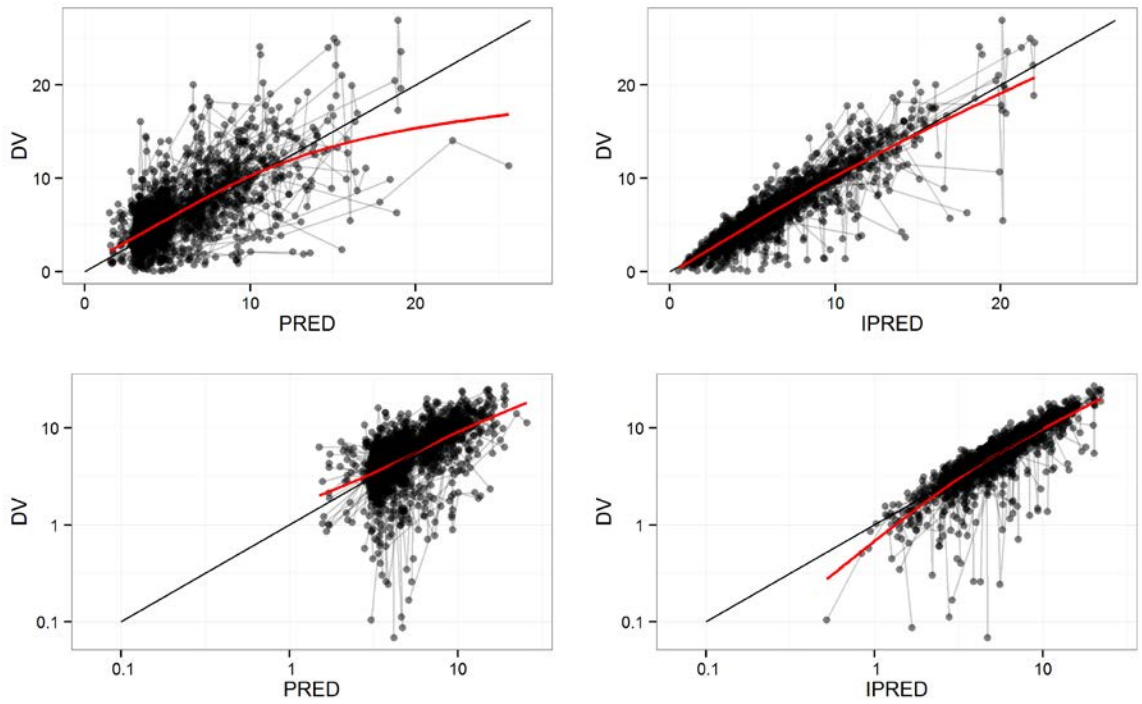


Figure 1: Goodness of fit plots for the LCM PK model. DV: dependent variable (LCM concentration in µg/mL), PRED: population predictions, IPRED: individual predictions; red line is a LOESS smoother. the black line is the line of unity; y-axis linear in top panels and logarithmic in bottom panels.

