Mechanism-based Pharmacokinetic-Pharmacodynamic Feedback Model of Thyroid Hormones after Inhibition of Thyroperoxidase in the Dog: Cross-species Prediction of Thyroid Hormone Profiles in Rats and Humans.

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Background

Circulating levels of thyroxine (T_4) and triiodothyronine (T_3) are regulated by homeostatic control mechanisms (Figure 1). TPO (thyroperoxidase) is a key enzyme involved in the synthesis of T_4 and T_3 in the follicular cells of the thyroid gland. Inhibition of TPO enzyme decreases plasma T_4 and T_3 levels which results in an associated elevation of TSH levels.

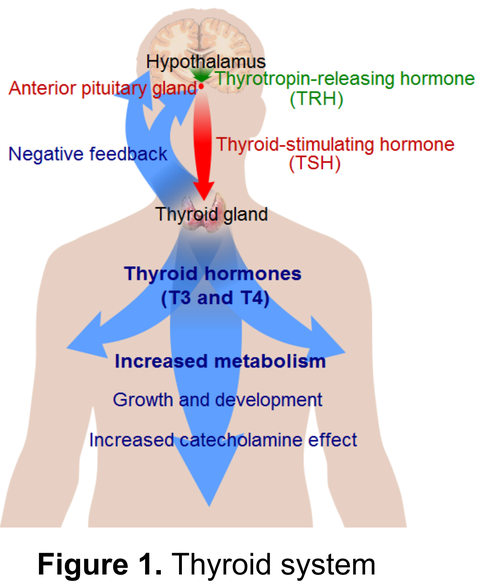

Figure 1. Thyroid system

Aim

To develop a mechanism-based pharmacokinetic-pharmacodynamic feedback model to describe the impact of TPO inhibition on thyroid hormone homeostasis in the dog and to predict thyroid hormone profiles in rats and humans based upon inter-species differences in hormone degradation rates and *in vitro* IC_{50} values for TPO inhibition.

Methods

The PKPD model was developed based on simultaneous analysis of concentration-time data of T_4, T_3 & TSH at multiple dose levels in dogs following once daily oral dosing of a TPO inhibitor (Cmpd I) for up to 6 months (Figure 2). First-order degradation rate constants for T_4 & T_3 were fixed at known physiological values (Table 1). C_{ss} of TPO inhibitor was used in the modeling. Model development was performed using NONMEM.

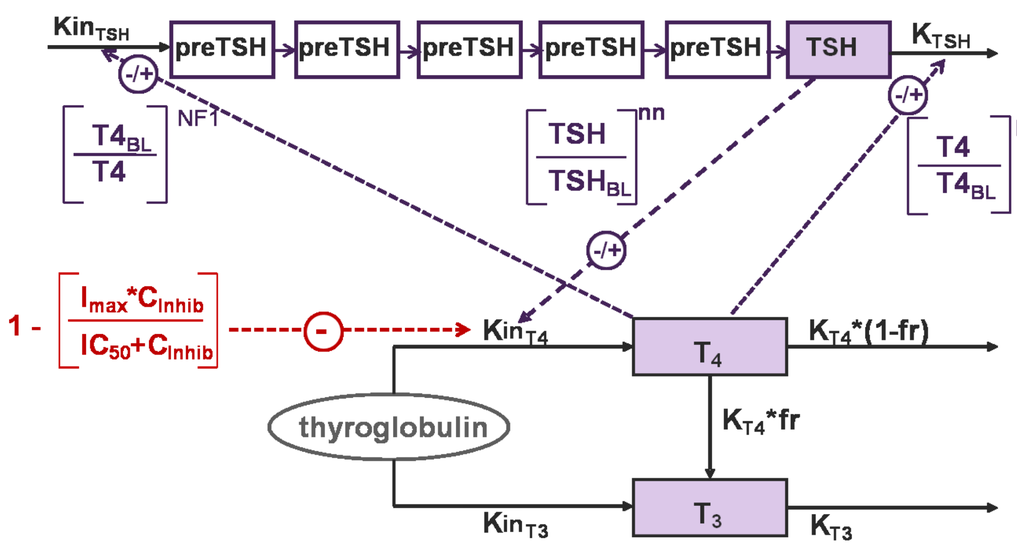

Figure 2. Mechanism-based PKPD feedback model of thyroid hormone homeostasis. Interactions are shown with dashed lines, where +/- indicate a positive or negative interaction. Purple compartments are those where thyroid hormone data is available. BL is baseline of the thyroid hormone.

