Population pharmacokinetic/pharmacodynamic modelling of the hypothalamic-pituitary-gonadal axis - DTU Orbit (02/10/2019)

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The present thesis deals with different aspects of population pharmacokinetic/pharmacodynamic (PK/PD) modelling of the male hypothalamic-pituitary-gonadal (HPG) axis. The thesis consists of a summary report and five scientific research papers. An overview of the main topics covered in the thesis is provided in the summary report including PK/PD modelling in drug development, the pathological, physiological, and pharmacological aspects of the male HPG axis, and a detailed description of the methodology behind non-linear mixed-effects modelling based on stochastic differential equations (SDEs). The main objective of the work underlying this thesis was to develop mechanism-based population PK/PD models of the HPG axis. The HPG axis is a multivariate closed-loop control system consisting of regulatory hormonal feedback mechanisms. The number and complexity of the physiological mechanisms involved in such models makes them difficult to develop and are often too complex to be conveniently described by empirical models. Hence, the use of SDEs in population PK/PD modelling was used as a tool to systematically develop a mechanism-based model of the HPG axis following treatment with gonadotropin-releasing hormone (GnRH) agonist triptorelin and GnRH antagonist degarelix in a combined model. The use of SDEs in non-linear mixed-effects modelling was investigated by implementing the Extended Kalman Filter in the NONMEM software. Non-linear mixed-effects models based on SDEs extend the first-stage model of the hierarchical structure by decomposing the intra-individual variability into two types of noise, i.e. a system noise term representing unknown or incorrectly specified dynamics and a measurement noise term accounting for uncorrelated errors such as assay error. This setup makes identification of structural model mis-specification feasible by quantifying the model uncertainty, which subsequently provides the basis for systematic population PK/PD model development. To support the model building process, the SDE approach was applied to clinical PK/PD data and used as a tool for tracking unexplained variations in parameters, identifying complicated non-linear dynamic dependencies, and deconvolving the functional feedback relationships of the HPG axis. The developed mechanism-based model of the HPG axis consisted of four compartments where the secretion of readily releasable LH from a pool compartment was stimulated and inhibited by the plasma triptorelin and degarelix concentrations, respectively. Circulating LH stimulated the testosterone secretion while the delayed testosterone feedback on the non-basal LH synthesis and release was modelled through a receptor compartment where testosterone stimulates the production of receptors. The derived mechanism-based model of the HPG axis was able to account for the observed LH and testosterone concentration-time profiles following treatment with both GnRH agonist triptorelin and GnRH antagonist degarelix thereby indicating that the model is sufficient at mimicking the underlying physiology of the endocrine system.

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