Drug Effects on Sleep Data from a 28-Day Clinical Study in Insomniac Patients: Covariate Analysis Using a Multinomial Mixed-Effect Markov-Chain Model

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Introduction

- Sleep quality is usually objectively assessed through polysomnography (PSG), from which clinical efficacy endpoints like sleep latency (LPS) or wake time after sleep onset (WASO) are evaluated.
- A new molecule under development (NCE) showed to decrease both LPS and WASO, to similar extent at low and high dose, and to greater extent after acute than chronic dosing: concentration-dependent tolerance was observed on WASO. Moreover, the NCE decreased time spent in slow-wave sleep (tSWS).
- Recently, a multinomial mixed-effect Markov-chain model has been validated for the description of PSG data through the modeling of probabilities of transitioning between the various stages of sleep during bedtime [1,2].

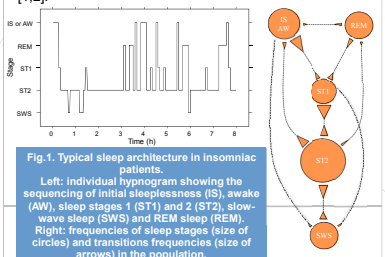

Fig.1. Typical sleep architecture in insomniac patients. Left: individual hypnogram showing the sequencing of initial sleeplessness (IS), awake (AW), sleep stages 1 (ST1) and 2 (ST2), slow-wave sleep (SWS) and REM sleep (REM). Right: frequencies of sleep stages (size of circles) and transitions frequencies (size of arrows) in the population.

Objective

The aim of this work is the evaluation of the drug effects on sleep architecture through the multinomial mixed-effect Markov-chain model, as an aid in the comprehension and extension of the knowledge gathered from the macroscopic clinical endpoints.

Methods

Data

- 342 subjects with primary insomnia were enrolled in a 28-day placebo-controlled parallel clinical study evaluating the sleep effect of a NCE (two doses).
- PSG data from nights 1 and 27 were analyzed.
- Plasma concentration values were measured 30 min before lights out and 90 min after lights on. A two-compartment mixed-effect linear PK model with first order absorption and absorption lag for depot compartment had been developed on a previous smaller study and was used to estimate the concentration-time profile during nighttime for each subject.

Multinomial logistic functions in a Markov-chain model

- Each individual sequence of sleep stages (initial sleeplessness IS, following wake AW, stage 1 ST1,stage 2 ST2, slow-wave sleep SWS and REM sleep) was treated as a Markov chain and transition probabilities were modeled through multinomial logit functions of nighttime and time after last sleep stage change ('stage time') [2,3]:

$$g_{ikm}(\tau) = \log \frac{p_{ikm}(\tau)}{p_{ikk}(\tau)}, \qquad \text{(Eq. 1)}$$

where $p_{ikm}(\tau)$ is the probability of moving from sleep stage k at time τ-1 to sleep stage m at time τ for subject i, and similarly for $p_{ikk}(\tau)$.

- All logit functions were piecewise linear, with one knot each. Logits at nighttime values A = 0.5 h after medication, B (to be estimated for each couple (k, m, $k \neq m$)) and C = 8.5 h can be expressed with a vector depending on stage time t:

$$\mathbf{G}_{ikm}(t_i) = [G_{ikmA}(t_{iA}), G_{ikmB}(t_{iB}), G_{ikmC}(t_{iC})]^T \qquad \text{(Eq. 2)}$$
$$= [(g_{ikmA} + \tilde{g}_{ikm} + s_{ikm}(t_{iA})), (g_{ikmB} + \tilde{g}_{ikm} + s_{ikm}(t_{iB})), (g_{ikmC} + \tilde{g}_{ikm} + s_{ikm}(t_{iC}))]^T.$$

Covariates analysis with plasma concentrations

- Stepwise forward inclusion followed by backward elimination [3], both based on log-likelihood ratio test, were used to attempt the inclusion of plasma concentration effects on logit values at any nighttime or stage time knot.
- Linear and piecewise linear (with one estimated knot) additive functions on logits were tested. Therefore Eq. 2 needs to consider concentration values *conc* and their effect *c* as follows:

$$\mathbf{G}_{ikm}(\mathbf{t}_i, \mathbf{conc}_i) = [G_{ikmA}(t_{iA}, conc_{iA}), G_{ikmB}(t_{iB}, conc_{iB}), G_{ikmC}(t_{iC}, conc_{iC})]^T$$
$$= [(g_{ikmA} + \tilde{g}_{ikm} + s_{ikm}(t_{iA}) + c_{ikmA}(t_{iA}, conc_{iA})), (g_{ikmB} + \tilde{g}_{ikm} + s_{ikm}(t_{iB}) + c_{ikmB}(t_{iB}, conc_{iB})),$$
$$(g_{ikmC} + \tilde{g}_{ikm} + s_{ikm}(t_{iC}) + c_{ikmC}(t_{iC}, conc_{iC}))]^T. \qquad \text{(Eq. 3)}$$

