A Population PK/PD Model of Technosphere® Insulin Administered to Healthy Subjects

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Abstract

Population PK and PK/PD models were developed using data from an euglycemic glucose clamp study in 32 healthy volunteers (NCT01490762), receiving one dose of sc regular human insulin (15IU) and 4 doses of TI (10U, 30U, 60U, 80U) [2].

The population PK/PD model (PK-GIR model) was based on an E_{max} model to relate insulin concentrations from an effect compartment to the glucose infusion rate (GIR). To capture the full effect of TI, especially at higher TI doses, the PK-GIR model simulated GIR responses until 20h post-dose.

In a second step, population dose-response models were developed relating insulin doses of TI and RHI with the area under the curve (AUC) of GIR, also by an E_{max} model (dose-GIR_{AUC} model). The ED_{50} of TI was found to be 5.1 fold higher than for RHI, a ratio that can be used as conversion factor for equivalent doses of RHI and TI. For the therapeutically relevant dose range the dose-response for TI and RHI can be described by a linear relationship (RHI up to 30IU and TI up to 120U) when integrating GIR over 20h.

Finally, GIR time curves were simulated for equivalent doses, i.e. a RHI dose of 8IU and a TI dose of 40U. The steeper cumulative GIR_{AUC} time curves reflect a faster onset of action ($T_{10\%}$-$GIR_{AUC,0\text{-}20h}$) and a shorter duration of action ($T_{90\%}$-$GIR_{AUC,0\text{-}20h}$).

Background & Objective

Technosphere® insulin (TI), an inhaled insulin with a fast onset of action, provides a novel option for the control of prandial glucose [1]. As shown in Scheme 1 the aim of this analysis is to use a PK/PD model based on data from an euglycemic glucose clamp study in healthy volunteers to a) quantify the dose response relationship for TI in comparison to subcutaneously (sc) administered regular human insulin (RHI) and b) compare the onset and duration of action of TI and RHI.

Scheme 1

Clinical Study

In study NCT01490762 thirty-two healthy volunteers received single doses of 10U, 30U, 60U, 80U TI and 15IU RHI in a crossover design [2]. After each dose a hyper-insulinemic clamp experiment was performed. Glucose was maintained at a pre-specified level by infusing glucose intravenously. Glucose infusion rates (GIR) were recorded over 4h for TI and 10h for RHI.

Methods

PK Model

Insulin concentrations corrected by the C-peptide values were fitted by NONMEM in the FOCE approximation to a structural model published previously [3]. The model consists of a two compartment model for distribution with a first order elimination. Absorption of inhaled insulin was described by a first order process. Absorption of RHI is modelled with two successive compartments with first order absorption. Figure 1 illustrates the model. Bioavailability of inhaled insulin. F_{TI} is relative to subcutaneous application. The table below summarizes the parameters identified for the final model.

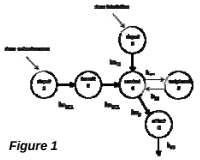

Figure 1

Parameter	Fixed effect mean (95% CI)	Random effect ω [%] (95% CI)
ka_{SC1} [1/h]	0.34 (0.22-0.47)	48 (34-59)
ka_{SC2} [1/h]	0.86 (0.55-1.17)	
ka_{TI} [1/h]	1.64 (1.49-1.78)	21 (15-25)
F_{TI}[1]	0.25 (0.21-0.28)	29 (16-38)*
V_4 [L]	4.5 (3.9-5.1)	22 (9-31)
V_5 [L]	56.4 (-)	102 (76-123)
Q [L/h]	29.6 (-)	
ke_0 [1/h]	8.55 (-)	
γ_{WT} [1]	-1.07 (-2.2- -1.3)	

ka_{SC1}, ka_{SC2} first order absorption rates RHI; ka_{TI} first order absorption rate of TI; F_{TI} bioavailability of TI relative to RHI; V_4, V_5 volume of central and peripheral compartment, Q inter compartment clearance; ke_0 elimination rate from central compartment, γ_{WT} power of covariate weight. on ka_{TI}. *IOV×30 (23-34)%

PK-GIR Model

Glucose infusion rates as a function of insulin concentrations were modelled as an E_{max} model published in [4].

$$GIR = GIR_0 + \frac{GIR_{max} * c^{\gamma}}{EC_{50}{}^{\gamma} + c^{\gamma}}$$

GIR glucose infusion rate; GIR_0 baseline; GIR_{max} maximum GIR; γ Hill coefficient; EC_{50} concentration of half max effect in effect compartment; K_{e0} elimination rate of effect compartment. *) IOV_{ED}= 61 (50-71) %

Parameter	Fixed effect mean (95% CI)	Random effect ω [%] (95% CI)
GIR_0 [mg/kg/min]	2.7 (2.2-3.1)	*
GIR_{max} [mg/kg/min]	11.9 (-)	31 (21-38)
EC_{50} [U/L]*	1.06 (0.90-1.19)	38 (23-49)
γ [1]	1.8 (1.5 – 2.1)	
K_{e0}[1/h]	1.24 (1.09-1.38)	

The model was developed in a two step procedure. Individual pharmacokinetic parameters (Bayesian estimates) were used to predict concentrations at all time points necessary for the integration of the PK-GIR model. An effect compartment was necessary to describe the delay between effect and insulin concentrations. As data were not baseline corrected, the baseline was part of the fit. The population GIR_{max} was calculated by profiling, starting with a literature value [4], individual GIR_{max} were fitted. Results are documented in the table above.

