Model Simplification

KLAUS LINDAUER, THOMAS FRANK, HEINER SPETH
TMED PKDM Modelling & Simulation Frankfurt, Sanofi–Aventis Deutschland GmbH, Frankfurt a.Main

Background

The GLP-1 receptor agonist analog is being developed for glycemic control in type 2 diabetes with beneficial weight loss. Single dose and multiple repeated dosing regime studies have been conducted in healthy volunteers and patients diagnosed with type 2 diabetes (table 1). During these studies PK samples have been taken and measured at various times.
In the course of developing population pharmacokinetic and pharmacodynamic models, often multiple different structural models are able to describe and predict the experimental data nearly equally well. Often the obtained models can be distinguished only by their differences in the respective objective function value (OFV). Even though a more complex model might be favourable based on a lower objective function value compared to a structurally simpler model, the reproducibility of the complex model might be questionable.
Therefore we developed a fast and elegant method to evaluate the robustness of the obtained model in varying the initial parameter set. We applied our newly developed method to a one - and two-compartment population pharmacokinetic model of a Glp1 receptor agonist analog.

Objectives

- The primary objective was to develop a method for the evaluation of population PK models in respect to the robustness and reproducibility of model development.
- Secondly the method was applied to the population PK model of the GLP-1 receptor agonist analog that is being developed for glycemic control in type 2 diabetes with beneficial weight loss.

Study design, subjects and data

The data included in the present analysis originate from single-dose, multiple repeated dosing, randomized, placebo-controlled, studies in healthy subjects and patients diagnosed with type 2 diabetes (table 1). The characteristics of the participants are summarized in table 2.

Table 1 - Treatment conditions

Study	population	study type	dosing regime in [mg]	N treated (placebo)	N
A	healthy volunteer	single (s.c.)	0.01	3 (1)	32
			0.03	3 (1)	
			0.05	6 (2)	
			0.075	6 (2)	
			0.1	6 (2)	
B	healthy volunteer	multiple (s.c.)	0.025 - 0.05 - 0.075	6 (2)	40
		21	0.05 - 0.075 - 0.1	6 (2)	
		days	0.05 - 0.1 - 0.15	6 (2)	
			0.06 - 0.12 - 0.18	6 (2)	
			0.05 - 0.1 - 0.2	6 (2)	
C	DM type 2	multiple (s.c.)	0.03 - 0.06 - 0.09	9 (3)	36
	DM type 2	28 days	0.06 - 0.12 - 0.18	18 (6)	
D	healthy volunteer	single (s.c.)	0.05	8 (0)	17
	healthy volunteer	single (i.v.)	0.025	9 (0)	

s.c. .= subcoutaneous administration, i.v. .= intravenous administration.

Table 2 - Characteristics of the participants

study	N	mean ($\overline{x}$)	std (σ)	min	median	max
BMI [$\frac{kg}{m^2}$] at t_0						
A	32	26.90	1.51	24.90	26.44	29.78
B	40	24.84	2.23	20.24	24.57	29.70
C	36	32.53	3.23	28.22	31.89	37.88
D	17	26.18	2.54	21.31	26.47	29.51
body weight [kg] at t_0						
A	32	88.03	7.74	73.8	87.3	106.3
B	40	80.11	8.22	65.50	78.30	98.10
C	36	98.41	15.21	80.60	94.50	134.60
D	17	79.11	10.16	56.70	80.00	98.50
lean body weight [kg] (LBW) at t_0						
A	32	66.43	4.99	57.34	65.40	79.26
B	40	62.46	4.62	52.82	61.73	71.92
C	36	65.17	9.39	46.91	63.78	83.14
D	17	59.60	7.52	41.92	62.41	71.31
CREA [$\frac{umol}{l}$] at t_0						
A	32	74.03	8.38	56.80	74.80	91.30
B	40	77.24	9.94	58.30	74.90	99.40
C	36	75.11	13.41	53.90	70.80	101.50
D	17	81.59	14.20	54.81	84.86	104.30

Robustness Test Method

The results of the fitting procedure are often dependent on setting of initial values. Therefore the successful NONMEM (version 7.3) [1] run of the one- and two-compartment model was used as a reference of a successful path for the identification of the model parameter respectively. Along this path the model that resulted previously in an OFV with at least 10 points larger than the one of the successful fitting, is used as a starting model for re-fitting purposes. The identified parameter values were modified based on a multivariate normal distribution $\mathcal{N}(\theta, \sigma = 0.01)$ and used as an initial parameter set for the re-fitting approach. The procedure was repeated 25 times. Therefore we obtained 25 models (NONMEM runs) and respective parameter sets.

