A Systematic Approach to PKPD Model Development to describe Sleep Effects of Compounds with Different Mechanisms of Action Using Semi-Mechanistic Markov Chain Models

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Objective

To describe the sleep effects of the non-benzodiazepine hypnotic agent Zopiclone (ZOP) 10 mg/Kg orally, and the selective 5-HT2$_A$ antagonist MDL 100,907 (MDL) 0.3 mg/Kg Intra-Peritoneal administration using a semi-mechanistic pharmacokinetic-pharmacodynamic (PK/PD) Markov-chain model previously developed for Zolpidem in healthy rats[1].

Methods

Experimental. For each 10 second interval, EEG data were converted into AWAKE, NREM or REM stages representing non-ordered categories. The data consisted of a 12 h baseline where EEGs were monitored in the absence of any type of perturbation and a 12 h period during which methylcellulose (MC) vehicle, ZOP or MDL were administered. (**Figure 1.** represents the study design).

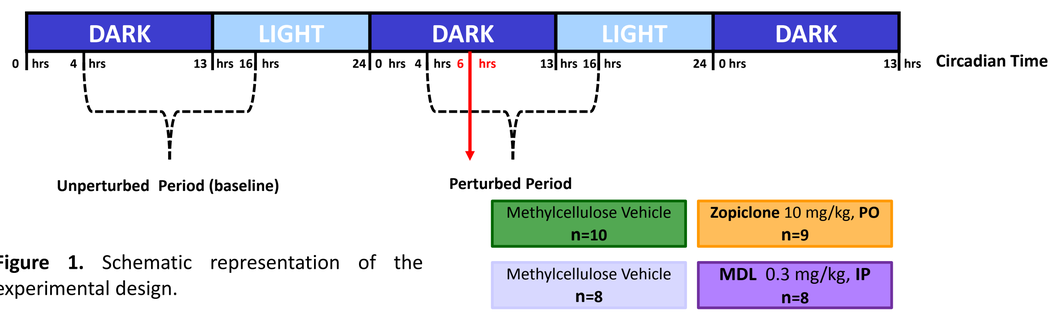

Figure 1. Schematic representation of the experimental design.

Data analysis. The time course of the 3 transition probabilities between the 3 sleep stages (**Figure 2**), was described using a non-homogeneous Markov chain model based on piecewise multinomial logistic functions[2], as previously described[1]. Literature PK data was used to generate concentrations of ZOP and MDL over time (**Figure 2,5**)[3-5].

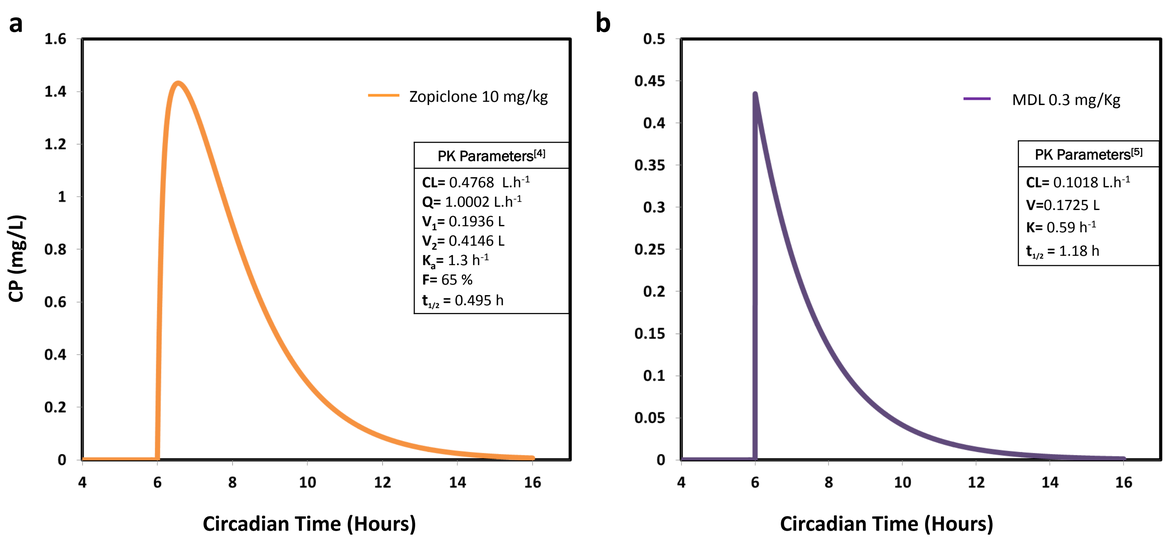

Figure 2. Typical model predicted profiles for the PK in plasma (**a** and **b**), induced drug effects. CP, plasma concentration of Zopiclone and MDL respectively.

