Modelling the sleep effects of Zolpidem in rats using non-homogeneous Markov chain models

Arianna Madrid[(1)], Nieves Vélez de Mendizabal[(1)], Kimberley Jackson[(2)], Andrew McCarthy[(2)], Dale M. Edgar[(2)], Iñaki F. Trocóniz[(1)]
[(1)]Department of Pharmacy and Pharmaceutical Technology; School of Pharmacy; University of Navarra; Pamplona 31080; Spain. [(2)] Eli Lilly and Company, UK

Objective

- To describe the sleep architecture in rats using Markov-chain model (MCM) and to investigate the impact of placebo/vehicle and Zolpidem on sleep model parameters.

Methods

Experimental

- Data were obtained from healthy Sprague-Dawley rats in which the electroencephalogram (EEG) was continuously recorded for at least two days of alternating dark/light cycles of 12 h duration.
- For each 10 second interval, EEG data were converted into awake, REM or NREM stages representing non-ordered categories.
- At 6 h clock time (ckt) during the second dark cycle, methylcellulose (MC) [saline group (n=16)], Zolpidem 10 mg/kg [group II, (n=16)], 20 mg/kg [group III, (n=20)], or 30 mg/kg [group IV, (n=11)] were administered orally (**figure 1** represents the study design).
- PK data were not available during the study.

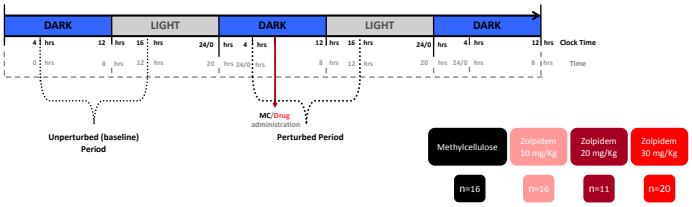


Figure 1. Schematic representation of the experimental design

Data analysis

- The time course of the nine transition probabilities, TP, (**figure 2**) was described using a non-homogeneous Markov chain model (**figure 3**) based on piecewise multinomial logistic functions (**figure 4**)[1].
- The pharmacokinetic model used to generate plasma concentrations of Zolpidem over time was taken from the literature[2,3].
- Analyses were performed using the LAPLACIAN estimation method with NONMEM VI[4].
- Model evaluation was done constructing visual predictive checks (VPCs) for TPs, the % of time spent in each sleep stage, the number of transitions, and the number of consecutive observations in each sleep stage.
- Non-parametric bootstrap performed with PsN[5] was used to obtain the precision of the model parameter estimates.

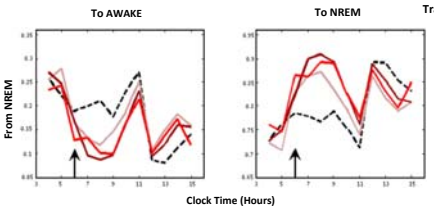


Figure 2. Time course of the transition probabilities from NREM to Awake (left panel) and to NREM (right panel). Lines shows mean data group in 60 min time intervals; black, baseline; pink, red and brown zolpidem 10, 20 or 30 mg/kg, respectively.

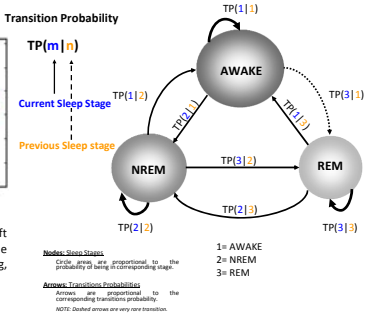
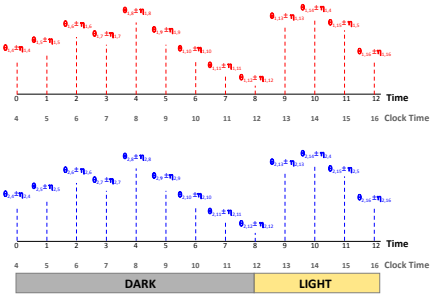


Figure 3. Schematic representation of the Markov chain Model



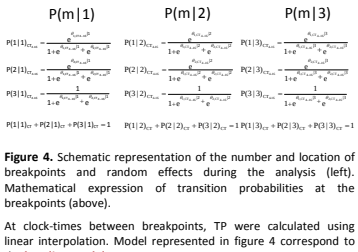


Figure 4. Schematic representation of the number and location of breakpoints and random effects during the analysis (left). Mathematical expression of transition probabilities at the breakpoints (above).

At clock-times between breakpoints, TP were calculated using linear interpolation. Model represented in figure 4 correspond to the **baseline model**.

Drug effect model (Effect$_{Drug}$)

- Exploration of the time course of raw transition probabilities revealed that Zolpidem elicited an:
  - Initial time dependent decrease in the transition probability from NREM to awake indicating the animals were more likely to remain asleep.
  - Increase in TP from NREM to AWAKE at later times which is interpreted as a rebound effect of Zolpidem.
- Drug effects including the rebound phenomena were described with a turnover feedback model (**figure 5**).

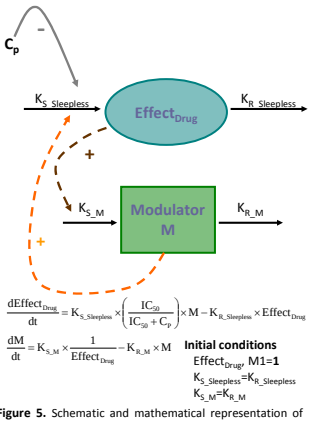


Figure 5. Schematic and mathematical representation of the model for drug effects.

