

USEFULNESS OF WEIBULL-TYPE ABSORPTION MODEL FOR THE POPULATION PHARMACOKINETIC ANALYSIS OF PREGABALIN



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BACKGROUND & OBJECTIVE

➤ Pregabalin

Pregabalin is an anticonvulsant used for the treatment of neuropathic pain and partial seizure in adults.

➤ Objective

The aim of this study was to develop a population pharmacokinetic (PK) model to describe the absorption characteristics of pregabalin given fasting or after meals.

METHODS

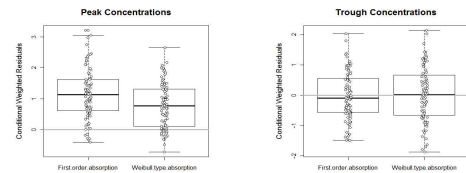
➤ Subjects and blood sampling

- Subjects : eighty-eight healthy male subjects from five phase I clinical trials with single or multiple oral dose of pregabalin.
- Dosage regimen : 150 mg pregabalin was administered twice daily, without meals or 30 min after meal (regular diet or high fat diet) in the morning and 30 min or 4 h after meal (regular diet) in the evening.
- Serial plasma samples were collected up to 24h after the last dose for PK analysis.
- Determination of plasma pregabalin concentrations : LC-MS-MS

➤ Population PK modeling

- To find the model that best describes the absorption process, first-order, transit compartment, and Weibull-type absorption models were compared using the non-linear mixed effect methods (NONMEM, ver. 7.2).
- The final model was evaluated by bootstrapping and visual predictive check (VPC).

Comparison of CWRES at Peak and Trough



FINAL PK PARAMETER ESTIMATES

Parameter	Estimate	% RSE	Bootstrap median (95% CI) [†]
Structural model			
$CL = \theta_{CL} * (CLCR/120)^{\theta_{CLCR}}$			
θ_{CL}	6.07 L/h	1.31	6.06 (5.90-6.22)
θ_{CLCR}	0.504	11.1	0.506 (0.403-0.608)
V2	12.7 L	4.91	12.3 (4.3-20.7)
Q	26.3 L/h	9.85	25.9 (20.6-30.2)
V3	30.2 L	2.82	30.4 (23.9-36.3)
$WB = CWB * (1 - \exp(-(K_{el}TAD)^{\theta_{WB}}))$			
$CWB = \theta_{CWFasting} * (1 - \theta_{CWFasting} * FED^{\dagger})$			
$\theta_{CWFasting}$	1.79	4.13	1.74 (1.13-3.69)
$\theta_{CWFasting}$	0.641	6.97	0.626 (0.503-0.815)
$Ka = \theta_{Kafasting} * (1 - \theta_{Kafasting} * FED^{\dagger})$			
$\theta_{Kafasting}$	1.96	8.42	1.95 (1.64-2.19)
$\theta_{Kafasting}$	0.638	9.76	0.643 (0.490-0.722)
$GA = \theta_{GAfast} * (1 - \theta_{GAfast} * FED^{\dagger})$			
θ_{GAfast}	4.69	5.01	4.66 (3.92-5.43)
θ_{GAfast}	0.457	9.06	0.452 (0.302-0.565)
Inter-individual variability			
ω_{CL}	10.7 %	21.5	10.4 (7.9-13.0)
ω_{V2}	25.0 %	75.8	24.0 (6.9-47.5)
ω_Q	Not estimated	-	-
ω_{V3}	Not estimated	-	-
ω_{CWB}	39.1 %	21.7	38.2 (28.3-47.6)
$\omega_{Kafasting}$	32.7 %	34.5	32.2 (20.0-44.1)
$\omega_{Kafasting}$	65.3 %	12.1	64.3 (51.8-74.4)
ω_{GAfast}	Not estimated	-	-
ω_{GAfast}	43.7 %	32.2	42.8 (25.3-58.2)
ρ_{CL-V2}	0.512	-	-
Residual error			
σ_{prop}	0.178	6.01	0.177 (0.156-0.199)

[†]FED is an indicator variable for fed (1) or overnight-fasted (0) status before dosing.

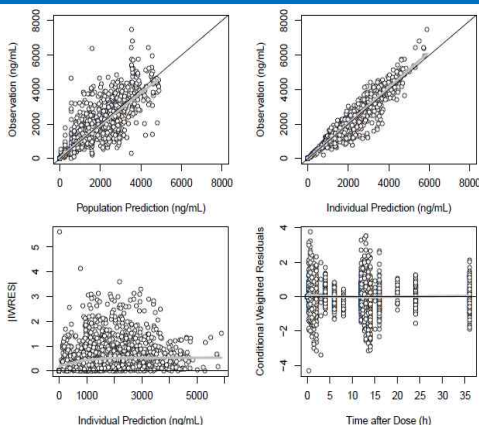
Subject Information

	number	Variable	Mean (range)
Total subjects	88		
study 1	7	Age (yrs)	48.1 (21~43)
study 2	16		
study 3	23	Weight (kg)	68.3 (53.4~88)
study 4	22		
study 5	20	Height (cm)	174.5 (162~186)

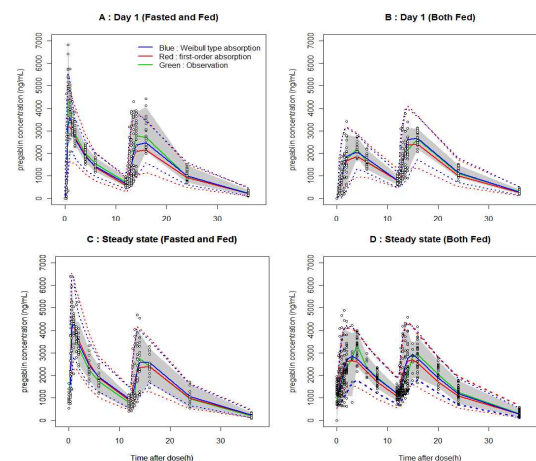
RESULTS

- A two-compartment linear PK model with Weibull-type absorption using its cumulative distribution function was better than the first-order absorption model with lag time.
- The conditional weighted residuals at T_{max} and visual predictive check plots obtained from the Weibull-type absorption model were less biased than those from the first-order absorption model.

Basic Goodness-of-Fit Plot



Visual Predictive Check



CONCLUSION

- We found that the Weibull-type absorption model best described the absorption characteristics of pregabalin regardless of meal status and the absorption model should be carefully chosen based upon the principle of model development and validation, not by following a conventional model for its popularity and simplicity, especially when the PK dataset includes densely sampled data.

REFERENCES

1. Bockbrader HN, Radulovic LL, Posvar EL, Strand JC, Alvey CW, Busch JA, Randinitis EJ, Corrigan BW, Haig GM, Boyd RA, Wesche DL. Clinical pharmacokinetics of pregabalin in healthy volunteers. J Clin Pharmacol. 2010 Aug;50(8):941-950