Simulations of GIR based on PK-GIR model

GIR responses were simulated out to 20h after dosing to capture the full effect of TI, especially higher doses. Figure 2 shows simulations of GIR in 15 subjects for a TI dose of 8IU. The figure reflects that after 4h GIR is not back to baseline, while GIR has declined to near-baseline after 20h.

Results

Dose response characterization

GIR-AUCs integrated over 20h were modelled as a function of dose

$$GIR_{AUC} = \frac{GIR_{AUC,max} * dose^{\gamma}}{ED_{50}{}^{\gamma} + dose^{\gamma}}$$

As the pharmacokinetics of TI and RHI differ, two separate models were developed. ED_{50} and E_{max} are not independent in E_{max} models. Fitting was significantly improved when maximum integrated GIR is used from the PK-GIR model to calculate $GIR_{AUC,max}$

$$GIR_{AUC,max,i} = GIR_{max,i} * 20h$$

Fits of the ED_{50}/ E_{max} model for TI and RHI are shown in Figure 3. The parameter values are given in the table below.

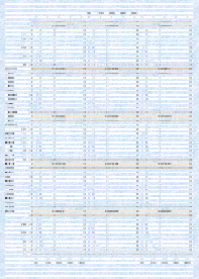

Figure 2 Simulations of GIR for dose of 80U TI based on PK-GIR model. GIR is simulated for up to 40h

	TI		RHI	
Parameter	Fixed effect Mean (95% CI)	Random effect ω [%] (95% CI)	Fixed effect Mean (95% CI)	Random effect ω [%] (95% CI)
ED_{50} [U]	249 (202-296)	40 (24-52)	43 (36-51)	49 (40-56)
γ [1]	1.07 (0.98-1.15)	17 (9-23)	1.15 (1.08-1.23)	17 (12-21)

Doses of TI and RHI producing the same total GIR_{AUC} are considered equivalent. Due to the fact that the Hill coefficients for the TI and RHI dose-response model are almost the same a simple conversion rule for equivalent TI and RHI doses can be derived:

$$dose_{TI} = {}^{ED_{50,TI}}/_{ED_{50,RHI}} * dose_{RHI}$$

Based on the ED_{50} values from the individual dose-response fits for TI and RHI the conversion factor is 5.8. Fitting the dose-response curves for TI and RHI together with a common Hill coefficient it becomes 5.1.

For the therapeutically relevant dose range a linear relationship has been used to fit the dose-response (RHI: 8, 30IU doses, TI: 10, 30, 120U doses)

$$GIR_{AUC} = dose * slope + intercept$$

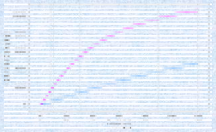

Figure 3 Dose-response for RHI (magenta) and TI (blue). GIR-AUC have been calculated from simulations for several doses.

	TI	RHI
slope [g/(kg*U)]	0.034 ±0.002	0.188 ± 0.008
intercept [g/kg]	0.36 ± 0.18	0.33 ± 0.30

Results

Onset of Action

In order to evaluate the onset and duration of action for an TI and an RHI dose that are equivalent in their PD effect as expressed by GIR-AUCs,GIR curves simulated for a 8IU RHI dose and 40U TI dose were used to calculate cumulative AUCs normalized to the maximum

$$GIR_{AUC,cum}(t) = \frac{\int_0^t GIR(t)dt}{\int_0^{20h} GIR(t)dt}$$

Figure 4 shows the time profiles for 15 patients. The steeper cumulative GIR_{AUC} time curves reflect a faster onset of action ($T_{10\%}$-$GIR_{AUC,0\text{-}20h}$ RHI, 122±23min, TI, 35±5min) and a shorter duration of action ($T_{90\%}$-$GIR_{AUC,0\text{-}20h}$ RHI, 621±152min; TI, 386±136min) for TI. Time to reach half of the overall effect was shorter for TI ($T_{50\%}$-$GIR_{AUC,0\text{-}20h}$ RHI, 296±64min; TI, 124±25min).

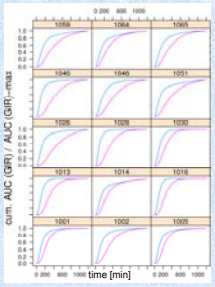

Figure 4 Cumulative GIR_{AUC} time profiles of PD matched doses of 40U TI (blue) and of 8IU RHI (magenta).

Conclusion

Dose–GIR_{AUC} models were successfully developed as mixed effect E_{max} models for inhaled and subcutaneous insulin. Developing a common dynamic PK-GIR model for both insulins was pre-requisite for extrapolations in time and dose to capture the full dose-response range without truncating parts of the PD effects. The resulting dose-response models are dependent on the applied integration time, especially the maximum value and the ED_{50}. Using an integration time of 20h the dose the GIR_{AUC} model suggests that TI doses equivalent to RHI doses can be calculated by multiplying the RHI dose by 5.1. The overall time profile of the pharmacodynamic effect is faster and shorter for TI when equivalent doses are compared. In the therapeutic dose range the dose–GIR_{AUC} model can be linearized.

References & Disclosures

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975-P/ 12-B Clinical Therapeutics/New Technology-Insulins / Robert Baughman / RBaughman@mannkindcorp.com