Integrated model

- The model integrating baseline time course of TPs (figure 4), MC, and drug effects (figure 5) is presented in **figure 6**.
  - MC effect (Effect$_{MC}$) has the form of
    - Effect$_{MC}$ = **1** before MC administration
    - Effect$_{MC}$ = **1–B$_1$x[e** $^{-k1x(ckt-6)}$ **- e** $^{-k2x(ckt-6)}$**]** after MC administration.
  - γ, is a scale parameter.

Transition probabilities from NREM to:

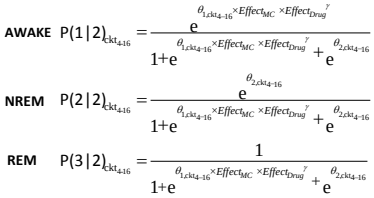


Figure 6. Mathematical representation of the integrated Markov-chain model. Random effects are omitted for clarity.

Results

- The simulated PK profiles of Zolpidem, the typical time course of induced drug effects and the pharmacodynamic relationship are represented in **figure 7$_{a-c}$**, respectively. **Table I**, lists the population parameter estimates corresponding to **Effect$_{MC}$** and **Effect$_{Drug}$**. **Figures 8 and 9** shows the results of the model evaluation.

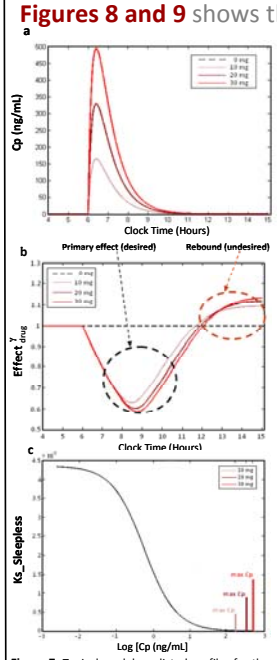


Figure 7. Typical model predicted profiles for the PK in plasma (a), induced drug effects (b), and pharmacodynamic relationship (c) Cp, plasma concentration of Zolpidem.

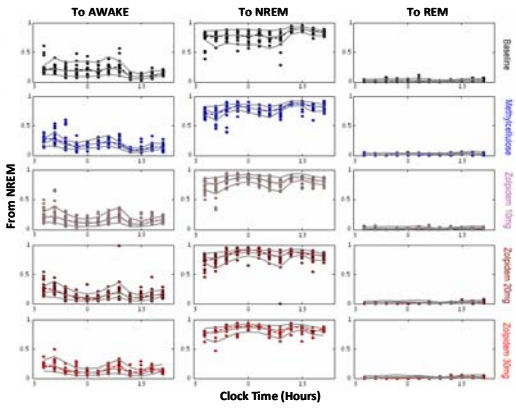


Figure 8. Visual predictive check of the transition probabilities from NREM to Awake, NREM and REM. Points, individual mean raw data; dashed lines, overall mean from raw data; solid lines, 5th, 50th, and 95th percentiles obtained from 1000 simulated animals.

Table I. Population MC and Zolpidem effect parameters

	Zolpidem	
	Estimate	Median(2.5th-97.5th)*
$K_{R\_Sleepless}$ (sec^{-1})	4.36 x 10^{-3}	4.37 x 10^{-3} (1.16-7.02x10^{-3})
K_{R_M} (sec^{-1})	6.87 x 10^{-5}	7.2 x 10^{-5} (7.2x10^{-6}- 1.3x10^{-4}
IC_{50} (ng/mL)	0.57	0.51 (0.16 - 8.32)
γ	0.146	0.15 (0.1 – 0.6)
	Methylcellulose	
	Estimate	Median(2.5th-97.5th)*
B_1	15.5	17.4 (12.6 – 34.4)
K_1 (sec^{-1})	2.42 x 10^{-3}	2.45 x 10^{-3} (1.6x10^{-3}- 2.9x10^{-3})
K_2 (sec^{-1})	2.5 x 10^{-3}	7.2 x 10^{-5} (1.6x10^{-5}- 3.1x10^{-3})

*, obtained from bootstrap analysis

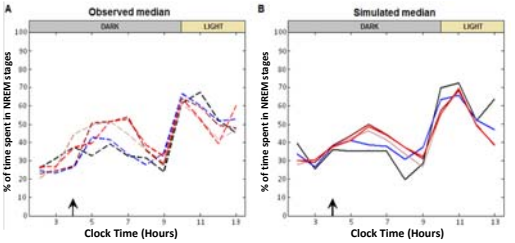


Figure 9. Comparison between the raw (left panel) and typical model simulated (right panel) profiles of the percentages of time spent in the NREM stage. Results are obtained from 1000 simulated animals. Arrows indicate time of administration.

- The model predicts a maximum increase in the % time spent in NREM with respect to the MC group of 7, 9 and 10 min, after administration of 10, 20 and 30 mg/kg of zolpidem.
- Maximum drug effects occurred at 2-3 h after administration.
- Rebound effects resulted in a 14, 12.4 and 14.2 decrease in the % spent in NREM after the 10, 20 and 30 mg/kg oral dose.
- Maximum rebound effects occurred 6-7 h after dosing, just at the first hour of the light cycle.

Conclusions

- The sleep architecture in rats was successfully described.
- The current analysis shows an application of the multinomial logistic approach applied through Markov chain models to described the time course of Zolpidem effects on sleep architecture in rats.
- The model presented here represents an integrated model including baseline, saline, and drug effect models.
- This type of approach supports the identification and the quantitative description of feedback mechanisms and represents a promising tool to describe the PD characteristics of different classes of sleep drugs.

References

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