PKPD modelling of the relationship between testosterone and PSA in patients with prostate cancer during treatment with leuprorelin

What is the optimal testosterone level?

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Introduction

The main goal in the treatment of prostate cancer with gonadotropin-releasing hormone (GnRH) agonists is to achieve and maintain testosterone concentrations below castration level:

- Traditionally in Europe: 50 ng/dL
- Proposed level: 20 ng/dL

A relationship between testosterone and clinical outcome, i.e. survival is lacking.

Prostate Specific Antigen (PSA) serum concentrations are used as a surrogate marker for disease control in clinical practice:

- PSA serum levels above 4 ng/mL are considered an indication for prostate cancer
Leuprolelin

Leuprolelin, a GnRH agonist, has been in clinical use for the treatment of prostate cancer for over 20 years in different long acting depot formulations.

GnRH agonist first stimulate the receptor (surge) and later down-regulate the receptor.

Due to receptor down regulation testosterone levels are reduced.
**Objective and Approach**

**Objective:**
- Identification of a target testosterone concentration which optimizes the balance of the benefits of testosterone suppression whilst reducing the risks of futile over-suppression

**Approach:**
- Characterization of the relationship between leuprolerein, testosterone and PSA concentrations over time in a quantitative manner

![Diagram showing the relationship between PK: leuprolerein concentration, Testosterone, PSA, and Clinical outcome: survival.](Image)
Pharmacokinetics

Population PK model

Depot 1
Fast absorption
frac

Ka_1

Central Compartment
(V_c)

Depot 2
Slow absorption
(1-frac)

Mixture model:
Pop1: Ka_2
Pop2: Ka_3 \times \text{TIME}

Peripheral Compartment
(V_p)

Q

CL

Adequate description of the data

6 months depot: 22.5 mg

6 months depot: 30 mg

Concentration (pg/mL)

0 1 2 3 4 5 6 7

Time (months)

-1 10 -1 10 0 10 1 10 2 10 3 10 4 10 5 10

Stochastic model:
- IIV: CL, Ka_2 and Ka_3, frac and relative bioavailability
- Proportional residual error

Data from single dose study in patients with prostatic cancer
6-month depot formulation: 22.5 and 30 mg
Population testosterone model

\[ K_{\text{in}_R} \times \text{DR} \rightarrow \text{Receptor (R)} \rightarrow k_{\text{out}_R} \]

\[ K_{\text{in}_T} \times R_{\text{AC}} \rightarrow \text{Testosterone (T)} \rightarrow k_{\text{out}_R} \]

\[ \text{FRAC} = \frac{(A + Cp/Kd)}{(1 + A + Cp/Kd)} \]

\[ R_{\text{AC}} = R \times \text{FRAC} \]

\[ \text{DR} = \frac{\text{DR}_{50}^{NH} + (\text{FRAC} \_ \text{NH})}{\text{FRAC} \_ \text{NH}} \]

\[ \text{FRAC} = \frac{(A + Cp/Kd)}{(1 + A + Cp/Kd)} \]

\[ \text{DR} = \frac{\text{DR}_{50}^{NH} + (\text{FRAC} \_ \text{NH})}{\text{FRAC} \_ \text{NH}} \]

Cp: leuprorelin concentration; Kd: dissociation constant
A: endogenous GnRH concentration over Kd

Stochastic model:
Â IIV: DR_{50}, Kd, K_{\text{out}_R}, BSL_T, NH, CPA
Â Proportional residual error

Adequate description of the data

Cyproterone effect: initial decrease
Agonistic effect: testosterone surge
Receptor down regulation: testosterone suppression

Testosterone
Steady-state concentration-effect relationship

Å Testosterone concentrations <50 ng/dL in 50% of the subjects are reached for leuprorelin concentrations > 5.5 pg/mL

Å Testosterone concentrations <50 ng/dL in 90% of the subjects are reached for leuprorelin concentrations > 70 pg/mL

Grey area: 90% prediction interval; Black line: predicted median; Grey lines: 80th and 90th percentile of the predictions
Population PSA model

\[ \text{Testosterone} \xrightarrow{1 + \text{EFF}} \text{PSA} \quad \text{PSA} \xrightarrow{k_{\text{out}_P}} \]

\( \text{EFF: Sigmoid } E_{\text{max}} \text{ model} \)

Stochastic model:
- IIV: \( E_{\text{max}}, \text{EC}_{50}, \text{NH}, k_{\text{out}_P}, \text{BSL}_P \)
- Proportional residual error

Adequate description of the data

\begin{align*}
\text{6 months depot: 22.5 mg} & : 22.5 \text{ mg} \\
\text{6 months depot: 30 mg} & : 30 \text{ mg}
\end{align*}
Predicted steady-state PSA levels *versus* testosterone

To reach PSA levels below **4 ng/mL** at steady state:

- in 50% of the subjects, testosterone concentrations should be lower than **250 ng/dL** at steady state
- in 80% of the subjects, testosterone concentrations should be lower than **130 ng/dL** at steady state (not shown)
- in 90% of the subjects: not reached. Subjects with a high baseline show a large decrease in PSA, but do not reach PSA < 4 ng/mL

Reducing testosterone concentrations below **35 ng/dL** does not result in a further reduction of PSA levels (>95% of the minimal PSA level)

Grey area: 90% prediction interval; Black line: predicted median; Dots: steady-state observations
Alternative model results in a different prediction of the relationship between testosterone and PSA. PSA goes to zero when testosterone goes to zero.

Grey area: 90% prediction interval; Black line: predicted median; Dots: steady-state observations.

There are more observations above the predicted median than below.
Steady-state and dynamic PSA data better described by the original model

- The original model predicts the steady-state observations better.
- More data is required to further support this relationship in the lower testosterone and PSA range.
- Testosterone is produced by the testes and adrenal glands.
  - Testosterone suppression via the HPG-axis will only inhibit the testosterone production by the testes.

Black and green line: predicted median alternative and original model, respectively; Dots: steady-state observations.
Conclusions and Future Perspectives

PK: leuprolelin concentration → Testosterone → PSA → Clinical outcome: survival

- The model-based analysis suggests that reducing testosterone concentrations below 35 ng/dl does not result in a further decrease in PSA levels.
- Lower testosterone levels could be related to certain side effects.
- Future research: quantification of the relationship between PSA levels and survival.