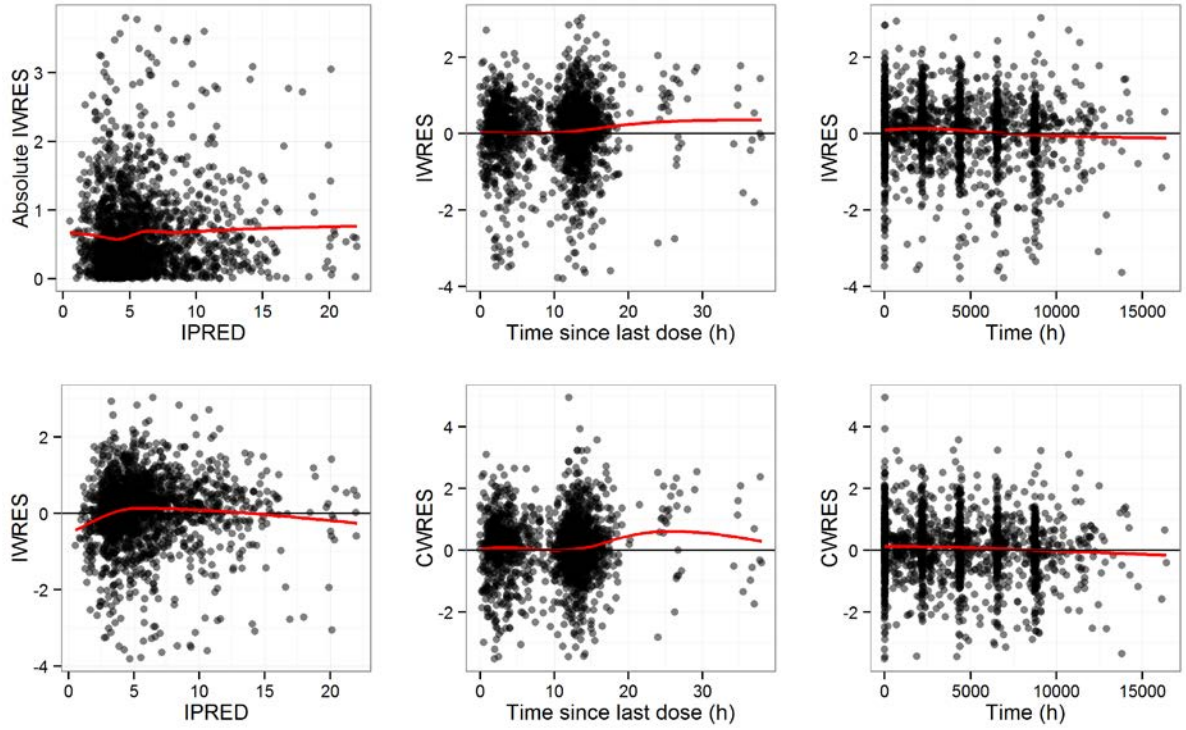


Figure 2: Residual plots for the LCM PK model. Time is relative to the first dosing event after the 3-week up-titration/stabilization period. IWRES: individual weighted residuals, CWRES: conditional weighted residuals, IPRED: individual predictions; red line is a LOESS smoother.

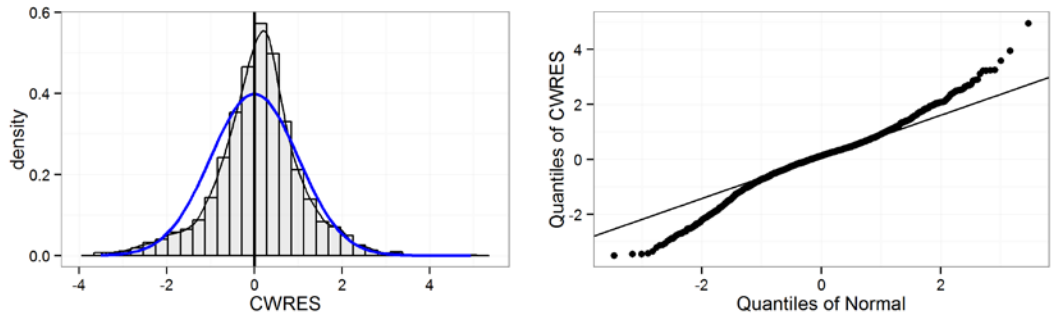


Figure 3: Distribution of conditional weighted residuals for LCM PK model. The blue curve shows the standard normal distribution for reference.

