RESEARCH ARTICLE

Development of a Physiologically Based Pharmacokinetic Model for the Rat Central Nervous System and Determination of an *In Vitro–In Vivo* Scaling Methodology for the Blood–Brain Barrier Permeability of Two Transporter Substrates, Morphine and Oxycodone

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ABSTRACT: A whole-body physiologically based pharmacokinetic (PBPK) model was developed for the prediction of unbound drug concentration-time profiles in the rat brain, in which drug transfer across the blood–brain barrier (BBB) was treated mechanistically by separating the parameters governing the rate (permeability) of BBB transfer from brain binding. An *in vitro–in vivo* scaling strategy based on Caco-2 cell permeability was proposed to extrapolate the active transporter-driven component of this permeability, in which a relative activity factor, RAF, was estimated by fitting the model to rat *in vivo* profiles. This scaling factor could be interpreted as the ratio of transporter activity between the *in vitro* system and the *in vivo* BBB, for a given drug in a given *in vitro* system. Morphine and oxycodone were selected to evaluate this strategy, as substrates of BBB-located efflux and influx transporters, respectively. After estimation of their respective RAFs using the rat model, the PBPK model was used to simulate human brain concentration profiles assuming the same RAF, and the implications of this were discussed. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: BBB; blood–brain barrier; Caco-2 cells; CNS; IVIVE; PBPK; pharmacokinetics; physiological model; scaling; transporters

INTRODUCTION

The need for predictive models of drug central nervous system (CNS) penetration is becoming increasingly important, as shown by the increasing costs, and yet high failure rates of CNS drug programs. It is essential to build knowledge from preclinical studies, and to develop prediction tools and strategies for the extrapolation of preclinical and *in vitro* data to man as early as possible.

Recently, the determination of drug CNS penetration has been improved by reassessing the critical parameters governing both the rate of blood–brain barrier (BBB) transfer and the extent of distribution at steady state.[1] Although traditionally, the extent of brain distribution at equilibrium was measured *in vivo* and expressed as K_p, that is, the ratio between brain and blood total drug concentrations, using K_p as an indicator of active drug concentrations in the brain could be misleading because it does not distinguish between unbound drug and drug which is bound to brain tissue components (i.e., unavailable to bind to receptor of action, according to the

Abbreviations used: AUC, area under the curve; BBB, blood–brain barrier; BCRP, breast cancer resistant protein; CL, clearance; CNS, central nervous system; fu, fraction unbound; IVIVE, *in vitro–in vivo* extrapolation; PBPK, physiologically based pharmacokinetics; P-gp, P-glycoprotein; PK, pharmacokinetics; PS, permeability–surface area product; RAF, relative activity factor; SF, scaling factor; TR-BBB13 cells, conditionally immortalized rat brain capillary endothelial cells

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general consensus).[2] More recently, $K_{p,uu}$—the unbound concentration ratio—has been preferred, as it is independent of binding.[2,3] Not only does $K_{p,uu}$ give a better idea of the pharmacologically active concentration ratio, but also a value higher or lower than unity can indicate whether active influx or efflux, respectively, are the dominant transport processes at the BBB.

The rate at which the drug crosses the BBB is determined by the permeability of the BBB to the drug, along with any transporter effects.[4] The net brain uptake rate can be measured at the *in vivo* BBB by *in situ* brain perfusion[5,6] and it represents the combined effect of passive permeability, plus active influx and efflux processes. Taken together, uptake rate and $K_{p,uu}$ are key elements in defining the brain entry of drugs.[7] However, they do not allow the prediction of time-dependent brain concentration profiles, and they can be difficult to scale between species. *in vivo* and *in situ* techniques such as microdialysis and brain perfusion can provide profiles, but are costly and time consuming and are therefore not routinely performed in early drug development. What is needed is a model framework incorporating the various rate processes and binding parameters involved in drug brain penetration, in which the kinetics of these processes is measured using routinely employed *in vitro* systems and which are then scaled to *in vivo* using a mechanistic strategy, to predict time-dependent pharmacokinetic (PK) profiles in a manner which allows extrapolation to man.

Physiologically based pharmacokinetic (PBPK) models have been successfully used from the early stages of drug development to predict time-dependent drug profiles in various body tissues based on *in vitro* input data and molecular and physicochemical properties.[8] Importantly, the physiological structure of the model facilitates interspecies scaling by the incorporation of the relevant species-specific parameters. Despite these advantages, very few PBPK models of the brain have been reported in the literature because of the complex, transporter-rich structure of the BBB which currently renders *in vitro–in vivo* extrapolations (IVIVE) difficult.[9] The few reported PBPK models of the brain to date either only consider drugs which are not transporter substrates,[10] or they estimate the rate constants of active transport by fitting to *in vivo* microdialysis data.[11–13] The success of a PBPK model for the prediction of brain PK depends on the selection of appropriate *in vitro* system(s) to estimate BBB permeability. If similarity in cell type is the only consideration, then logically primary brain microendothelial cell cultures[14] would be the system of choice. However, because these are not routinely implemented during industrial drug development, other surrogate systems used to measure membrane permeability must be evaluated. There has already been some success in comparing efflux ratios and permeability in various P-glycoprotein (P-gp)-expressing *in vitro* cell lines, such as Caco-2, with the *in vivo* brain K_p in preclinical species.[7,15] Because cell lines such as Caco-2 are often used to predict intestinal permeability despite not being derived from the jejunum, it could also be possible to use them to predict brain permeability, provided that suitable scaling methods are applied.

This paper focuses therefore on the determination of appropriate *in vitro* systems to predict BBB permeability for two CNS drugs, morphine and oxycodone. Despite significantly different *in vitro* affinities for the μ-opioid receptor, they demonstrate equipotency *in vivo* in the rat.[16] This has been explained by difference of at least sixfold between the $K_{p,uu}$ of oxycodone (~3) and morphine (0.3–0.5) for the same blood concentration because of their net transporter-driven influx and efflux at the BBB, respectively.[17] Here, a whole-body PBPK model was developed to predict morphine and oxycodone unbound brain concentration profiles using *in vitro* permeability data, and appropriate *in vitro–in vivo* scaling factors (SFs) were estimated. Finally, the evaluation of model extrapolation from rat to man was discussed.

MATERIALS AND METHODS

Model Structure

The whole-body PBPK and brain model was constructed using the software acslX (version 2.5.0.6, Aegis Technologies, Huntsville, Alabama) as depicted in Figure 1. The brain was divided into two separate compartments, one representing the brain vasculature, and the second representing brain tissue, separated by the BBB. The BBB transfer coefficients were determined as described below.

Determination of BBB Transfer Coefficients

The net uptake clearance across the BBB, CL_{uptake} (mL/min), as is often determined from *in situ* brain perfusion is given in Eq. 1:

$$\frac{dA_{br}}{dt} = CL_{uptake} C_{u,br,vasc} \tag{1}$$

where dA_{br}/dt is the rate of change of the amount of drug in brain, and $C_{u,br,vasc}$ is the arterial blood concentration which passes through the brain vasculature. However, because the transport of drug across the BBB is generally the result of both passive and active transporter-driven effects, Eq. 1 can be reparameterized as Eq. 2 to distinguish these separate

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