

Optimization of PK/PD profiles by optimal control methods

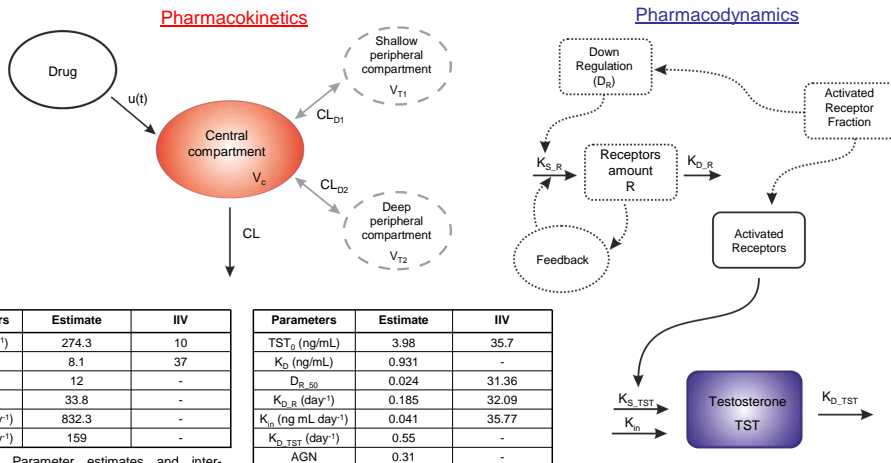
Application to a triptorelin-testosterone PD model

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BACKGROUND

Triptorelin is a gonadotropin-releasing hormone agonist indicated mainly for the treatment of hormone-dependent prostate cancer. Its typical effect on testosterone profile is characterized by an undesired initial flare-up where concentrations are greater than baseline (~4 ng/mL). Once testosterone reaches its maximum value, its level decreases to the castration limit ($TST_{cast} = 0.5$ ng/mL) due to a receptor down-regulation phenomena and keeps below it for a finite period of time (see Figure 1). Recently, a semi-mechanistic pharmacokinetic/pharmacodynamic (PK/PD) model has been developed to describe the dynamics of system triptorelin-testosterone [1].



Parameters	Estimate	IIV	Parameters	Estimate	IIV
CL (L day ⁻¹)	274.3	10	TST ₀ (ng/mL)	3.98	35.7
V _c (L)	8.1	37	K _D (ng/mL)	0.931	-
V _{t1} (L)	12	-	D _{R,50}	0.024	31.36
V _{t2} (L)	33.8	-	K _{D,R} (day ⁻¹)	0.185	32.09
CL _{D1} (L day ⁻¹)	832.3	-	K _{S,R} (ng mL day ⁻¹)	0.041	35.77
CL _{D2} (L day ⁻¹)	159	-	K _{D,TST} (day ⁻¹)	0.55	-
			K _{S,TST} (day ⁻¹)	0.31	-

Table 1.- Parameter estimates and inter-individual variability of the PK/PD model [1].

OBJECTIVES

Motivated by previous works [2,3], the aim is to derive the pharmacokinetic profiles of triptorelin to achieve the following therapeutic objectives:

- 1) $TST_{max} < 150\%$ of TST_0 .
- 2) $t_{cas} < 21$ days.
- 3) Prolong the drug efficacy up to $t_{effect} > 250$ days.

METHODOLOGY

We applied pseudospectral optimal control methods performed by the open-source software GPOPS [4,5]. By means of this technique, we are able to find a control law $u(t)$ (in our case the drug absorption rate) for the dynamical system described by the mentioned PK/PD model that obeys the objectives proposed. The problem is divided into two phases with two different cost functionals J to minimize (see figure 1 and table 2).

minimize J

subject to

$$\forall t \in [t_0, t_f]: \dot{c}_1(t) = -\frac{CL_{D1}}{V_{t1}} c_1(t) + \frac{CL_{D1}}{V_c} C_{TRP}(t)$$

$$\forall t \in [t_0, t_f]: \dot{c}_2(t) = -\frac{CL_{D1}}{V_{t1}} c_1(t) + \frac{CL_{D1}}{V_c} C_{TRP}(t)$$

$$\forall t \in [t_0, t_f]: \dot{C}_{TRP}(t) = u(t) + \frac{CL_{D1}}{V_{t1}} c_1(t) + \frac{CL_{D2}}{V_{t2}} c_2(t) - \frac{CL_{D1}}{V_c} C_{TRP}(t) - \frac{CL_{D2}}{V_c} C_{TRP}(t) - \frac{CL}{V_c} C_{TRP}(t)$$

