A semi-physiological biopharmaceutical model for simulation and prediction of 2-hydroxyflutamide concentrations in plasma and prostate tissue in prostate cancer patients following local administration of an injectable depot formulation.

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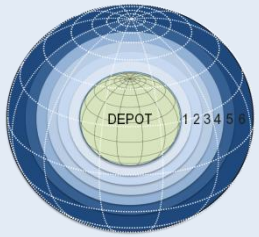
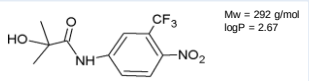
BACKGROUND

Prostate cancer (PC) is a common disease and primarily affects men older than 65 years. About 90 % of men diagnosed with prostate cancer will have a clinically localized disease. The range of currently available treatment options (radiation, surgery, androgen depravation) does not fully match the spectrum of localized prostate cancer. To meet this medical need a novel parenteral modified release formulation for local injections into the prostatic gland (Liproca® Depot (LIDDS AB, Sweden) has been developed and studied in patients with localized PC.



Schematic depiction of the prostate tissue shell model applied for local distribution studies for Liproca Depot. The prostatic tissue compartments are numbered 1 to 6. Input to the semi-physiological model and the diffusion distance of 2-HOF from the depot was estimated based on this approach.

2-hydroxyflutamide



Mw = 292 g/mol
logP = 2.67

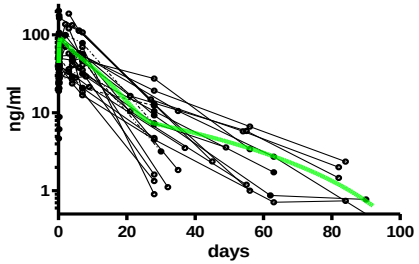
Prostate Compartment	ShTh (cm)	PLd (cm)	PLs (cm)	PV (ml)	PAr (cm²)	PBV (ml)	PBQ (ml min⁻¹)	PBAr (cm²)
P1	0.2	0.1	0.2	2.78	16.6	0.0528	3.9	186
P2	0.2	0.3	0.2	3.93	22.9	0.0747	5.5	263
P3	0.2	0.5	0.2	5.29	30.2	0.100	7.3	354
P4	0.2	0.7	0.2	6.85	38.5	0.130	9.5	459
P5	0.2	0.9	0.281	8.61	47.8	0.164	12	577
P6	0.36	1.18		20.7	67.1	0.393	29	1390
Total	1.35			48.2			67	

Prostate tissue compartment shells thickness (ShTh), prostate tissue compartment volume (PV), prostate tissue compartment area (PAr), mean distances between the prostate tissue compartment shells (PLs), mean distance from prostate tissue compartment to depot (PLd), prostate blood compartment volume (PBV), prostate blood compartment blood flow (PBQ) and prostate blood compartment area (PBAr)

The physiological input for the prostatic tissue in the semi-physiological pharmacokinetic model.

PURPOSE

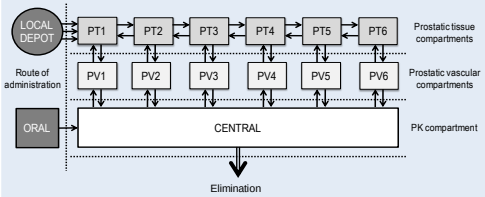
The objective of this study was to develop a semi-physiological biopharmaceutical model describing the concentration-time profiles of 2-hydroxyflutamide (2-HOF) in plasma and prostate tissue after a single intra prostatic injection in one lobe and repeated oral administration



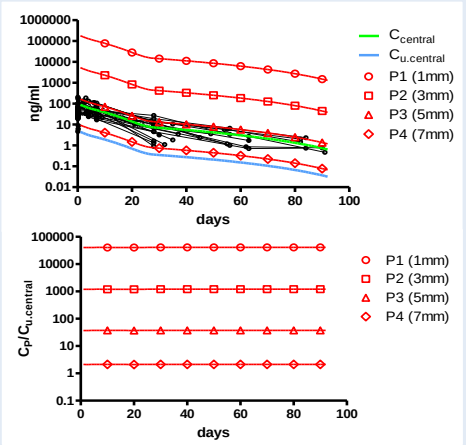
Individual plasma concentration-time profiles of 2-HOF from the clinical study (connected dots) and model fitted curve (green solid line).

METHODS

Clinical data originated from a phase II study in 24 patients with localized PC (T1-T2) that was treated with a single injection Liproca® Depot (400-1600 mg of 2-HOF). Human physiological values and specific physicochemical properties of 2-HOF implemented in the model were gathered from literature or calculated via established algorithms. The prostate gland was modeled as a number of compartments representing tissue and blood. Discrete flows connecting blood compartments were described by representative blood flows whereas tissue-to-tissue and tissue-to-blood flows were described by a one-dimensional diffusion approximation. Based on *in vitro* data the intraprostatic release of 2-HOF from the formulation was described by an empirical dissolution approach.



A schematic depiction of the semi-physiological pharmacokinetic model of the biopharmaceutical properties and local disposition determining the tissue concentration of 2-HOF.



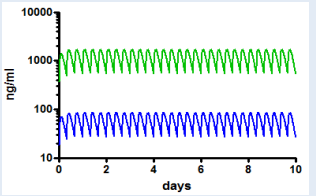
Top: Individual plasma concentration-time profiles of 2-HOF from the clinical study (connected black dots) and simulated concentration-time profiles of 2-HOF in central (total=green, unbound= blue) and prostatic compartments (red) 1 to 4 (P1-P4) mean distance to local depot in brackets.
Bottom: Concentration (unbound) ratio, prostatic (1 to 4) vs. central compartment.

RESULTS

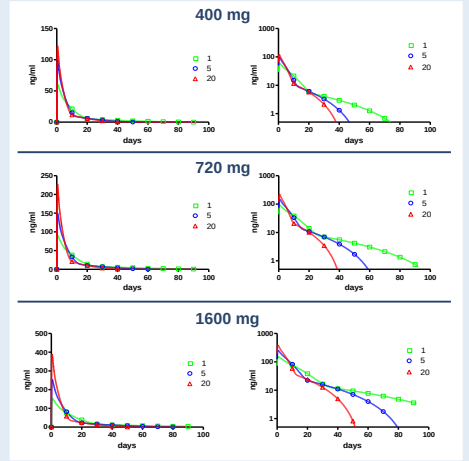
The model adequately described the plasma concentration-time profiles. Predictive simulations indicated that within a distance of 5 mm from the formulation the local tissue concentration of 2-HOF was more than 40 times higher than in the plasma compartment. The simulations also indicated that spreading of the formulation throughout the prostate gland as multiple units would increase the release rate of 2-HOF as a consequence of a larger surface area. This would initially increase the tissue and plasma concentrations but also reduce the terminal half-life of 2-HOF in plasma.

CONCLUSION

This study supports the prospect that the sustained exposure of 2-HOF due to the formulation design in combination with the local drug accumulation will significantly contribute to reduce the tumor volume and obtain a good cancer control, without side-effects related to high plasma concentrations of 2-HOF.



Simulated concentration-time profiles of 2-HOF (total (green) and unbound (blue)) in the central compartment during repeated oral administration of 250 mg (TID) flutamide



Simulations of the impact of dose and multiple units, i.e., increased depot area, on the concentration of 2-HOF in central compartment shown for 1 (green, default), 5 (orange) and 20 units (red). Plots are both in lin-lin and lin-log scale. Doses were chosen based on the clinical study, 400 mg (minimum dose), 720 mg (mean dose) and 1600 mg (maximum dose).