References

[1] Nonlinear mixed effects model program (NONMEM) version 7.3.0, originally developed by Stuart Beal, Lewis Sheiner and Alison Boeckmann, current developers are Robert Bauer, Icon Development Solutions, and Alison Boeckmann. Implementation, efficiency and Standardization performed by nous Infosystems.

Acknowledgements

We acknowledge the contribution of all Sanofi staff, in particular Diether Rüppel, Ashley Strougo, Willem De Winter, investigators, nursing staff, staff of the planning and execution of the trials used in this poster.

Population PK modeling methods

one compartment model

A one-compartment structural PK model with first-order absorption and elimination was constructed to describe the PK data.
An empirical differential equation was used to fit the observed concentration-time data to a one-compartment model with first-order absorption and elimination.

$$\begin{aligned}\frac{dA_1}{dt} &= -KA \times A_1 \times F_1 \\ \frac{dA_2}{dt} &= KA \times F_1 \times \frac{A_1}{V} - \frac{CL}{V} \times A_2\end{aligned} \tag{1}$$

Whereas KA is the absorption rate constant ($[\frac{1}{h}]$), CL is the clearance ($[\frac{l}{h}]$), V is the volume of distribution ($[l]$) and F_1 represents the absolute bioavailability.

$$\begin{aligned}PHI &= \ln \frac{\theta_{BIO}}{1.0 - \theta_{BIO}} \\ F_1 &= e^{\left(\frac{PHI + \eta_{BIO}}{1 + e^{PHI + \eta_{BIO}}}\right)}\end{aligned} \tag{2}$$

It is well known, that CL (clearance) and V (volume of distribution) are body weight dependent. Therefore the influence of body weight on CL and V are considered a priori.

$$\begin{aligned}CL &= \theta_{CL} \times e^{\eta_{CL}} \times \left(\frac{\text{body weight}}{75.0\ \text{kg}}\right)^{\gamma \times e^{\eta_\gamma}} \\ V &= \theta_V \times e^{\eta_V} \times \left(\frac{\text{body weight}}{75.0\ \text{kg}}\right)\end{aligned} \tag{3}$$

The comparison of the PK profile obtained for healthy volunteers and patients diagnosed with diabetes mellitus type 2 revealed that bioavailability in the patient population is about 20% lower compared to healthy volunteers. Therefore the bioavailability is considered as population dependent.

$$\begin{aligned}\theta_{BIO} &= \theta_{BIO}^{\text{healthy volunteers}} \times (1.0 - \theta_{BIO}^{\text{DM type 2}} \times population) \\ population &= \begin{cases} 0 & \text{for healthy volunteer} \\ 1 & \text{for DM type 2} \end{cases}\end{aligned} \tag{4}$$

two compartment model

A two-compartment structural PK model with first-order absorption, elimination and exchange to a depot compartment was constructed to describe the PK data.
An empirical differential equation was used to fit the observed concentration-time data to a two-compartment model with first-order absorption and elimination.

$$\begin{aligned}\frac{dA_1}{dt} &= -KA \times A_1 \times F_1 \\ \frac{dA_2}{dt} &= KA \times F_1 \times \frac{A_1}{V_{central}} - \frac{CL}{V_{central}} \times A_2 \\ &= -K2F \times V_{central} \times A_2 + K2R \times V_{depot} \times A_3 \\ \frac{dA_3}{dt} &= K2F \times V_{central} \times A_2 - K2R \times V_{depot} \times A_3\end{aligned} \tag{5}$$

Whereas KA is the absorption rate constant ($[\frac{1}{h}]$), CL is the clearance ($[\frac{l}{h}]$), $V_{central}$ is the volume of distribution ($[l]$), V_{depot} is the volume of the depot ($[l]$), F_1 represents the absolute bioavailability, $K2F$ is represents the rate constant from the central compartment to the third (depot) compartment and $K2R$ is considering the reverse reaction.
As for the one-compartment model the distinction between volunteers and patients diagnosed with diabetes mellitus type 2 is considered for estimating absolute bioavailability.

