Mathematical Model of Homeostasis of Endogenous Hormones Following Hormone Replacement Therapy

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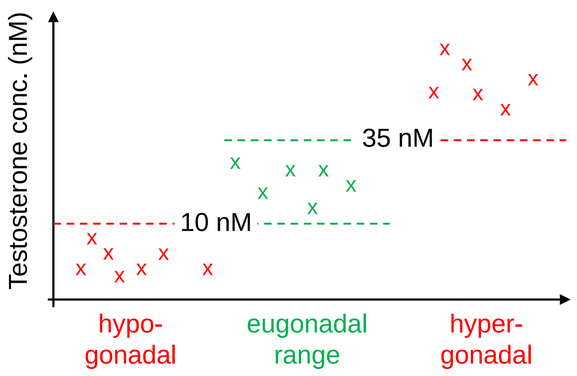
Background

Hormone replacement therapy (HRT) is widely used to compensate for low levels of endogenous hormones as e.g. in menopause and hypogonadism. In the determination of the pharmacokinetics and bioequivalence of exogenously administered hormones, the level of endogenous hormones has to be taken into account. Current bioequivalence guidelines [1] recommend the analysis of time matched differences between observations under placebo and active treatment in cross-over studies. However, the exogenous introduction of hormones may lead to down-regulation of the endogenous hormone production that may result in declining endogenous hormone concentrations under active treatment over time. Not taking into account the dynamics of this hormonal interplay and feedback mechanism thus may lead to a bias in AUC and volume of distribution of exogenously administered hormones. Consequently, bioequivalence may falsely be concluded which may increase patient risk.

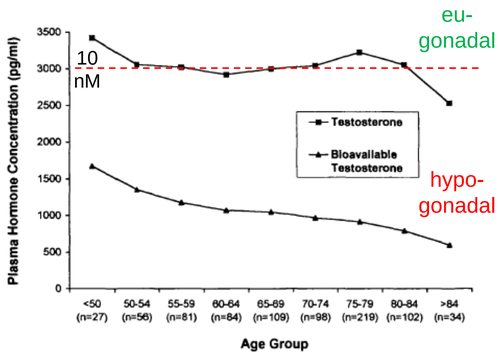
Exemplified for Testosterone, we propose a mathematical model to describe the down-regulation of endogenous hormone production under HRT as well as recovery of homeostasis after treatment stop.

Testosterone Replacement Therapy

Figure1. Testosterone concentration ranges in the hypogonadal, normal and hypergonadal state



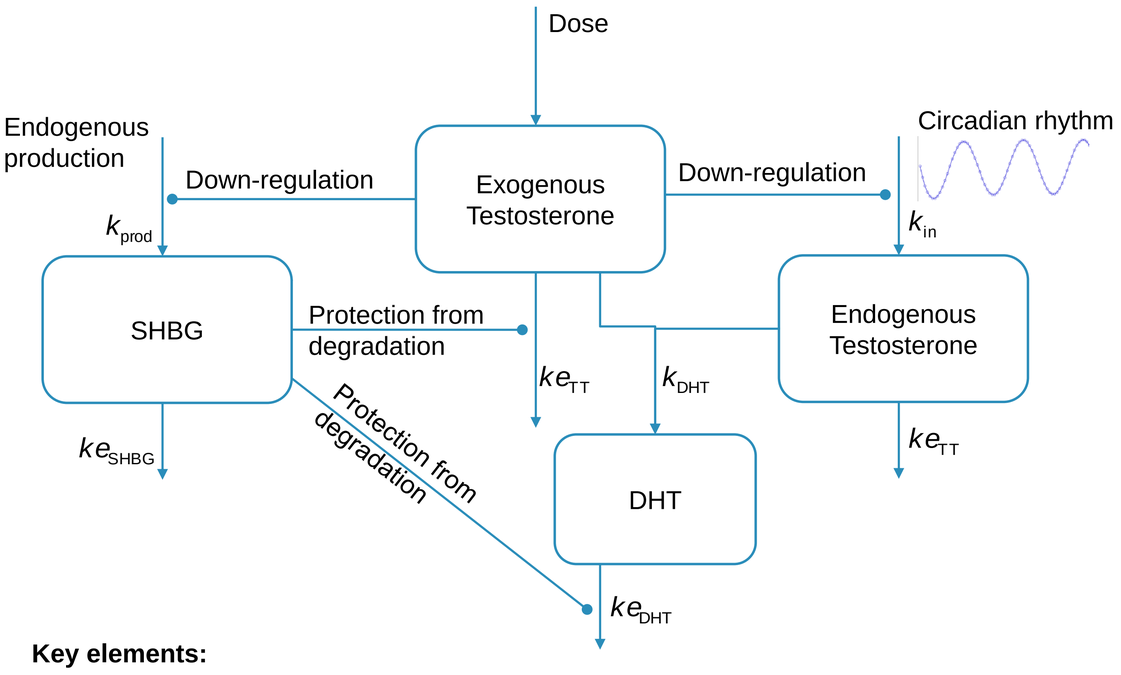
Need for HRT in elderly men:
Testosterone concentration decreases with age. Figure taken from [2].



