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

**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 deprivation) does not fully match the spectrum of localized prostate cancer. To meet this medical need a novel parental 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.

**PURPOSE**

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

**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 intraprostatal release of 2-HOF from the formulation was described by an empirical dissolution approach.

**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.

**REFERENCES**

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**Schematic depiction of the prostate tissue compartment model applied for local distribution studies for Liproca® Depot**: The physiological input for the prostatic tissue in the semi-physiological pharmacokinetic model of the prostatic tissue compartment was gathered from literature or calculated via established algorithms. The prostate gland was 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 intraprostatal release of 2-HOF from the formulation was described by an empirical dissolution approach.

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

**Simulated concentration-time profiles of 2-HOF total (gray) and unbound (blue) in the central compartment during repeated and administration of 255 mg (5x) LIPROCA® Depot**

**Simulated concentration-time profiles of 2-HOF total (gray) and unbound (blue) in the central compartment during repeated and administration of 255 mg (5x) LIPROCA® Depot**