Final PK parameters

one– & two–compartment model
The different parameter sets (table 4 & 5) for the one– and two–compartment model were obtained in fitting the pooled dataset (table 1) to the respective model.

Table 4 - one–compartment model (fit 88723)

Parameter	Fixed effect[a] (RSE in %)[b]	95% CI	Interindividual variability ω^2 (RSE in %)[b]
CL (h^{-1})	0.395 (4.5)	0.36–0.43	0.061 (22.9)
V (l)	6.768 (4.4)	6.176–7.36	0.077 (17.8)
KA (h^{-1})	0.187 (6.3)	0.163–0.210	0.178 (17.9)
$\theta_{BIO}^{\text{healthy volunteers}}$ (%)	98.4 (3.1)	92.2–100	-
$\theta_{BIO}^{\text{DM type 2}}$ (%)	20.4 (16.9)	13.5–27.4	-
$\gamma^{\text{body weight}}$	1.226 (16.9)	0.82–1.631	1.02 (25.5)
Residual error:	σ^2 (RSE in %)[b]	95% CI	
Additive	0.035 (11)	0.027–0.043	
Proportional	0.013 (3.7)	0.012–0.014	

Table 5 - two–compartment model (fit 137601)

Parameter	Fixed effect[a] (RSE in %)[b]	95% CI	Interindividual variability ω^2 (RSE in %)[b]
CL (h^{-1})	0.398 (3.9)	0.37–0.43	0.052 (22.2)
V (l)	4.66 (5.5)	4.16–5.16	0.037 (26.7)
KA (h^{-1})	0.128 (6.8)	0.11–0.15	0.164 (17.5)
$V3$ (l)	1.84 (20.5)	1.18–2.5	0.66 (35.5)
$K2R$ (h^{-1})	0.046 (19.4)	0.028–0.064	-
$K2F$ (h^{-1})	0.006 (16.6)	0.004–0.008	-
$\theta_{BIO}^{\text{healthy volunteers}}$ (%)	99.3 (2.3)	94.8–100	-
$\theta_{BIO}^{\text{DM type 2}}$ (%)	21.0 (15.5)	14.5–27.5	-
$\gamma^{\text{body weight}}$	1.02 (20.9)	0.603–1.44	1.185 (27.4)
Residual error:	σ^2 (RSE in %)[b]	95% CI	
Additive	0.035 (12.8)	0.021–0.033	
Proportional	0.014 (3.5)	0.013–0.015	

[a] Population mean values. [b] Relative standard errors are calculated as 100 × (standard error/parameter estimate).

Visual Predictive Check

The results of the visual predictive check for the one– and two–compartment models are shown in figure 1 and 2 respectively. There are no differences between the results of the one– and two–compartment model.

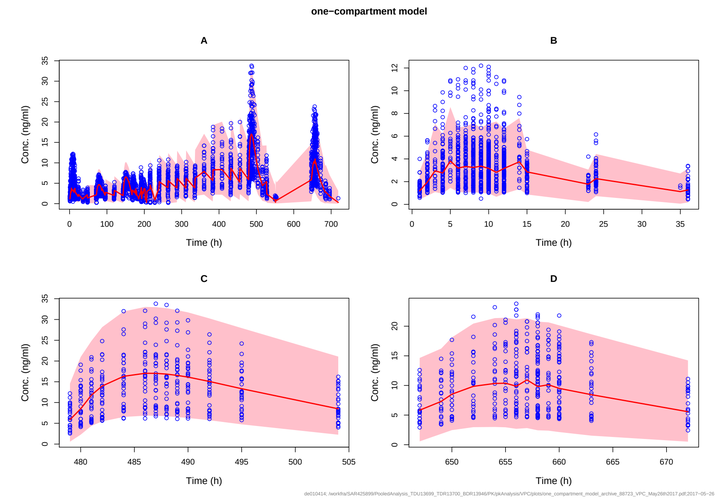

Figure 1: shows the visual predictive check of the one–compartment model. Part A covers the whole study period of 4 weeks, part B the first 36 h, part C day 21st and part D day 28th.