Aim of HRT:
Restore eugonadal Testosterone concentration without entering hypergonadal range.

Semi-Physiological Model

Figure 2. Schematic representation of the pharmacokinetic model



Key elements:

- Distinction between endogenous and exogenous species
- Inclusion of the primary active metabolite 5α-Dihydrotestosterone (DHT)
- Negative feedback of exogenous Testosterone on endogenous production
- Binding to sex hormone binding globulin (SHBG) & protection of SHBG-bound Testosterone and DHT
- Feedback of Testosterone on SHBG levels
- Circadian rhythm for endogenous Testosterone production

Mathematical representation:

$$\frac{d}{dt}A_{TTex} = v_{dosing} - k_{DHT}A_{TTex} - ke_{TT}A_{TTex}$$

$$\frac{d}{dt}A_{TTen} = k_{in}\cdot\underbrace{\left(1+\alpha\cdot\cos\left(\left(t-t_{lag}\right)\frac{2\pi}{24}\right)\right)}_{\text{Circadian rythm}}\cdot\underbrace{\left(\frac{A_{TTen}+A_{TTex}}{A_{base}}\right)^{\gamma}}_{\text{Down-regulation}}A_{TTen} - k_{DHT}A_{TTen} - ke_{TT}A_{TTen}$$

$$\frac{d}{dt}A_{DHT} = k_{DHT}\left(A_{TTex}+A_{TTen}\right) - ke_{DHT}A_{DHT}$$

$$\frac{d}{dt}A_{SHBG} = k_{prod}\underbrace{\left(1-\frac{A_{TTex}}{IC_{50}+A_{TTex}}\right)}_{\text{Down-regulation}} - ke_{SHBG}A_{SHBG}$$

ke_{TT}, ke_{DHT} dependent on SHBG conc.

Data and Methods

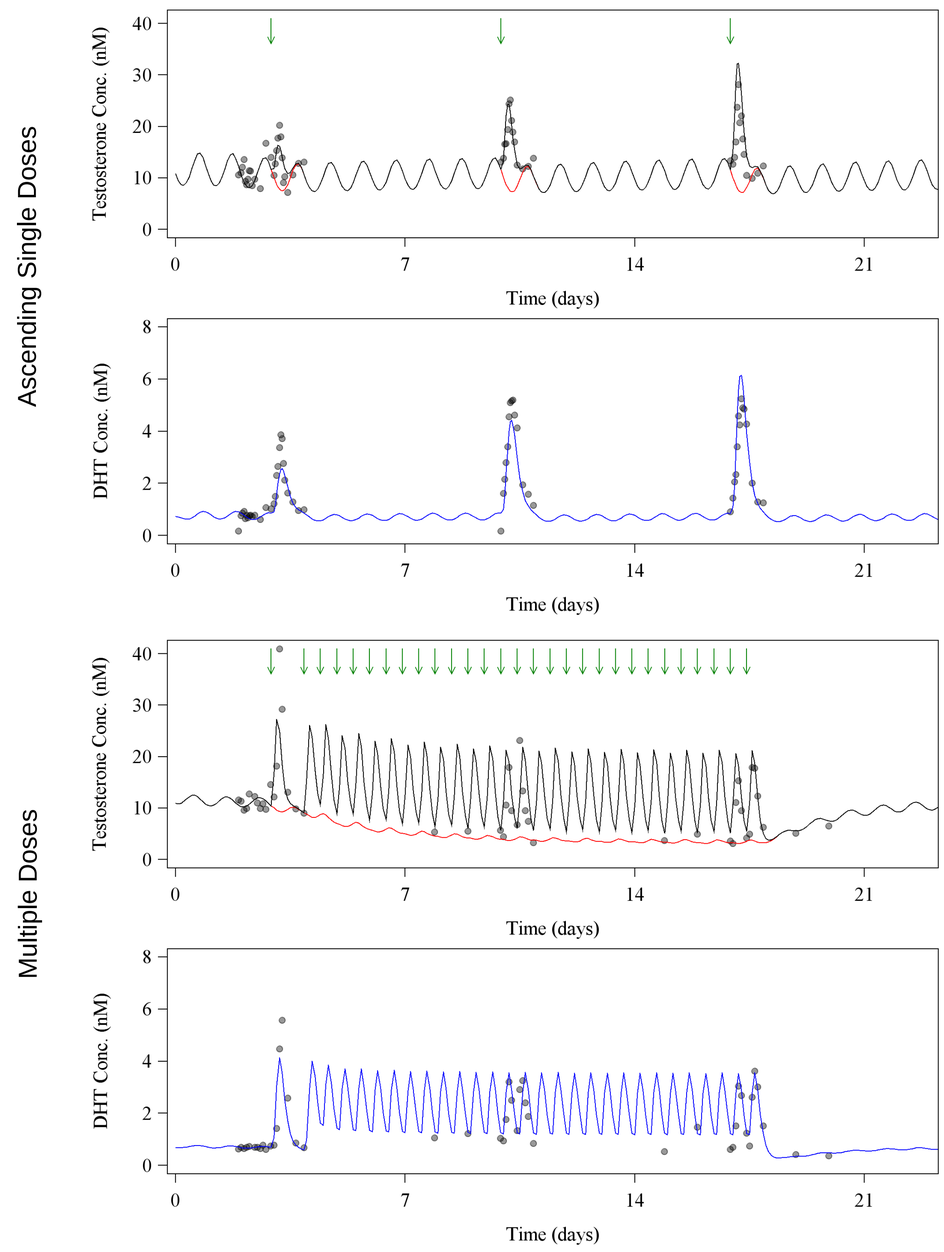
- Meta analysis of a ascending single and multiple dose studies
- In total, 84 subjects were included in model development