Table 1: Parameter estimates for the lacosamide PK model

Parameter	Description	Estimate	SE[a]	90% CI[b]	Shrinkage(%)[d]
Fixed effects parameters					
CL (L/h)	Clearance	1.92 (fixed)	-	-	-
V (L/h)	Volume of distribution	59.5 (fixed)	-	-	-
ka (1/h)	Absorption rate constant	1.74 (fixed)	-	-	-
RACE~CL	Race effect on clearance	0.827 (fixed)	-	-	-
BW~F	Exponent of weight~ F relationship	0.375 (fixed)	-	-	-
Random effects parameters					
IIV_CL	Inter-individual variability in CL	0.0353 (fixed)	-	-	48.4
IIV_V	Inter-individual variability in V	0.426 (fixed)	-	-	49.5
IIV_F1 (CV%)[c]	Inter-individual variability in F	28.8	0.0314	22.8 - 33.9	28.5
Residual variability					
propRUV (%)	Proportional residual error	23.8	-	21.4 - 26.2	11.2
addRUV	Additive residual error	0.482	0.105	0.309 - 0.655	-

CV: Coefficient of variation, SE: Standard error

[a] SE on SD scale for variability estimates

[b] Asymptotic confidence interval derived from NONMEM standard errors

[c] CV = 100*sqrt(exp(variance)-1)

[d] Epsilon-shrinkage is the overall shrinkage for related elements of the residual error

2. PK model for carbamazepine

The population PK model described by Vucicevic et al. (9) was used to describe CBZ concentrations in the present analysis and to obtain individual PK parameter estimates. The published model was based on concentration measurements of CBZ obtained from 265 patients for the purpose of therapeutic drug monitoring in routine clinical care. In this retrospective study, the majority of samples were taken at the end of the dosing interval (trough); therefore, the authors fixed unidentifiable parameters:

V/F was fixed at 1.4 L/kg and ka at 0.077 h^{-1} (CR formulation), respectively. Absorption rate constants were estimated using the following relationship: t_{max} = ln (ka/ke)/(ka – ke) based on a literature value of elimination half-life of 36 hours after a single dose corresponding to elimination rate constant (ke) of 0.0193 h^{-1}, and t_{max} of 24 hours.

Several covariates were identified as significant predictors of CBZ clearance: body weight (BW [kg]), daily dose of CBZ (DCBZ [mg/day/kg]), daily dose of phenobarbital (DPB [*mg/day/kg*]), valproic acid given yes/no (VPA: 1/0).

The equation of the final model is shown below:

$$\frac{CL}{F}\left(\frac{L}{h}\right) = 5.35 \times \left(\frac{BW}{70}\right)^{0.564} \times 1.18^{VPA} \times \left(\frac{DCBZ}{15}\right)^{0.591} \times \left(1 + 0.414 \times \frac{DPB}{2}\right)$$

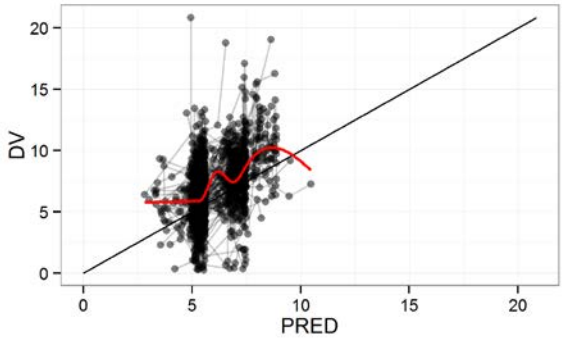
Note that for the present analysis, co-medication with AEDs was an exclusion criterion, hence covariates DPB and VPA were not of relevance.

While the structural form of the model was maintained, random effect parameters were re-evaluated on the N01061 dataset.

An exponential relationship was used for the inter-individual variability in CL and/or F.

For the residual unexplained variability an additive relationship was applied to log-transformed data.

