Development of a mechanistic-based pharmacodynamic model to describe the effect of a prolonged administration of a GnRH agonist on testosterone levels

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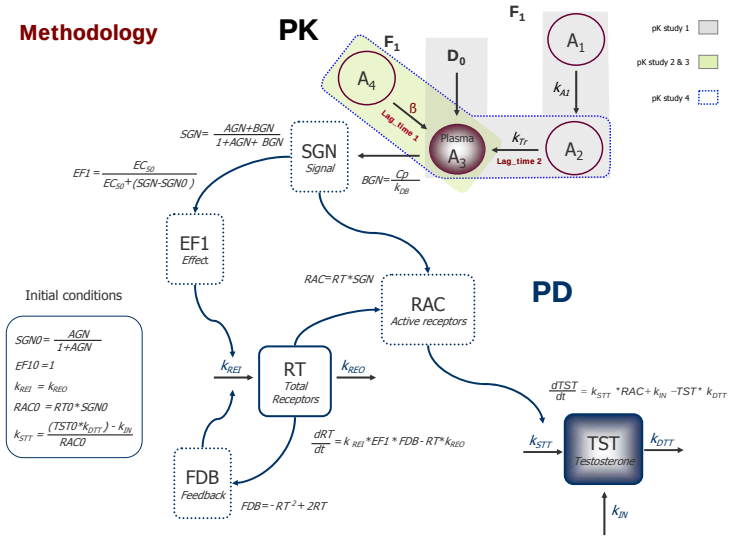
Background The implementation of PD models to characterize specific processes between drug administration and its effect, are now substantially explored in order to describe the behaviour of receptor mediated drug effects.

Objective To analyze the performance on the pharmacodynamic (PD) of an agonist, we developed a receptor-mechanism-based PD model able to describe the changes in testosterone concentrations observed after prolonged exposure of a GnRH agonist.

Methodology



Mechanistic-based pharmacodynamic model of a GnRH agonist effect on testosterone levels after prolonged administration. Description of pharmacokinetic models for each study are schematically represented.

Clinical phase

Study	1	2	3	4
Population	Patients/healthy	Patients	Patients	Patients
No. subjects	19	12	12	24

Subcutaneous administration

Blood samples taken until effect was over (recuperation of normal testosterone levels) (3 - 6 months)

- Pharmacokinetic simulated from Bayesian predictions parameters previously reported [1].
- Structural design of PD model Developed through VENSIM (Ventana Systems, Inc., MA, United States.) computing environment. The effect-versus-time data were evaluated during the analysis by the program NONMEM v7.
- Performance evaluation between models was done by the exploration of visual predictive check and other statistical evaluation tools [PsN version 3.2.4, R v 2.10.1, MATLAB Version 7.9.0529 (R2009b)] [4].

Results

Pharmacokinetic table of parameters

Study	1		2		3		4	
Pharmacokinetic parameters	Typical value Estimate (%RSE)	IIV %CV (RSE%)	Typical value Estimate (%RSE)	IIV %CV (RSE%)	Typical value Estimate (%RSE)	IIV %CV (RSE%)	Typical value Estimate (%RSE)	IIV %CV (RSE%)
CL/F (L.day)	279 (12)	-	140 (9)	-	416 (13)	-	41.04 (4)	-
V_2/F(L)	2450 (16)	39(43)	249 (25)	-	28 (20)	-	11.6 (18)	26 (42)
F_1	0.09 (7)	34(62)	-	-	-	-	0.26 (7)	42 (36)
F_2 [b]	0.91	-	-	-	-	-	0.74	-
F_{rel}	1	-	1	25 (49)	1	40 (40)	-	-
β	-	-	0.51 (11)	47 (46)	0.38 (8)	18 (54)	0.815 (3.4)	-
k_{A1}(day^{-1})	0.27 (18)	-	168 (19)	16 (50)	32 (45)	-	0.068 (6)	23 (41)
k_{A2}(day^{-1})	-	-	-	-	-	-	7.51 x 10^{-5} (12)	-
k_{Tr} [c] (day^{-1})	0.028 (18)	-	-	-	-	-	-	-
Lag time_1(day)	-	-	-	-	4.4 x 10^{-3} (23)	-	-	-
Lag time_2(day)	-	-	-	-	-	-	1.57 (7)	-
D_0 (day)	0.028 (9)	-	-	-	-	-	-	-
σ_{Aditt} (%)	54 (2)	-	40 (8.5)	-	53 (17)	-	16	-
σ_{Prop} (%)	-	-	32 (33)	-	-	-	-	-

Estimates are listed with their corresponding coefficient of variation (CV(%).
β, Derived parameter from Weibul function, *Aproximated interindividual variability (IIV) for logit-transformed parameter, i.e. *CV(θ) = θ(1-θ)ω*. [b], F2 = 1-F1, [c], *kTr = kA1*

Pharmacodynamic table of parameters

Pharmacodynamic Parameters	Typical value Estimate	Median* (5-95th)	IIV %CV	Median* (5-95th)
TST0 (ng.mL^{-1})	3.98	3.98 (3.43 - 4.55)	35.07	35.2 (31.2 - 41.4)
k_{DB} (day^{-1})	0.946	0.938 (0.81 - 1.09)	-	
E_{50}	0.0247	0.025 (0.022 - 0.027)	31.36	31.9 (30.8 - 41.1)
k_{REO}(days^{-1})	0.21	0.21 (0.19 - 0.24)	32.09	32.6 (31.8 - 39.7)
k_{IN} (ng·mL^{-1} ·days^{-1})	0.036	0.036 (0.031 - 0.042)	35.77	36.3 (34.4 - 47.1)
k_{DTT}(days^{-1})	0.59	0.59 (0.52 - 0.72)	-	-
AGN (ng·mL^{-1}·day^{-1})	0.335	0.34 (0.31 - 0.39)	-	-
σ_{Aditt} (%)	44.7	44.7 (40.9 – 47.2)	-	-

