

PKPD modelling of drug induced inhibition of thyroxine production in rat

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Aim

To determine the *in vivo* potency of drug induced reduction in plasma thyroxine, T_4 , levels for three different drugs in rat and to explore how *in vivo* potency correlates with *in vitro* data.

Methods

A three day toxicological study with a one day washout period in rat was performed. Vehicle and three different compounds were tested at two or three dose levels. The study was designed to monitor the onset and extent of T_4 reduction, as well as the return of T_4 levels to baseline during washout. In all blood samples collected, the drug exposure and T_4 levels were measured. In addition to the three day toxicological study, available single dose data from dose range and screen studies was included to support the pharmacokinetic analysis. An overview of the pharmacokinetic and pharmacodynamic models used in the data analysis is shown in Figure 1. All PKPD analysis was performed using the NMLE module in Phoenix.

Pharmacokinetic models

The drug exposure was analyzed using either an one or two compartment model with different modifications of the absorption, Figure 1. A transit compartment model with saturable absorption, a linear absorption with a saturable first pass elimination and a combination of rapid saturable and delayed linear absorption was used for compound 1, 2 and 3, respectively. As exposure data following intravenous administration was not available for compound 1 and 3, bioavailability fixed to 1 was added to the models to allow inclusion of inter-occasion variability (IOV) and inter-individual variability (IIV) on the extent of absorption, respectively. In addition, IOV was added to the fraction absorbed, f_a , of compound 2.

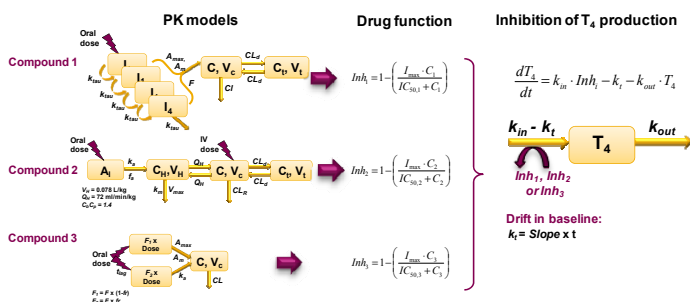


Figure 1. Schematic illustration of PK models, drug functions and turnover model of drug induced inhibition of T_4

Pharmacodynamic model

The T_4 levels in rat were modeled using a standard turnover model, Figure 1, where a correction for drift in the baseline levels was accounted for by adding the function, $k_i = \text{Slope} \times t$. The drug-induced changes in T_4 concentration of each compound was included by adding an inhibitory drug function (Inh_i) to k_{in} , Figure 1, where I_{max} and IC_{50} are the maximal drug induced inhibition of k_{in} and the *in vivo* potency, respectively. The I_{max} was set to 1 for all compounds, but a unique IC_{50} were estimated for each compound. The inhibitory drug function was driven by the individual predicted drug concentrations profiles for the corresponding compound.

Results

Pharmacokinetics

Pharmacokinetic parameters were derived by simultaneously fitting the different PK models to all dose levels and routes of administrations available for respective compound. Visual predictive checks (VPC) with the 95% prediction interval of the model are shown in Figure 2 for one dose of each compound.

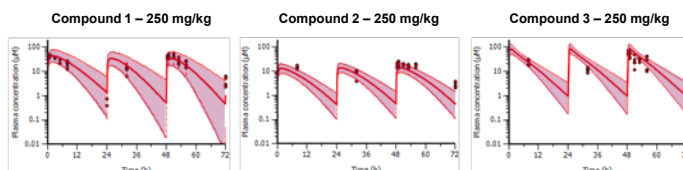


Figure 2. VPC of drug exposure ($n=1000$). Observed data is depicted in circles. The bold solid line is the model predicted median concentration and the shaded area the 95% confidence interval for the prediction

Pharmacodynamics

The T_4 levels of all individuals, dose levels and compounds were simultaneously fitted to determine the potency of the corresponding compound. VPC's of the drug induced change in T_4 concentration is shown in Figure 3.

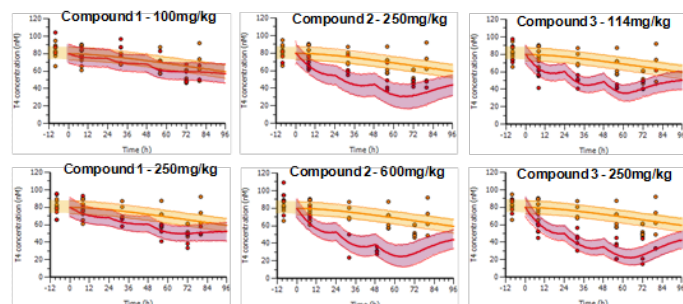


Figure 3. VPC of drug induced change in T_4 levels ($n=1000$). The bold solid line is the model predicted median concentration and the shaded area is the 95% confidence interval for the prediction. The vehicle treated animals (yellow) is included in all plots to visualize the drug treatment effect (red).

The obtained parameter estimates and variability of T_4 turnover and the unbound drug potency is shown in Table 1.

Table 1. Population estimates and variability of pharmacodynamic parameters

Parameter	Unit	Estimate	RSE (%)	Ω	RSE (%)	Shrinkage	<i>In vitro</i> IC_{50}
tvk_{out}	h^{-1}	0.043	12	-	-	-	-
tvT_0	nM	80	2	0.006	46	0.30	-
$tvSlope$	nM h^{-1}	0.0114	22	0.144	73	0.38	-
$tvIC_{50,1, unbound}$	μM	17.3	37	-	-	-	43
$tvIC_{50,2, unbound}$	μM	5.2	30	0.749	88	0.60	26
$tvIC_{50,3, unbound}$	μM	3.5	27	0.272	68	0.62	8.5
$stdevT_4, proportional$	-	0.13	7	-	-	-	-

The determined unbound *in vivo* potency of T_4 inhibition successfully generated the same ranking of as determined *in vitro* in buffer, Table 1.

Conclusions

- By using a population based approach we estimated *in vivo* potency with adequate precision to allow ranking of drugs, despite sparse PD data
- Ranking of potency were the same *in vivo* as *in vitro*, which gave confidence in subsequent compound ranking using *in vitro* data alone