Goodness-of-fit plots and residual plots for the final population pharmacokinetic model of CBZ are shown in Figure 4 and Figure 5. The model generally described the data well with no indication of bias or model misspecification. A few individual observations were not very well described by the model indicated by IWRES values >5. However, given that this affects only about 10 observations, it was judged that overall the model is nevertheless adequate. The distribution of conditional weighted residuals shown in Figure 6 is close to normality.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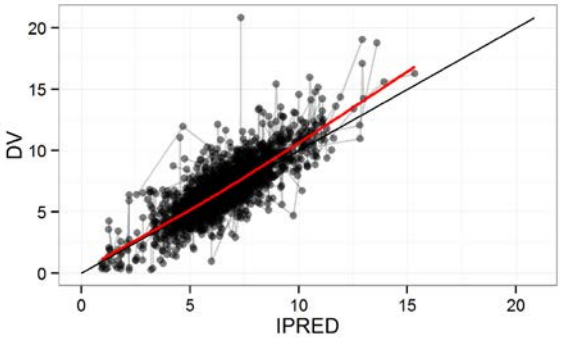
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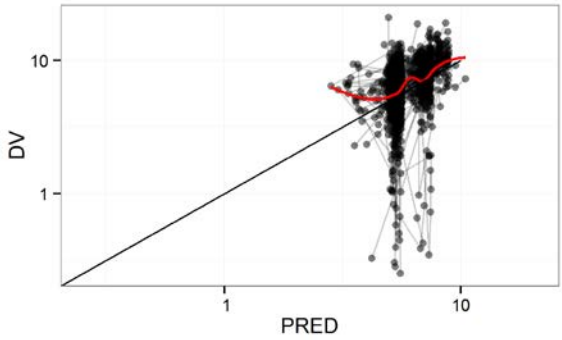
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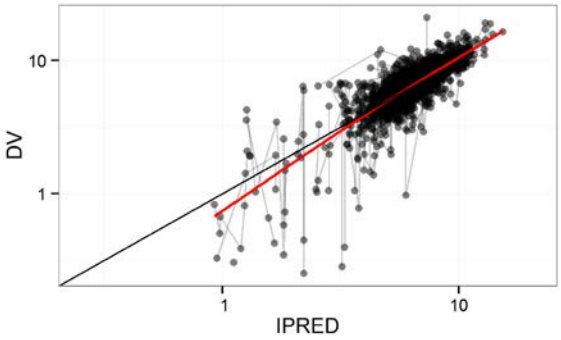
DV
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Figure 4: Goodness-of-fit plots for the CBZ PK model. DV: dependent variable (CBZ concentration in µg/mL), PRED: population predictions, IPRED: individual predictions; red line is a LOESS smoother; the black line is the line of unity; y-axis linear in top panels and logarithmic in bottom panels.