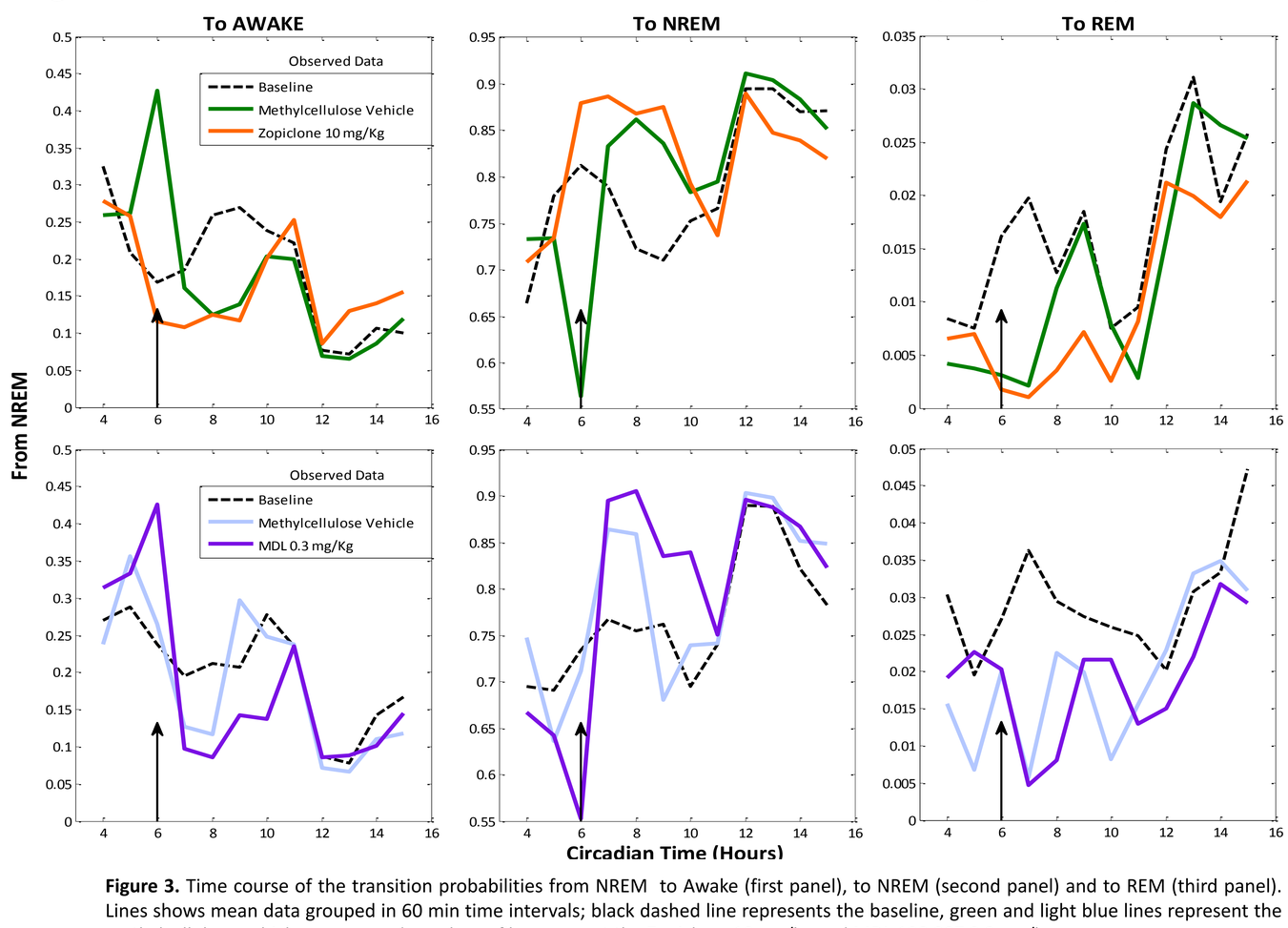

Figure 3. Time course of the transition probabilities from NREM to Awake (first panel), to NREM (second panel) and to REM (third panel). Lines shows mean data grouped in 60 min time intervals; black dashed line represents the baseline, green and light blue lines represent the methylcellulose vehicle; orange and purple profile represent the Zopiclone 10 mg/kg and MDL 100,907 0.3 mg/kg.

