Background and Objective

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

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 transitioning 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.

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 in 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 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.

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.