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Quantitative Prediction of Circadian Variation Impacts on Pharmacokinetics (PK): Dependence on Route of Administration in the Case of BCS/BDDCS Class II and CYP3A4 Substrate Drug Nifedipine

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Introduction

Many physiological processes which determine pharmacokinetics (PK) of drugs, including drug absorption, distribution, metabolism and excretion, follow circadian rhythm [1]. Although this may have impact on drug safety and efficacy depending on time of administration [2], potential effect of circadian variation is not regularly assessed during drug development. Physiologically based pharmacokinetic (PBPK) models for absorption and disposition such as those implemented within Simcyp Simulator [3] (Figure 1) are capable of incorporating circadian variations in physiology to quantitatively estimate their impact on PK and pharmacodynamics (PD). This can help with assessing the need to conduct any clinical studies to evaluate circadian effect (or otherwise). Gastric emptying rate and hepatic blood flow, among other factors, are known to show diurnal changes (reduced level in the evening/night as compared to morning/day) that may change the rate and extent of absorption of acid-labile drugs, enteric-coated formulations and drugs with significant gut-wall and hepatic metabolism. Here we examine such a case.

Purpose

To predict the nature and magnitude of the diurnal variations in pharmacokinetics (PK) of Nifedipine (NIF) after oral immediate release (IR) and intra-venous (IV) infusion administration and to compare the mean and population variability with clinical observed results.

Materials and Methods

All simulations were run in the Simcyp Simulator (V12 R1) using the Nifedipine compound file with permeability predicted from MDCK data, *in vivo* clearance option and full PBPK with Kp scalar of 0.58.

Known circadian variations in systems (physiological) data were considered with no attempt to adjust or fit any parameter to get better match between predicted and clinical circadian effect. Circadian variations in physiology included - gastric emptying rate (53.6% reduction [4]) and hepatic blood flow (12.33% reduction [5]) during evening as compared to morning.

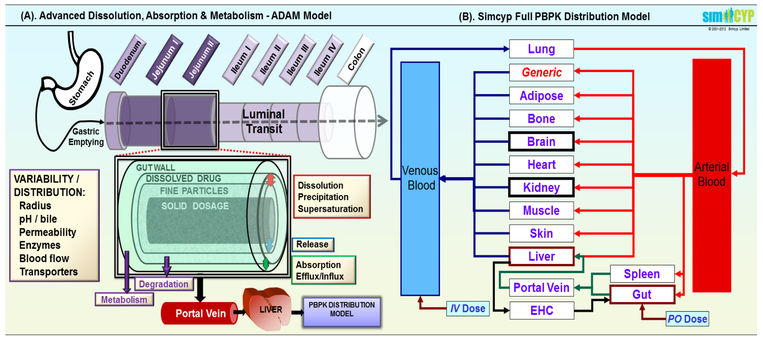

Figure 1. (A) ADAM Model [3]; [B] Simcyp full PBPK Distrubution Model

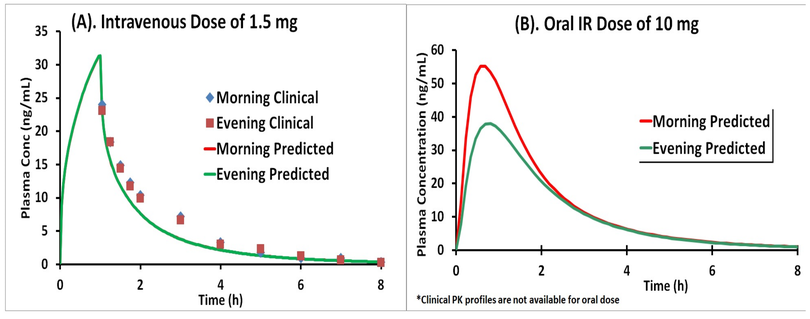

Figure 2. (A) Simulated mean PK profiles after IV and Oral administration in morning and evening overlaid with clinical data, where available