$$\forall t \in [t_0, t_f]: \dot{R}(t) = K_{SR} \frac{D_{R50}}{D_{R50} + \frac{AGN + C_{TRP}(t)/K_D}{1 + AGN + C_{TRP}(t)/K_D}} (2R(t) - R(t)^2) - K_{DR} R(t)$$

$$\forall t \in [t_0, t_f]: \dot{TST}(t) = K_{S,TST} R(t) \frac{AGN + C_{TRP}(t)/K_D}{1 + AGN + C_{TRP}(t)/K_D} + K_{in} - K_{D,TST} TST(t)$$

Phase I	Phase II
$t \in [0, t_{cast}]$	$t \in [t_{cast}, 270]$
$J = t_{cast}$	$J = \int_{t_{cast}}^{270} u(t)^2 dt$
$0 < R(t) < 1$ $TST_{cast} < TST(t) < TST_{max}$ $0 < u(t) < 2$ $18 < t_{cast} < 21$	$0 < R(t) < 1$ $0 < TST(t) < TST_{cast}$ $0 < u(t) < 2$ $18 < t_{cast} < 21$

Table 2.- Cost functionals and constraints for the optimal control problem.

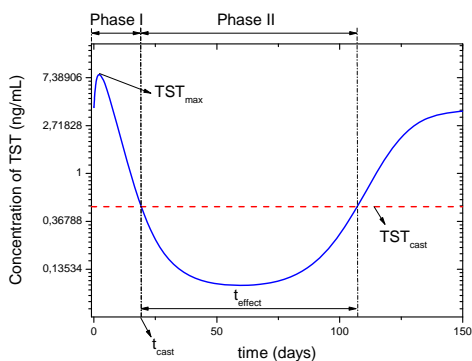


Figure 1.- Typical Testosterone profile after triptorelin administration.

RESULTS

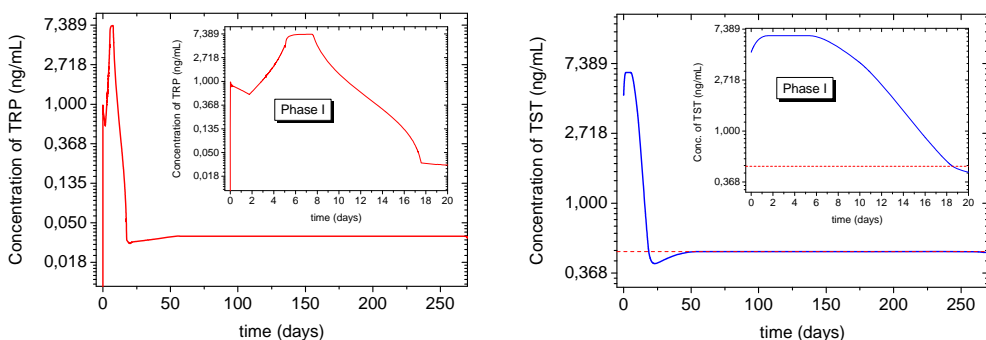


Figure 2.- Optimal pharmacokinetics and pharmacodynamics profiles obtained from the optimal control method. The insets correspond to the profiles for phase I.

The results obtained from the optimal control analysis show that forcing the concentration at the flare-up to be lower than 140% of basal levels, the castration can be achieved in periods not exceeding 21 days after drug administration. The corresponding pharmacokinetic profiles are characterized by a fast increase of triptorelin in plasma up to a 7 ng/mL, level which is maintained for 5 days. After that period, the concentration of triptorelin decreases to levels around 0.035 ng/mL, which are close to the value of the $CTRP_{min}$ descriptor obtained previously [1]. Linking these results, we are able to prolong the effect of the sustained release formulations up to seven months.

CONCLUSIONS

The optimal control methods are a useful technique that allows to derive from a PD model the desired effect profiles and the corresponding pharmacokinetics to obtain them. These methods are more relevant in the case of complex systems where the dynamics are not easily extrapolated and there is a lack of clear relationship between the drug concentration and the effect profiles. Moreover, the flexibility of the method allows to change easily the constraints of concentrations and the objective to obtain new optimal profiles. Therefore, all these features suggest that the optimal control methods could be a helpful tool to optimize and design new drug formulations.

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