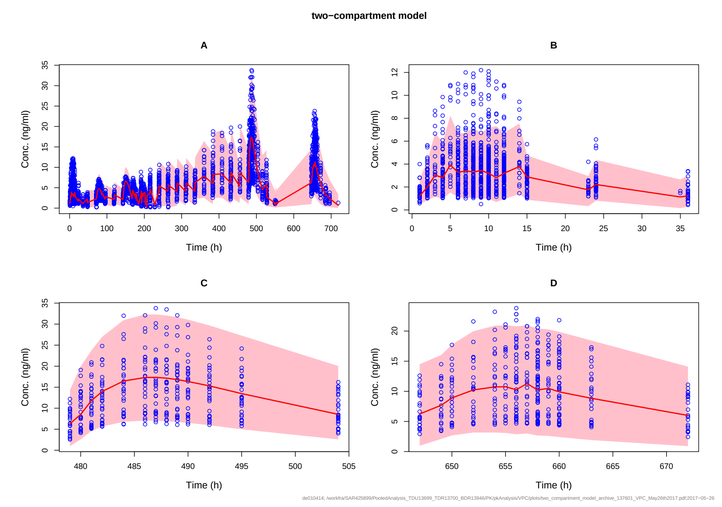

Figure 2: shows the visual predictive check of the two–compartment model. Part A covers the whole study period of 4 weeks, part B the first 36 h, part C day 21st and part D day 28th.

Results of robustness test

Our newly developed method for evaluating the robustness and validity of the model parameter obtained, was applied to a Glp1 receptor agonist analog. For the one-compartment model all 25 fitting attemps converged into the same parameter set (table 6), whereas less than 1/2 (12) of the 25 re-fitting runs converged in case of the two-compartment model (table 7). Although the OFV was significantly lower for the two-compartment model, due to the lower robustness of the model, the more simple PK model was selected for our further analysis.

Table 6 - robustness test of the one–compartment model

ARCHIVE NUMBER	n-PSE	EIGEN-RATIO	OBJ
136220	12	11.44	497.16
136221	12	13.19	497.16
136222	12	9.29	497.16
136223	12	11.42	497.16
136224	12	16.68	497.16
136225	12	15.83	497.16
136226	12	37.42	497.16
136227	12	14.40	497.16
136228	12	12.58	497.16
136229	12	21.98	497.16
136230	12	16.33	497.16
136231	12	16.80	497.16
136232	12	14.87	497.16
136233	12	14.91	497.16
136234	12	14.43	497.16
136235	12	13.98	497.16
136236	12	15.53	497.16
136237	12	12.42	497.16
136238	12	52.55	497.16
136239	12	15.54	497.16
136240	12	11.58	497.16
136241	12	13.71	497.16
136242	12	14.55	497.16
136243	12	14.04	497.16
136244	12	14.83	497.16
88723	12	16.81	497.16

Table 7 - robustness test of the two–compartment model

ARCHIVE NUMBER	n-PSE	EIGEN-RATIO	OBJ
137601	16	28.10	402.87
138798			402.87
138799			402.87
138800			402.87
138801			402.87
138802	16	226.76	402.87
138803	16	52.12	402.87
138804			402.87
138805	16	34.56	402.87
138806	16	58.97	402.87
138807	16	39.06	402.87
138808			402.87
138809	16	63.43	402.87
138810	16	135.14	402.87
138811	16	71.08	402.87
138812			402.87
138813			402.87
138814	16	117.82	402.87
138815			402.87
138816	16	115.41	402.87
138817	16	42.11	402.87
138818			402.87
138819			402.87
138820			402.87
138821			402.87
138822	16	135.11	402.87

Conclusions

According to the objective function value (OFV) the two–compartment model seems to be favourable, which is also supported by the visual predictive check plots. However the reproducibility of the final parameter set was poor. Therefore the simpler one–compartment model was chosen, because of the robustness of the resulting parameter set.