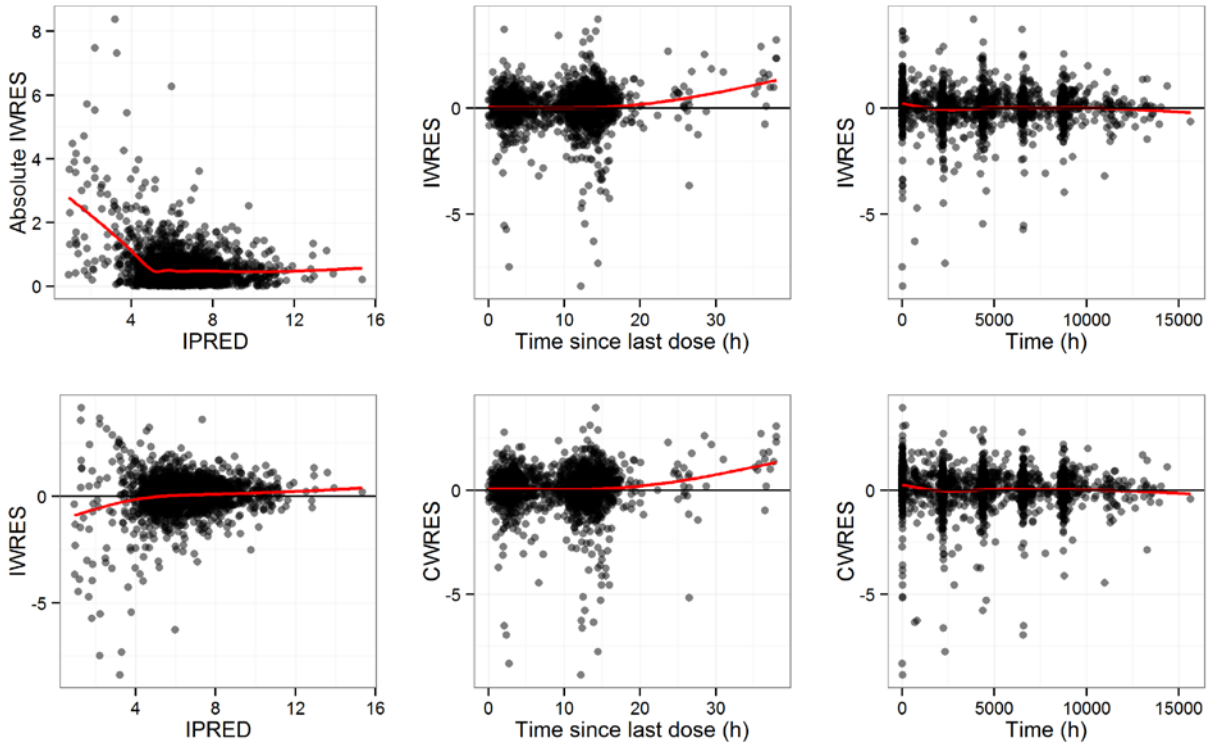

Figure 5: Residual plots for the CBZ PK model. Time is relative to the first dosing event after the 3-week up-titration/stabilization period.IWRES: individual weighted residuals, CWRES: conditional weighted residuals, IPRED: individual predictions; red line is a LOESS smoother.

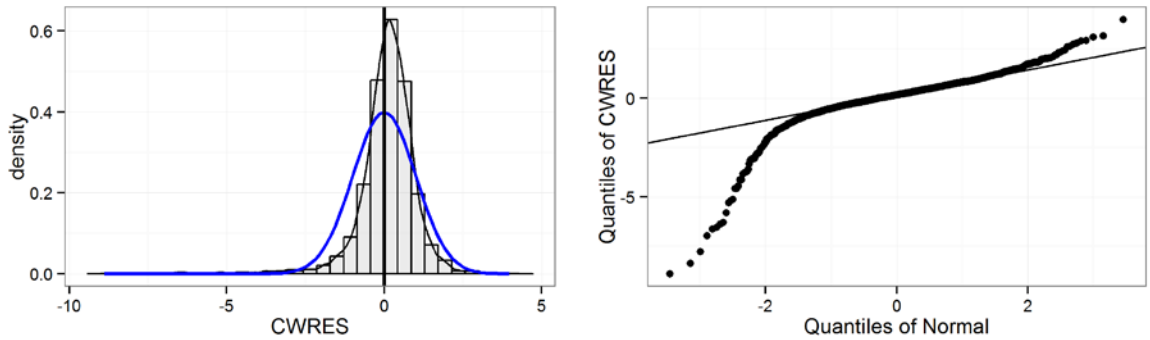

Figure 6: Distribution of conditional weighted residuals for the CBZ PK model. The blue curve shows the standard normal distribution for reference.

Table 2: Parameter estimates for the carbamazepine PK model

Parameter	Description	Estimate	SE[a]	90% CI[b]	Shrinkage(%)
Fixed effects parameters					
CL (L/h)	Clearance	5.35 (fixed)	-	-	-
V (L)	Volume of distribution	1.4 (fixed)	-	-	-
ka (1/h)	Absorption rate constant	0.077 (fixed)	-	-	-
DOSE~CL	Exponent of dose~CL relationship	0.591 (fixed)	-	-	-
BW~CL	Exponent of weight~CL relationship	0.564 (fixed)	-	-	-
Random effects parameters					
IIV_F (CV%)[c]	Inter-individual variability on F	32.4	0.0325	26.2 - 37.8	10.7
Residual variability					
expRUV (%)	Residual unexplained variability	28.9	-	25.9 - 32	9.34

CV: Coefficient of variation, SE: Standard error

[a] SE on SD scale for variability estimates

[b] Asymptotic confidence interval derived from NONMEM standard errors

[c] CV = 100*sqrt(exp(variance)-1)