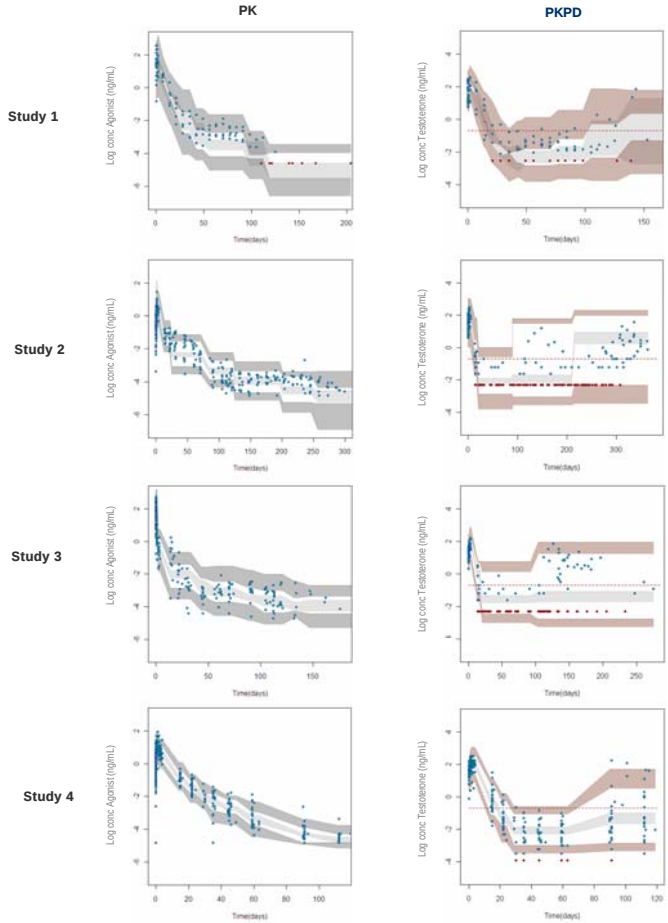
*, Results obtained from nonparametric bootstrap 200 samples , IIV, Interindividual variability.
Parameters described in model scheme

Table of descriptors

Study	Cmax Agonist (ng/mL)		$AUC_{0-\tau}$ (μg.day.L^{-1})		Castration time (days)		Cmax (ng/mL)Testosterone	
	Observed Mean	Predicted Mean* (5-95th)	Observed Median	Predicted Median* (5-95th)	Observed Median	Predicted Median* (5-95th)	Observed Median	Predicted Median* (5-95th)
1	3.88	4.29 (3.05 – 5.94)	27.10	21.23 (16.62-27.54)	42.00	42.0 (0 - 119)	2.23	2.47 (1.73 – 3.24)
2	2.12	2.29 (1.70 – 3.05)	32.27	29.22 (24.41-34.81)	278.00	178.99 (74 – 314)	1.88	2.35 (1.59 – 3.16)
3	10.50	11.57 (7.92 – 16.91)	19.21	18.07 (13.99-23.37)	119.97	111.06 (0 – 245)	1.77	2.34 (1.57 – 3.17)
4	3.36	3.64 (3.10 – 4.32)	27.88	28.33 (24.78-32.03)	90.00	83.00 (34 – 97)	2.09	2.46 (1.65 – 3.33)

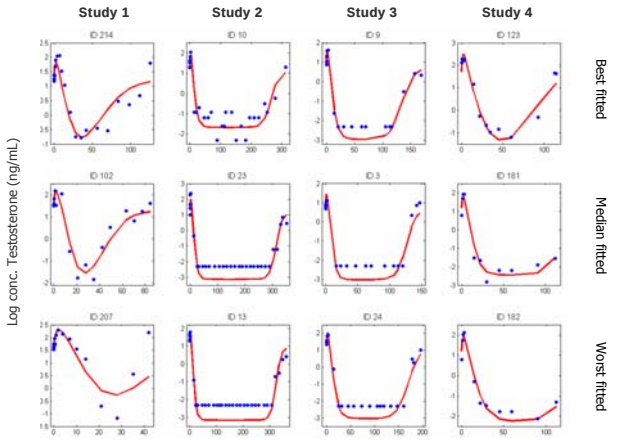
*Confidence intervals and median data from 1000 simulates studies

Pharmacokinetic and Pharmacodynamic VPC´s



Panels correspond to the pharmacokinetic (grey) and pharmacodynamic (salmon) visual predictive checks (1000 simulated studies) for all studies. The area covering the 95% confidence interval of the predicted median. Green points represent observed data, red points represent data below limit of quantification (BLQ). Dashed red line, represents the limit of castration (0.5 ng/mL).

Performance of fitted individuals



Individual observed (points) and model-predicted (lines) concentration of testosterone versus time profiles for the best (upper panels), median (middle panels) and worst (lower panels) fitted individuals participating at each study.

Conclusions A mechanism-based PD model was successfully developed allowing us to explore the influence of receptors occupancy and the effect of a prolonged administration of a GnRH agonist on testosterone levels.

Bibliography

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