Results: Model Development

The PKPD model could well describe the concentration-time profiles of T_4, T_3 and TSH in the dog after repeated administration of Cmpd I (Figure 3). The validity of the model was confirmed by successfully predicting T_4, T_3 & TSH levels for Cmpd II in the dog on basis of *in vitro* IC_{50} for TPO inhibition.

The estimated half-life of TSH was longer than expected (approx 55 min in human [1]). One explanation for the discrepancies might be that circadian changes in hormones levels were not modelled, since only data from morning measurements were used. In the 6-month dog study the levels of T_4 seemed to decline over time in control animals, which will be considered in further model development.

Parameter estimates and hormone $t_{½}$ for rat, dog, human

Table 1. Population PKPD parameters. Proportional residual error models were used.

Parameter	Unit	Estimate	CV (%)	IIV (%)
TSH_{BL}	ng/mL	0.16 Fix		48
K_{TSH}	1/Days	0.35	6.8	
$T_{4,\ BL}$	nmol/L	16.7	5.2	27
$T_{3,\ BL}$	nmol/L	1.13 Fix		23
Fraction[a]	%	32	27	
I_{max}		0.74	4.0	
NF1		2.5	7.6	
NF2		1.9	18	
nn		0.11	25	

[a]Fraction of T_4 peripherally converted to T_3

Table 2. Cross species comparison of thyroid hormone half-lives & %T_3 derived from peripheral converison of T_4

Species	T_4, half-life	T_3, half-life	% T_3 derived from peripheral conversion of T_4
Man	7 days [2]	1 day [2]	72 [3]
Rat	21 hrs [4]	6 hrs [4]	65 [5]
Dog	14-16 hrs [6]	5-6 hrs [6]	37 [7]