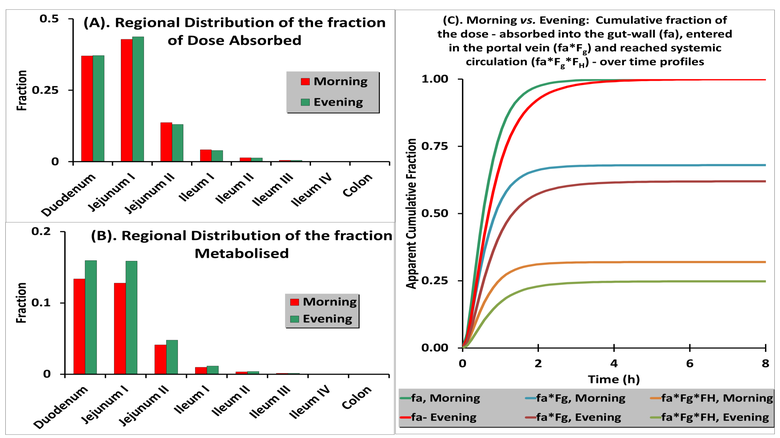

Figure 3. Morning versus evening regional distribution of (A) fraction absorbed; (B) fraction metabolised and (C) cumulative fraction of the dose - absorbed into the gut-wall (fa), entered the portal vein ($fa*F_g$) and reached systemic circulation ($fa*F_g*F_H$)

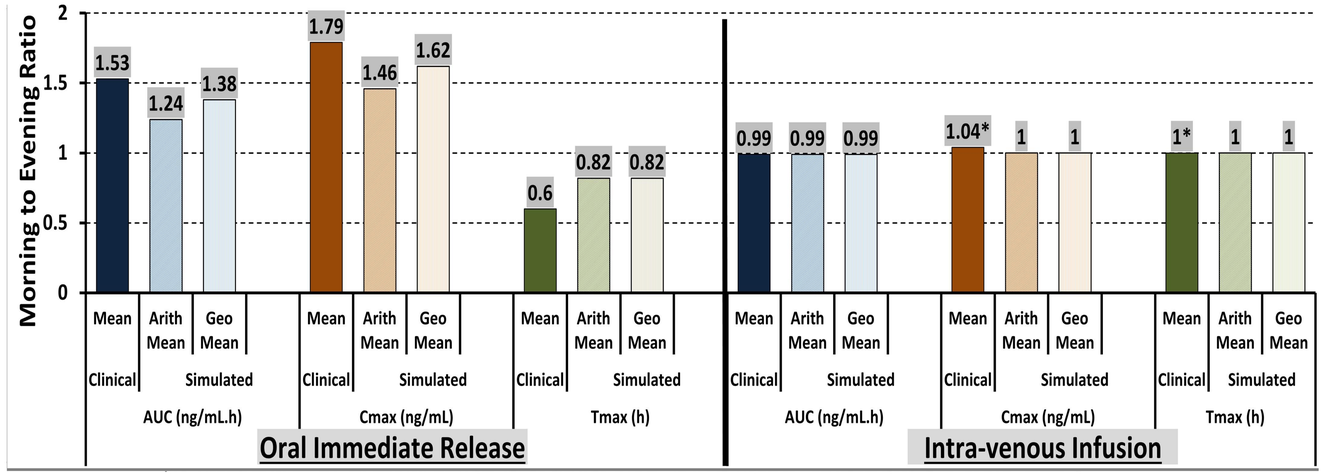

Figure 4. Morning to evening ratio of simulated (arithmetic and geometric mean) PK parameters after oral and IV administration compared with clinical (mean) results (* the maximum concentration reported in clinical study was measured at 3 minutes after the infusion was stopped)

Results and Discussion

The predicted plasma drug concentration (Cp) profiles of NIF IR and IV formulations in morning and evening overlaid with clinical values [6] are shown in Figure 2. NIF, a CYP3A4 substrate has significant gut-wall and hepatic metabolism. Hence, when GI transit of drug and blood flow to liver and villi get reduced in night, the rate at which drug is carried away from these first-pass metabolism sites namely gut-wall and liver is lowered leading to higher first pass metabolism in evening as compared to the morning Figure 3). This is evident from the significantly reduced C_{max} and AUC in night after oral dose but minimal difference in AUC or C_{max} after IV infusion (Figure 4).

Conclusions:

For the drug chosen in this study, PBPK models predicted the diurnal changes in PK profiles. Applying the modelling strategies used in this study and exploring various "what if" scenarios related to diurnal changes based on *priori* knowledge of the physiological changes, would help with to optimise the design of clinical studies regarding the timing of dose administration especially for narrow therapeutic index drugs and plan for assessment of circadian variations when needed. [**Note**: This poster was presented at 5th World Conference on Drug Absorption, Transport and Delivery (WCDATD) held at Uppsala, Sweden on 24-26 June, 2013]

References:

[1] Lemmer 1999 JPP 51, 887, [2] Polak et al. 2013 PAGE meeting Abstract ID 2877 [3] Jamei et al. 2009 AAPSJ 11(2), 225; [4] Goo et al. 1987 Gastroenterology, 93(3), 515; [5] Lemmer and Nold 1991, BJCP, 32, 627; [6] Lemmer et al. 1991 Chronobiol Int, 8, 485.