Data analysis

- Non-linear mixed effect modeling using NONMEM VII

Modeling Results

Figure 3. Exemplary model fits: Predicted (solid lines) vs observed (dots) Testosterone and DHT concentrations. For Testosterone, the endogenous (red) and exogenous (black) species are shown. Doses times are indicated by arrows.



Impact of Endogenous Hormone Levels on AUC and Cmax

Figure 4. Levels of endogenous (red) and total (black) Testosterone for increasing doses (median, 5th and 95th percentiles) as well as circadian rhythm (blue line).

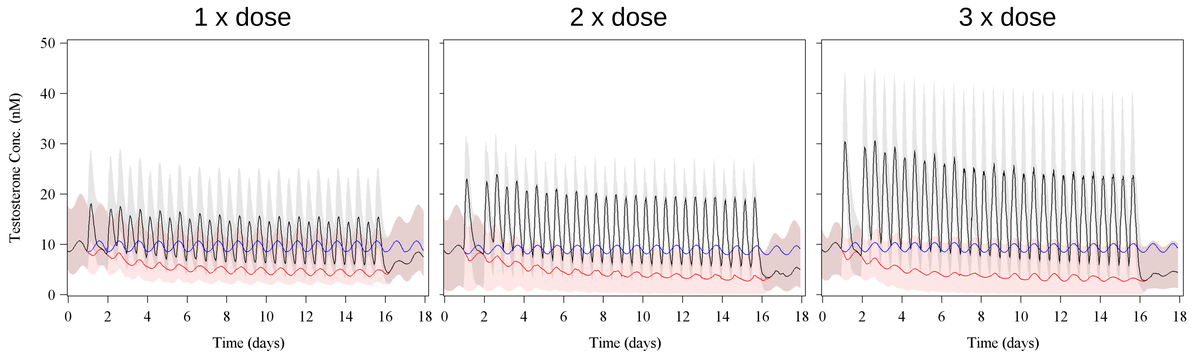


Table 1. Cmax and AUC at last treatment day based on different handling of endogenous testosterone concentration

	Cmax (nM)			AUC (nmol*day/L)			
	1 x dose	2 x dose	3 x dose	1 x dose	2 x dose	3 x dose	
True (total – endogenous TT)	10.7	16.5	22.0	5.9	9.4	12.3	
No correction (total TT)	15.5	19.8	24.8	10.7	12.2	14.4	→ Over-prediction
Baseline corrected (total – circ. rhythm)	5.9	10.6	17.2	1.6	3.9	7.9	→ Under-prediction

Conclusions

- Hormone replacement therapy (HRT) may lead to a shutdown or down-regulation of endogenous hormones
- Incorrect handling of endogenous hormone levels may lead to erroneous predictions of pharmacokinetic parameters and bioequivalence may falsely be concluded
- Current bioequivalence guidelines [1] do acknowledge the influence of endogenous hormone levels but do not adequately reflect the importance of the temporal dependency
- To quantify and predict the impact of HRT on endogenous hormone, it is indispensable to extensively collect data prior to HRT, under treatment as well as in the washout phase
- Alternatively, the use of radio-labeled hormones or additional enrollment of patients without an endogenous production would make it possible to distinguish exogenous and endogenous hormone levels but are likely beyond the scope of typical phase I units

References

[1] European Medicines Agency, *Guideline on the Investigation of Bioequivalence* 2010

[2] Ferrini & Barrett-Connor, *Am J Epidemiol* 1998;147:750–4