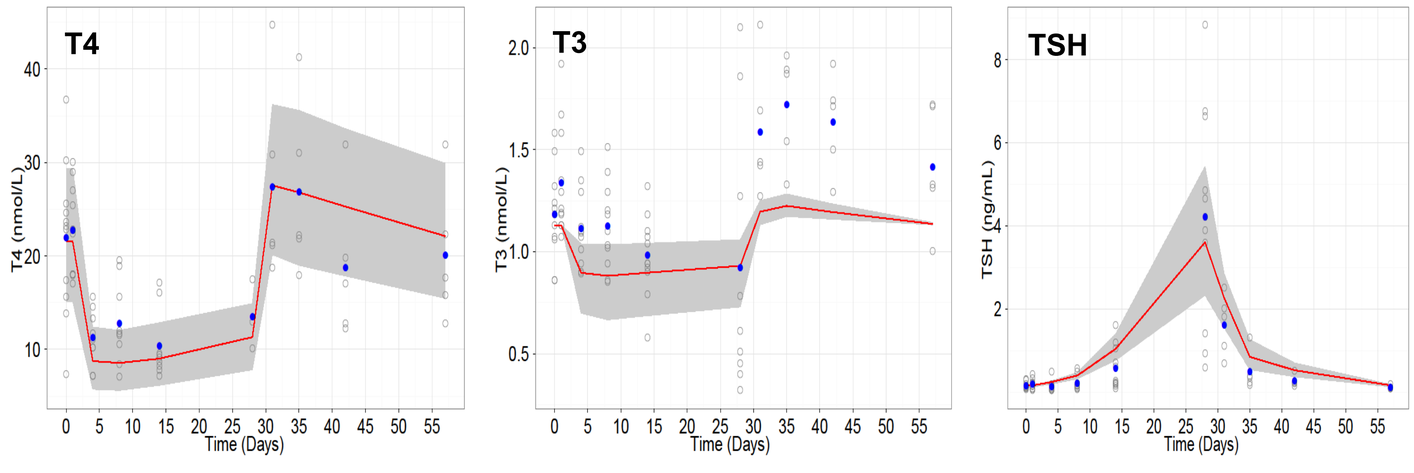

Figure 3. VPC plots (for T_4, T_3 and TSH) based on uncertainties in population parameter estimates following oral dosing of a high dose of Cmpd I to dogs. Solid line (red)=mean of predictions, closed symbols (blue)=mean of observations, open symbols (grey)=individual observations, Shaded area=95% prediction interval.

Results: Interspecies extrapolation to rat and human

By scaling K_{T4} and K_{T3} to reflect interspecies differences in hormone turnover $t_{1/2}$, adjusting *in vivo* IC_{50} (to maintain a constant *in vitro* IC_{50}/*in vivo* IC_{50} ratio cross-species) and adjusting fraction of T_3 converted from T_4 , the model successfully predicted the observed T_4 profiles in the rat for Cmpd I (Figure 4, table 2). In addition, the model could successfully predict the small (non-significant) effects on T_4 and TSH observed in human (Figure 4).

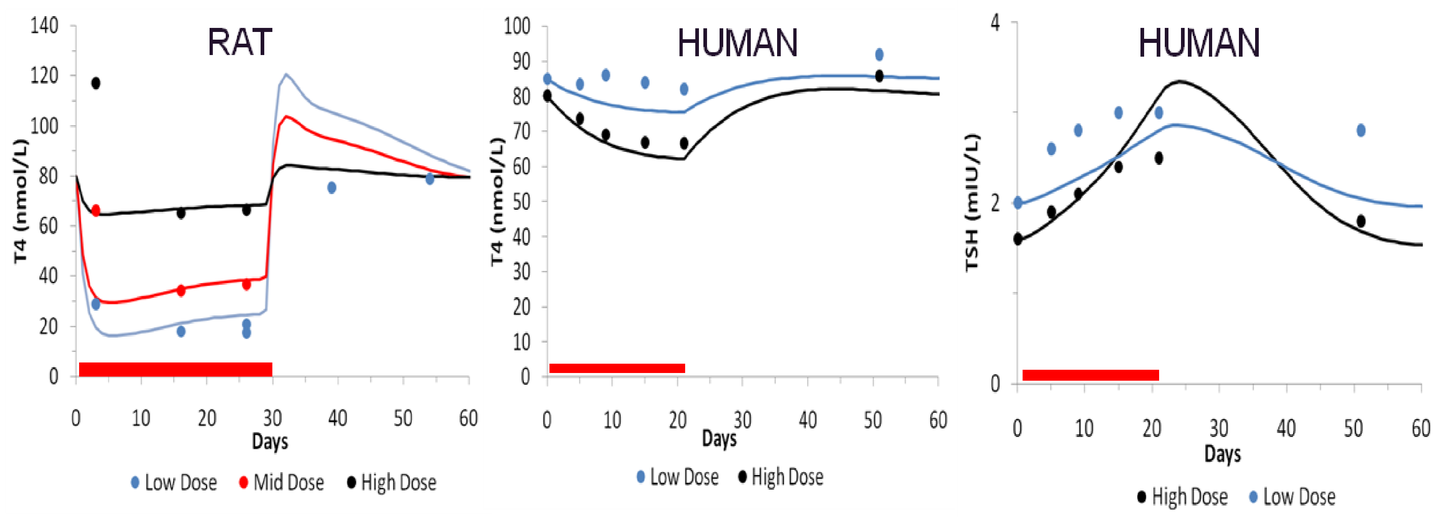

Figure 4. Mean measured (closed circles) and model predicted levels of TSH and/or T_4 in rats and humans following oral dosing of Cmpd I. The horizonal square (red) indicate the treatment duration.

Conclusions

The proposed mechanism-based PKPD feedback model provides a scientific basis for the prediction of TPO inhibition mediated effects on plasma thyroid hormones levels in humans based on results obtained in animals studies.

References

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