PK-PD modeling of Wake after Sleep Onset time-course

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Introduction

- Wake after Sleep Onset (WASO) quantifies the night time spent awake after falling in a persistent sleep state and is considered one of the key sleep parameters to characterize the effect of a hypnotic drug.
- SB-649868 is a potent orexin antagonist with demonstrated ability of decreasing WASO. A pharmacokinetic-pharmacodynamic (PK-PD) model using total WASO (i.e., WASO on the whole night) has recently been developed [1].

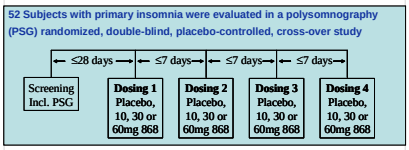
Objectives

a) To model SB-649868 effect on WASO time course (i.e., WASO by hour), and to compare WASO time-course vs. total WASO model outcomes.
b) To evaluate the impact of these PK-PD models on the power calculation for a new dose with an improved formulation.

Methods

Data

Data were obtained from a 2-days polysomnography (PSG) study. The pharmacokinetic profile of SB-649868 were also investigated after 2 consecutive days dosing.



Model Development

- PK profiles were modeled with a one compartment oral with absorption lag ('model PK1'). Log-normal inter-individual variability and inter-occasion variability were assumed for each model parameter (clearance CL, volume V, absorption rate constant KA and lag time ALAG1).
- Modeled PK profiles were then used to develop the PK-PD model on WASO time-course
- The final PK-PD model (on **WASO time-course**) was validated through goodness-of-fit plots and visual predictive check (VPC) on both WASO time-course and total WASO.
- VPC on total WASO was compared with the one obtained from the PK-PD model on **total WASO** [1].

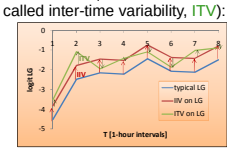
Simulations / Power Calculation

- The model on WASO time-course ('model B') and the model on total WASO ('model A') were used to predict total WASO after treatment with different doses using an improved formulation (1000 simulated individuals).
- New formulation was modeled with a 1-compartment PK model as the old formulation but with no inter-occasion variability and reduced inter-individual variability ('model PK2').
- Power calculation was performed using simulations from the two models for a dose not previously explored (20 mg).

Results

PK-PD model

- The final model for WASO time-course assumed that each contribution to total WASO (observed at 1-hour intervals), LG_T, T in [1, 8], was described by its own typical parameter, in the logit scale.
- The individual deviation from the typical logit value was assumed to belong to a normal distribution and correlated to the deviations for the same subject in the other intervals (one ETA for all LG_T, IIV, plus 8 ETAs, one for each LG_T, taken from a 'SAME' OMEGA, called inter-time variability, ITV):



- First night effect and treatment effect (with different values for each LG_T) were found to be statistically significant. Inter-occasion variability (IOV) was also considered, with a unique value for all LG_T:

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LG1=THETA(1)+DAY2*THETA(2)+IIV+ITV+IOV+TRT*THETA(Z)
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- A Weibull model was found to best describe the concentration-related effect:

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; TIME can take values in [2, 9]
; T is (TIME- 1)
; WASL is LGT
; F is the drug concentration at time TIME
WASO=60*EXP(WASL)/(1+EXP(WASL))
EFF=0
IF (DOSE.GT.0.AND.TIME.GT.2) THEN
  EFF=WASO*(EXP(-(F/TB)**(-ALPHA)))
ENDIF
WASOEF=WASO-EFF
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- ALPHA and TB were assumed to be described with two parameters each, one at TIME in [2, 3], one for TIME > 3. A first night effect and log-normal inter-individual variability (IIV) were assumed on TB, with no differences among TIME values.
- All parameter values are shown in Table I.
- VPC showed good performance of the model for both WASO time-course (Fig. 1) and total WASO (Fig. 2, right panel).

Table I. Parameter estimates for PK-PD model on WASO time-course. Standard errors are shown within parenthesis.