Results

Baseline model. A model selected previously[1] was used to generate VPCs for the baseline data from the new studies. Results indicated that this model was adequate to describe and predict the new data.

MC model. The effects of MC vehicle administered orally or IP were incorporated using a Bateman function to reflect an increase in the transition probability from NREM to awake as observed in the data.

***Drug effect model*.** Exploration of the time course of transition probabilities revealed that: ZOP effects were described using a turnover feedback model (**Figure 4.A**)[1, 6]. For MDL, the PK/PD models that best described the data were the link[7] or indirect response[8] (IDR) models (**Figure 4. B**).

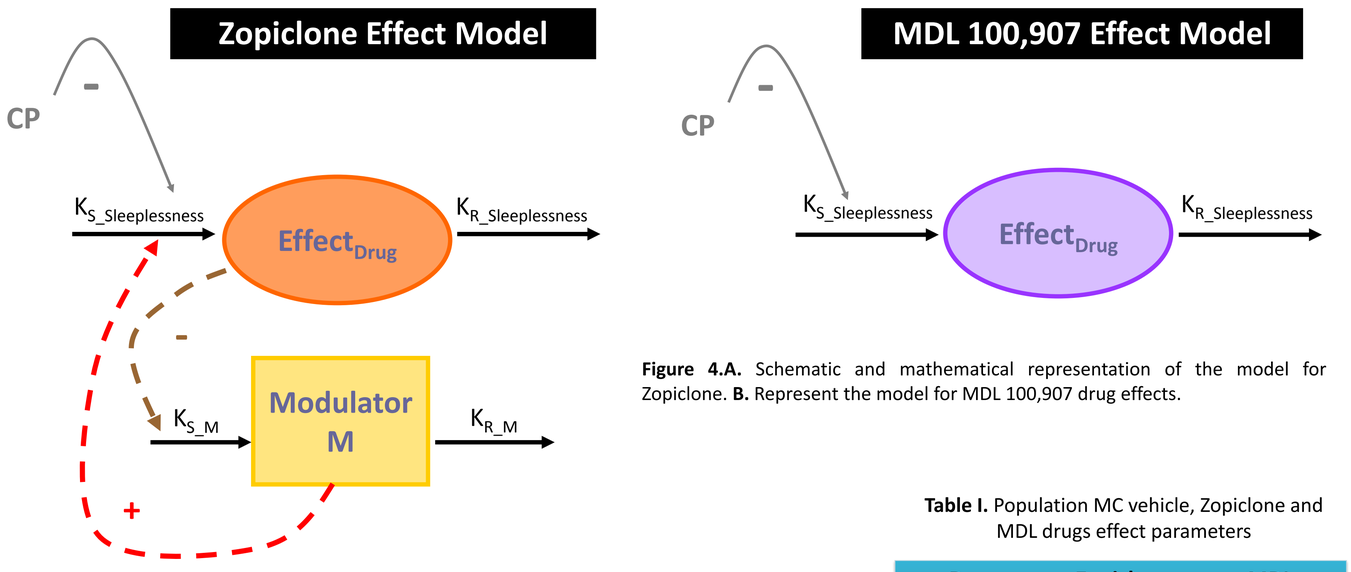

Figure 4.A. Schematic and mathematical representation of the model for Zopiclone. **B.** Represent the model for MDL 100,907 drug effects.

- ZOP exhibited a rebound effect approx. 8-10h after dosing, whereas such rebound phenomena were not observed in the data with MDL.
- MDL observed an increase in the transition probability from NREM to NREM and REM sleep stage for approximately 4 hours after dosing.
- ZOP and MDL elicited a temporal decrease in the transition probability from NREM to awake indicating that sleep was promoted (**Figure 2,5**).

Table I. Population MC vehicle, Zopiclone and MDL drugs effect parameters

Drugs	Zopiclone	MDL
Parameters	**Estimate**	**Estimate**
$K_{R\_Sleepless}$ (sec^{-1})	$1.49x10^{-2}$	$5.71x10^{-2}$
K_{R_M} (sec^{-1})	$2.87x10^{-4}$	-
IC_{50} (mg/L)	$1.03x10^{-1}$	$4.78x10^{-1}$
γ	$2.97x10^{-1}$	$1.55x10^{+1}$
Methylcellulose Vehicle		
Parameters	**Estimate**	**Estimate**
B1	13.20	17.70
K_1 (sec^{-1})	$1.02x10^{-2}$	$4.32x10^{-1}$
K_2 (sec^{-1})	$9.54x10^{-3}$	$3.98x10^{-1}$