Here, using for each k *a* as zero stage time, b as the central estimated knot for stage time effect and c as the median observed stage time, four options are tested for modeling c at the different nighttime and stage time points of interest:

$$c_{ikmA}(t_{iA}, conc_{iA})|_{t_{iA}=a} = \begin{cases} 0 \\ \text{piecewise\_linear}_A(conc_{iA}) \text{ or linear}_A(conc_{iA}) = \alpha \\ \text{piecewise\_linear}_C(conc_{iA}) \text{ or linear}_C(conc_{iA}) = \beta \\ \alpha + \beta \end{cases}$$

$$c_{ikmA}(t_{iA}, conc_{iA})|_{t_{iA}=b} = \begin{cases} 0 \\ \text{piecewise\_linear}_A(conc_{iA}) \text{ or linear}_A(conc_{iA}) = \alpha \\ \text{piecewise\_linear}_C(conc_{iA}) \text{ or linear}_C(conc_{iA}) = \chi \\ \alpha + \chi \end{cases}$$

$$c_{ikmA}(t_{iA}, conc_{iA})|_{t_{iA}=c} = \begin{cases} 0 \\ \text{piecewise\_linear}_A(conc_{iA}) \text{ or linear}_A(conc_{iA}) = \alpha \\ \text{piecewise\_linear}_C(conc_{iA}) \text{ or linear}_C(conc_{iA}) = \delta \\ \alpha + \delta \end{cases} \qquad \text{(Eq. 4)}$$

and equivalently for nighttime values B and C.

- Stepwise drug effect selection was done on night 1 and 27 separately.
- Each step in the analysis was performed with NONMEM VI. Stepwise covariate modeling was automated through PsN.

Results

- Several statistically relevant effects were included in the final Markov-chain model. The probabilities of most transitions were modified by either linear or piecewise linear functions of the estimated NCE concentration time-course (Fig. 2).
- Significant drops in the objective function values were mostly connected to the effects added on the transitions from ST1 and ST2.

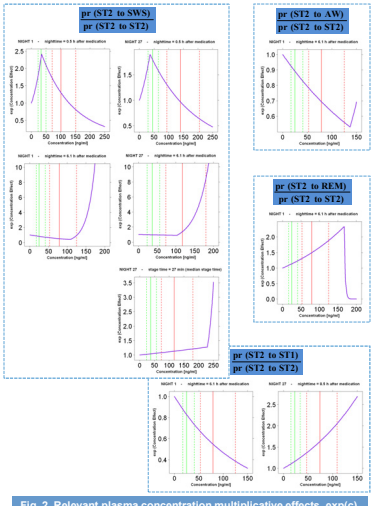

Fig. 2. Relevant plasma concentration multiplicative effects, exp(c), on logits (see Eq. 4) estimated for the typical individual (purple line). The odds involved in each panel are specified by the blue squares (see Eq. 1).

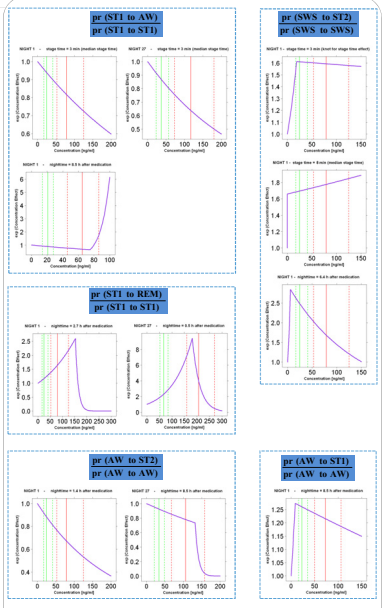

Fig. 2. Cont'd.

- The final model could separate the drug effects observed on LPS, WASO and tSWS into more detailed effects on the transition probabilities between AW, ST1, ST2, SWS and REM.
- The effect on LPS is likely mainly promoted by reduced probability of transitioning from ST1 to AW at both nights 1 and 27.
- With respect to WASO, in the second part of night 1 increasing plasma concentrations increased the transition probability ST2 to REM and decreased the transition probabilities ST2 to AW and ST2 to ST1 (the latter was increased at night 27 instead). Again in the second part of night 1 the NCE promoted transition AW to ST1, but with stronger effect at low concentrations.
- With respect to tSWS, in the first part of the night transitions from ST2 to SWS were promoted by lower exposures and reduced by higher exposures. In the later part of night 1, transitions from SWS to ST2 were more likely under drug treatment, mostly at low concentrations.

Conclusions

- Stepwise forward inclusion and backward elimination based on statistical criteria was able to develop a second-stage multinomial Markov-chain model including drug effects on many parameters.
- The final model provided a valuable explanation of the reducing effects observed on the clinical endpoints LPS, WASO and tSWS, and on the concentration-dependent tolerance observed on WASO.
- The multinomial Markov-chain model appeared a suitable tool for the exploration of drug effects on sleep architecture.

References

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