T	1	2	3	4	5	6	7	8
typical values of LG	-4.53 (0.43)	-2.48 (0.30)	-2.15 (0.22)	-2.22 (0.18)	-1.44 (0.21)	-2.07 (0.22)	-2.12 (0.24)	-1.49 (0.30)
shift of LG at day 2	0 FIX	-0.94 (0.25)	-0.85 (0.20)	-0.42 (0.19)	-0.87 (0.22)	0 FIX	0 FIX	0 FIX
TB	not used	458 (467)				33 (25)		
ALPHA	not used	0.49 (0.14)				0.46 (0.07)		
shift of LG with treatment	0.76 (0.47)	0.61 (0.39)	0.44 (0.35)	1.37 (0.38)	0.93 (0.35)	1.13 (0.42)	1.66 (0.56)	2.27 (0.93)
Other parameters not dependent on T								
relative deviation of TB at day2	0.90 (0.22)	additive error	0.18 (0.05)	prop. error		0.92 (0.02)		
var. IIV on LG	0.24 (0.07)	var. ITV on LG	0.28 (0.08)	var. IOV on LG		0.70 (0.12)	var. IIV on TB	1.57 (0.83)

VPC on WASO time-course ('model PK1' & 'model B')

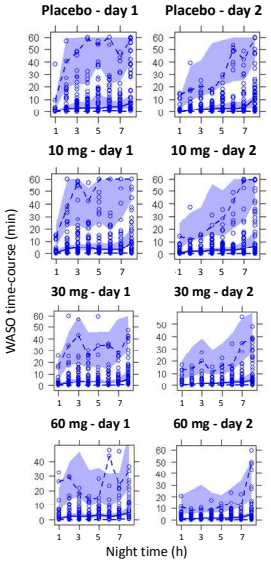

Fig. 1. Results from visual predictive check on WASO time-course. 'Model PK1' and 'model B' are used.

PK-PD models comparison

VPC

When comparing the PK-PD model on WASO time course ('model B') to the previous one on total WASO ('model A'), similar outcomes were obtained on the VPC level (Fig. 2). IIV is slightly over estimated in the former and slightly under estimated in the latter.

VPC on total WASO ('model PK1')

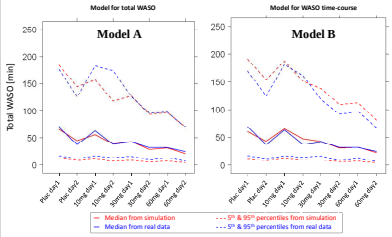

Fig. 2. Results from visual predictive check on total WASO.

Simulations with new formulation

'Model B' reduces residual unexplained variability (RUV) (Fig. 3): in the simulations using the improved formulation RUV dropped from 30% with PK-PD model on total WASO to 10% with PK-PD model on WASO time-course.

Total WASO simulations with 'model PK2'

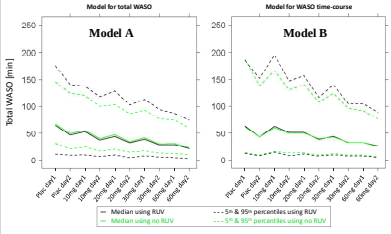

Fig. 3. Statistics on simulated values of total WASO with and without residual unexplained variability. 'Model PK2' is used together with PK-PD model for total WASO (Model A) or for WASO time-course (Model B).

'Model A' appears to associate most of the PD data variability to PK variability: consequently, variability reduction in the formulation (variance on CL IIV from 0.18 to 0.10 $[L/hr]^2$, variance on CL IOV from 0.10 to 0 $[L/hr]^2$) produces strong variability reduction in the simulations in Fig. 3, left panel. On the contrary, it appears that the new PK-PD model ('model B') is less influenced by PK variability (Fig. 3, right panel).

Power Calculation

The different IIV variability estimates in the two PK-PD models bring to different outcomes for power calculation (PK2, 20 mg, n=50 subjects): the power of detecting an effect size in total WASO of 11 minutes at α=0.05 is 56% with the new PK-PD model and 74% with the old one.

Conclusions

- A new PK-PD model has been developed for accurately assessing both the time-course and the total WASO, after treatment with SB-649868.
- Residual unexplained variability was reduced considering the time-course model instead of the total WASO model proposed in [1].
- Variability estimation is crucial when characterizing the potential effect of changes in doses and formulation to properly design future studies.

References

- [1] Zamuner S, Nucci G, Bettica P, Gerrard P, Squassante L, Gomeni R. *SLEEP*, Volume 32, Abstract Supplement, 2009. Abstract nr 0853

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