Simultaneous Modelling of PSA in BPH and Cancer Patients Treated by Prostate Surgery

Alexandre SOSTELLY (1,2), Emilie HENIN (1), Benoit YOU (2), Pascal GIRARD (2) and Mats O. KARLSSON (1)

(1) Department of Pharmaceutical Biosciences, Uppsala University, Sweden

(2) Université Lyon 1, EA3738 CTO, Faculté de Médecine Lyon Sud, Oullins, France

Backgrounds and Objectives

- **Prostate Specific Antigen (PSA):**
  - mainly produced by prostate
  - biomarker for prostate diseases
- **Benign Prostatic Hyperplasia (BPH):**
  - adenoma develops into transition zone [1]
  - treated by transition zone removal (Millin's adenomectomy)
- **Prostatic adenocarcinoma (cancer):**
  - tumour initially develops into peripheral zone
  - treated by radical prostatectomy [2]

Aims: To characterize PSA production from each part of the prostate using a non linear mixed effects model

Patients and Methods

Patients:

- 81 BPH patients with a mean of 2.5 PSA assays
- 68 cancer patients with a mean of 9 PSA assays

Patients demographics are similar in the two cohorts

Methods:

- **PSA baseline estimation:**
  - No preoperative PSA concentration was available
  - Prostate zone volumes were assessed after surgery
  - Basal PSA values were resulting from the contribution of each zone as a function of corresponding volumes
- **Missing prostate volumes:**
  - Prostate volumes were not reported in 20% of patients
  - Measured volumes were taken for patients where such a measurement was performed and treated as covariates
  - Estimation of missing volumes from the observed volume distribution
- **Censored PSA values:**
  - 33% of PSA values were below the limit of quantification
  - *M3 method* was used to deal with censored values [3]

Results

Model Characteristics:

- Peripheral compartment represents PSA distribution and PSA is eliminated from the plasma compartment with a first order constant
- Different rates of PSA production for peripheral zone, transition zone and cancer zone were estimated
- Linear two-compartment disposition [4]

	Parameters (%IIV)		Parameters (%IIV)
Transition Zone + Adenoma Volume (BPH cohort) (cm^3)	109 (%IIV:39%)*	$K_{in\ CA}$ ($ng.cm^{-3}.h^{-1}$)	1.19
Peripheral Zone Volume (cm^3)	22.2 (%IIV:37%)*	K_{12} ($ng.cm^{-3}.h^{-1}$)	0.445
Transition Zone Volume (Cancer cohort) (cm^3)	43.6 (%IIV:39%)*	K_{21} ($ng.cm^{-3}.h^{-1}$)	0.608
Cancer Zone Volume (cm^3)	4.29 (%IIV:122.88%)*	K_{out} (h^{-1})	0.707 (%IIV:52%)
$K_{in\ TZ}$ ($ng.cm^{-3}.h^{-1}$)	0.0433	σ_1 (Additive error)	1.31
$K_{in\ PZ}$ ($ng.cm^{-3}.h^{-1}$)	0.0323	σ_2 (Proportional error)	0.322

Table 1: Parameter Estimates
Typical value (CV%)
*: Observed means and IIV

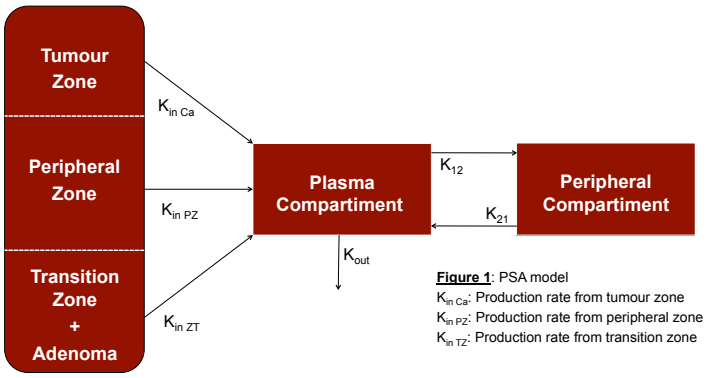

Figure 1: PSA model
$K_{in\ Ca}$: Production rate from tumour zone
$K_{in\ PZ}$: Production rate from peripheral zone
$K_{in\ TZ}$: Production rate from transition zone

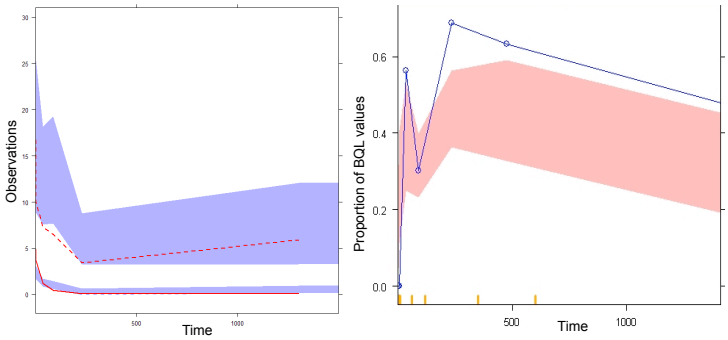

Figure 2: Visual Predictive Check
Left panel: VPC for observations
Blue area: 90% predictive interval for the median and 95th percentile; *Red line*: 50th and 95th percentile of the distribution
Right panel: VPC for proportion of BQL

Many values were below the quantification limit, it was therefore impossible to compute 5th percentile. We compared instead the proportion of BQL as observed with simulated.

Discussion & Perspectives

Parameter estimation was supported by both datasets. PSA elimination was "directly" observed in cancer patients after surgery (no more PSA production) and PSA production from transition zone was observed in BPH patients after adenomectomy (residual production).

This simultaneous approach allows a better estimation of model parameters even with sparse data.

Estimated PSA production rates were in accordance with our expectations : $K_{in\ CA} > K_{in\ TZ} > K_{in\ PZ}$. PSA half life was estimated to 1 hour which is in accordance to the fast PSA elimination in kidneys [5].

Conclusion

PSA production and its interindividual variability was quantified for each zone of the prostate. The originality of PSA model lies in the simultaneous analysis of two cohorts with different prostatic diseases.

In the future, PSA model will be useful to assess the quality of prostate surgery and to help the prediction of risk relapse after surgery.

References :

1. Linton, Marks, *et al. Clin Chem. 2003 Feb;49(2):253-9.*
2. Stamey, Yang, *et al. N Engl J Med. 1987 Oct 8;317(15):909-16.*
3. Beal. J Pharmacokinet Pharmacodyn. 2001 Oct;28(5):481-504.
4. You, Perrin, *et al. Clin Biochem. 2008 Jul;41(10-11):785-95*
5. Partin, Piantadosi, *et al.* Prostate Suppl. 1996;7:35-9.