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Scope and intent of investigations

Development of drugs for central nervous system (CNS)-associated diseases has suffered from high attrition rates (1,2) due to safety and efficacy issues (3). To improve the prediction of CNS drug effects, knowledge of the CNS target-site pharmacokinetics (PK) of especially the unbound drug is indispensable (4). However, measuring drug concentrations in the CNS of healthy volunteers or patients has major practical and ethical constraints. Plasma concentrations are therefore still the mainstay in the selection of optimal dose regimens in clinical CNS drug development, even though these concentrations may differ substantially from the local concentrations in the CNS. The differences in drug concentrations between plasma and CNS originate from the barrier properties of the blood-brain barrier (BBB) and the processes that govern intra-brain distribution (5). Therefore, it is important to search for robust approaches that can aid in the prediction of CNS target-site PK to improve CNS drug development.

The ultimate aim of the research described in this thesis is to develop a comprehensive mathematical PK model for the prediction of concentration-time profiles of (unbound) small molecule drugs in multiple CNS compartments in humans. This model is created in a step-wise manner in chapters 3, 4 and 5.

Chapter 2 starts with a summary review of the CNS systems properties and processes (physiological characteristics) that are relevant for the prediction of CNS PK, both in healthy and in disease conditions. In addition, an overview on experimental techniques and approaches to obtain direct or indirect information on CNS concentrations is given. Finally, state-of-the-art model-based approaches to predict CNS PK are provided. This chapter forms the base knowledge for the models developed in the successive chapters of this thesis.

The CNS consists of several major physiological components such as the brain vasculature, the cells that form the BBB and the blood-cerebrospinal fluid-barrier (BCSFB), the brain parenchymal cells, the brain extracellular fluid ($brain_{ECF}$) and several spaces filled with cerebrospinal fluid (CSF). In addition, physiological flows such as the cerebral blood flow, $brain_{ECF}$ bulk flow and CSF flow exist. These physiological CNS components and the physicochemical properties of the drug, govern in concert the rate and extent of drug transport across the BBB and BCSFB and its intra-brain distribution, which can display substantial variations among different drugs. While the drug properties are a given, CNS systems characteristics are condition dependent, and single or multiple CNS systems characteristics may be altered by diseases. Alterations in CNS systems characteristics may have a significant impact on CNS drug distribution (6–24) and must therefore be considered in drug development.

Currently available experimental techniques and approaches to measure CNS drug concentrations have focused mostly on steady state conditions, and often do not distinguish between total and unbound drug concentrations. As, even in chronic dosing, drug concentrations in plasma and CNS will vary over time, and transport processes are time-dependent, time-course concentration data are crucial to properly understand and predict CNS PK. In addition, information on unbound drug concentrations is a prerequisite not only because it drives the drug effects, but also the different transport processes. Microdialysis is a highly valuable technique, as it allows the *in vivo* measurement of unbound drug concentration kinetics, at different CNS locations (25–30). However, though minimally invasive, the use of microdialysis in humans is highly restricted. Therefore, approaches that can predict time-dependent and CNS location-dependent unbound drug concentration in human are of great relevance. Of all the mathematical PK modeling approaches that have been proposed to predict CNS PK (28–42), so far none has captured enough CNS systems complexity, which indicates the need for the development of more comprehensive CNS PK models.

Chapter 3 describes the development of a multi-compartmental CNS PK model. By the use of microdialysis unbound drug concentration-time data (in rat plasma, $brain_{ECF}$, and two CSF sites) for nine drugs with wide range of drug physiochemical properties, and rat CNS system characteristics taken from literature, a generic multi-compartmental CNS PK model structure is identified. The model consists of plasma and main CNS physiological compartments ($brain_{ECF}$, the brain intracellular fluid ($brain_{ICF}$), and four different CSF sites) that can adequately describe the *in vivo* rat PK data of the nine different drugs. Subsequent scaling of the model from rat to human makes it possible to predict unbound drug concentration-time profiles in human CNS at multiple locations. This generic CNS PK model structure is then used further for the development of comprehensive physiologically based pharmacokinetic (PBPK) models for rat and human CNS in the next two chapters.

Chapter 4 describes the development of a comprehensive rat CNS PBPK model, which includes descriptors of multiple CNS physiological compartments and drug distribution processes in the CNS. In contrast to the generic multi-compartmental CNS PK model (Chapter 3), the comprehensive CNS PBPK model is able to predict unbound drug PK profiles in multiple CNS physiological compartments in the rat without the need to have PK data from *in vivo* animal studies. This is possible on the basis of information of drug-specific parameters that can be obtained either by *in silico* predictions or *in vitro* studies. The predictive performance of the model is evaluated using detailed unbound drug concentration-time profiles from ten small molecule drugs in rat plasma, $brain_{ECF}$, two CSF sites, and total brain tissue.

Chapter 5 describes the scaling of the comprehensive CNS PBPK model developed in Chapter 4 from rat to human. The predictive value of this model is evaluated using unbound drug concentration-time data in $brain_{ECF}$ and/or CSF from three drugs, which are obtained from human subjects under physiological CNS conditions. Furthermore, the model is applied to investigate the underlying factors that may explain altered CNS PK in pathophysiological CNS conditions in patients with traumatic brain injury and epilepsy.

Chapter 6 summarizes and discusses the results presented in this thesis on the prediction of unbound drug concentration-time profiles in multiple CNS compartments in human. Furthermore, this chapter provides future perspectives towards a comprehensive PBPK-Pharmacodynamic model to predict drug efficacy in human CNS.

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