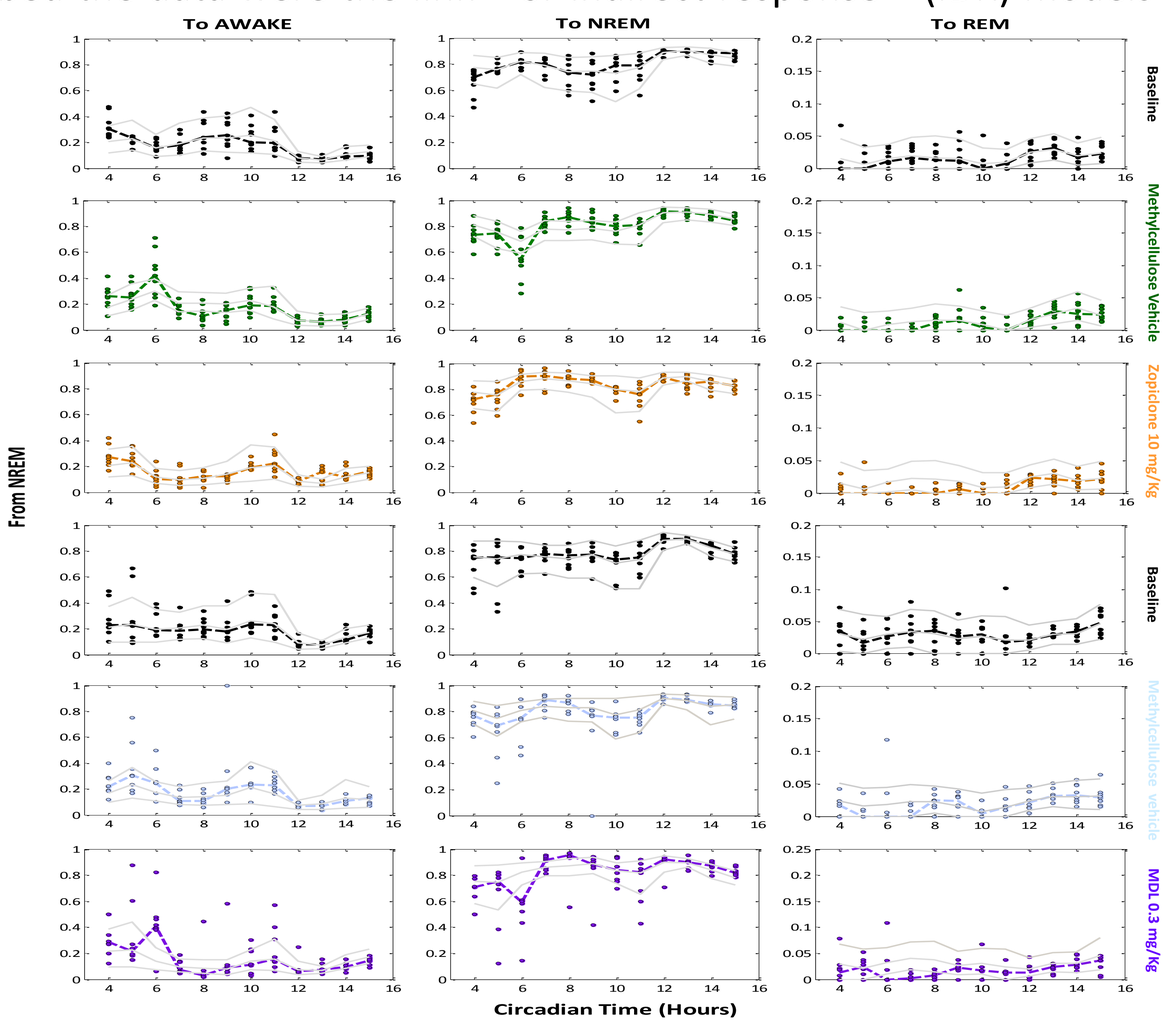

Figure 5. Visual predictive check of the transition probabilities from NREM to Awake, NREM and REM. Points, mean from raw data; Solid Lines, 5th, 50th, and 95th percentiles obtained from 1000 simulated animals. individual mean raw data; dashed lines, overall

Conclusions

The baseline response model used to describe the underlying physiological system (a non-homogeneous Markov chain model based on piecewise multinomial logistic functions) has been shown to be conserved across several studies, thereby supporting its application for future studies. Drug level effects need to be considered separately, contingent on their mechanism of action and the observed responses.

References

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