Modeling Sleep using Markov Mixed Effects Models

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Background and Objective

Using Markov models to describe the complex pattern of sleep by modeling the probability of transiting from one stage to another has been done previously for the drug effect of temazepam[1].

The current analysis describes the effects of two drugs with different mechanism of action than temazepam and of each other, using Markov mixed-effect models.

The aim of this investigation was to characterize the time course of sleep stages and the concentration-effect relationship of drug X relative to placebo and to an active comparator using Markov models in patients with primary insomnia.

Methods

Data were obtained in a 4-way crossover study of low and high doses of drug X, a standard dose of an active control and placebo in 43 patients with primary insomnia. Sleep stages were measured for 8 hrs overnight at screening (baseline) and for 2 nights of dosing following each treatment.

The probability of transiting from a sleep stage to another was modeled as a function of relative nighttime, stage time, placebo effects and drug effects using NONMEM V, including between subject (BSV) and between occasion variability (BOV). Models for baseline, placebo and drugs were developed for each transition, and these were later merged into a joint sleep model used for simulations.

A posterior predictive check (PPC) and 3 simulation scenarios were performed using the joint sleep model. To assess the PPC and the simulations, 18 pre-defined efficacy statistics used to describe sleep architecture and quantity were calculated both for the observed and the simulated data.

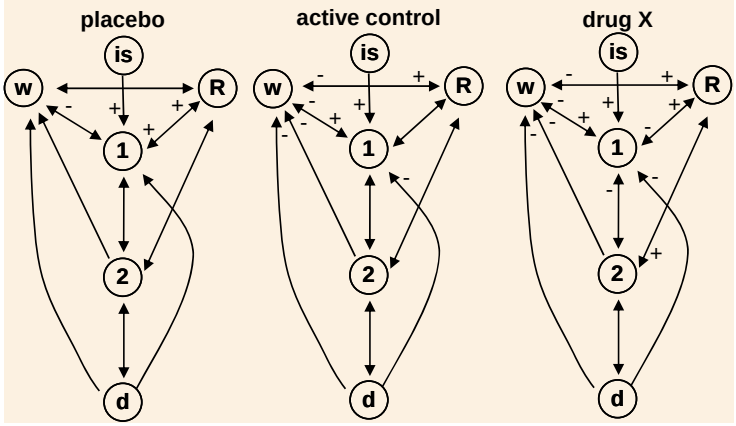

Figure 1. *The effects found of placebo, the active control and drug X. An arrow is indicating that the transition was modeled. is – initial sleeplessness, w – wake, R – REM sleep, 1 – stage 1, 2 – stage 2, 3 – stage 3, 4 – stage 4, d – deep sleep (stage 3 and 4). + drug is increasing transition probability, - drug is decreasing transition probability.*

Results and Discussion

Out of 20 possible transitions, 15 were chosen to be modeled, based on the amount of information and abundance of appearance for the transitions. An additional stage was added to describe the transition probability the first time of falling asleep; initial sleeplessness. All modeled transitions are shown in figure 1, indicated with an arrow.

The baseline model, for almost all transitions, was best described by a piece-wise linear function of both night time and stage time. The piece-wise function had two slopes and an internal breakpoint, which was either fixed at the median of the data of the transition or estimated. BSV was characterized in most transitions and BOV was estimated in about half of the transitions.

Placebo effects were found on 4 transitions: in both directions between REM sleep and stage1, from initial sleeplessness to stage 1 and from stage1 to awake.

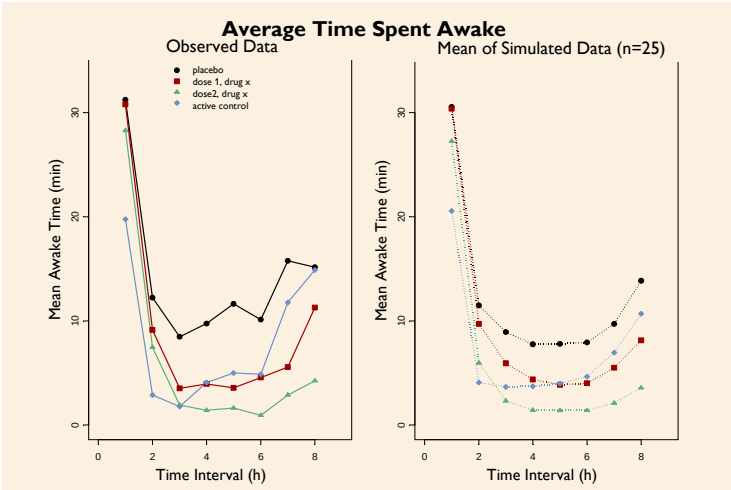

Figure 2. *Average time spent awake in each time interval of 1 hour for all treatments. The left panel is showing the observed data and the right panel is showing the mean of 25 simulated data.*

A majority of the drug effects of drug X were best described using a linear effect compartment model. The drug effects of the active control were all described with a linear model with population predicted concentrations as driving force. The placebo effects and the drug effects are summarized in figure 1.

The observed data were well predicted by the model, figure 2 and 3. 16 of 18 efficacy parameters defined for the PPC were well described by the simulation model. The number of awakenings for placebo was slightly overpredicted and so was sleep efficiency in the last part of the night (6-8 hours of sleep) for placebo and active control.

The predicted effects of changing the dose of drug X were small compared to changing the dosing schedule. For example, changing the dosing from ½ hour to 1 hour prior to bedtime resulted in a predicted decrease in time to fall asleep from 35 minutes to 21 minutes. Hence, giving drug X earlier before going to bed would increase the efficacy of the drug in the early part of the night.

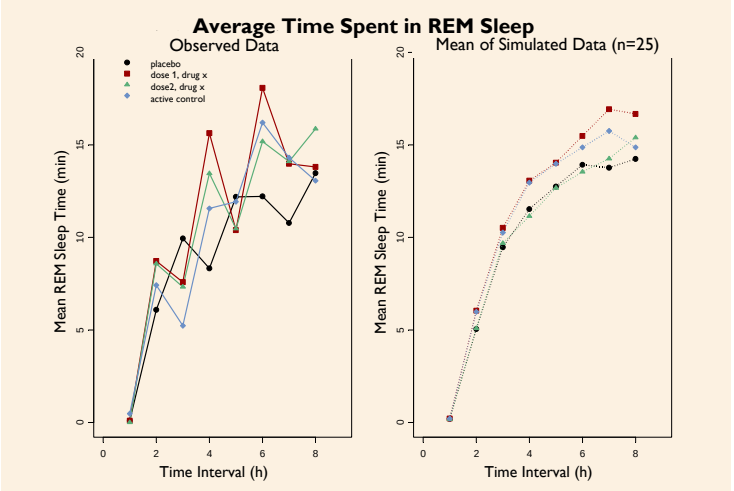

Figure 3. *Average time spent in REM in each time interval of 1 hour for all treatments. The left panel is showing the observed data and the right panel is showing the mean of 25 simulated data.*

Conclusion

The joint sleep model adequately describes the sleep pattern during a night after no treatment, placebo, low and high dose of drug X and active control. The simulations indicate a change in the time to fall asleep by administering drug X at least 1 hour prior to bedtime.

1. Karlsson MO *et al.* A pharmacodynamic markov mixed-effects model for the effect of temazepam on sleep. *Clinical Pharmacology and Therapy* 2000; 68(2): 175-88