Quantification of the effect of AZD5213 on sleep in patients with Alzheimer's disease or mild cognitive impairment using a two-state Markov model

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Background

H_3 antagonists have been extensively investigated for the (symptomatic) treatment of cognitive disorders, such as Alzheimer's disease (AD) or mild cognitive impairment (MCI).

H_3 antagonists are effective across multiple cognitive domains (attention, memory) in preclinical studies at high receptor occupancy. However, clinical administration of this class of drug is often accompanied by alterations in sleep patterns. This may be the result of enhanced histamine release during prolonged H_3 receptor occupancy (extending into the night). Therefore, in a Phase 2 study in patients with mild AD and MCI the effect of AZD5213, a novel and highly selective histamine H_3 antagonist, on sleep was investigated.

Objectives

To quantify the effect of AZD5213 on sleep in patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI)

To predict the total time awake for a range of dose strengths

Methods

A PK model was developed to describe the plasma AZD5213 concentration-time profiles. The highly correlated longitudinal data was analyzed using a **Markov modeling approach**, in which **two states** were considered, WAKE and SLEEP with the latter obtained by merging the states REM, Sleep Stages 1, 2, 3 and 4.[1] It was investigated if placebo and/or modeled AZD5213 concentration influenced the intensity of acquisition (u) and clearance of sleep (v). For both the PK and PK-PD analysis NONMEM was used.

Study design

81 patients with mild AD or MCI were randomized in this double-blind, parallel group, placebo-controlled study of 4 weeks of treatment of three different doses of AZD5213 (low-med-high).

Blood samples were taken to evaluate the pharmacokinetics (PK) of AZD5213 at Weeks 2 and 4.

Repeated, nightly polysomnography (PSG) assessments were conducted at baseline (Nights -1 and -2), at Week 2 (Nights 13 and 14) and at Week 4 (Nights 27 and 28).

During the PSG assessments the percentage of the time that the patient is awake was reported, as well as the sleep state per 30 second epoch, between lights on and lights off (8 hours). In total 960 observations (percentage awake and sleep state) per patient per night were reported.

Two-State Markov Model

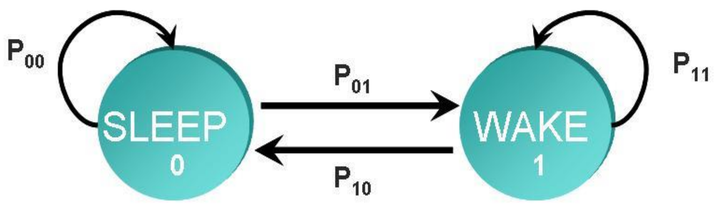

Figure 1: Schematic representation of a two-state Markov model

P_{00}: probability of staying in the SLEEP state; P_{01}: probability of transitioning from SLEEP to WAKE state; P_{11}: probability of staying in the WAKE state; P_{10}: probability of transitioning from WAKE to SLEEP state.[1]

Base Model

Probability of transitioning from **SLEEP → WAKE** state

$$P_{01}(t) = \frac{v}{u+v} \cdot (1 - e^{-(u+v)\cdot t})$$

Probability of transitioning from **WAKE → SLEEP** state

$$P_{10}(t) = \frac{u}{u+v} \cdot (1 - e^{-(u+v)\cdot t})$$

Baseline, placebo and drug concentration can influence the rate constant for aquisition of sleep (u) or clearance of sleep (v):

$$x = e^{X_0 + BSL_x + PLAC_x + DRUG_x}$$

with x is *u* or *v*

Baseline, Placebo, Drug Effect

Baseline (BSL_x)

$$BSL_x = \frac{KAP_x \cdot TGM_x \cdot (KAP_x - KP_x) \cdot (e^{-KP_x \cdot t} - e^{-KAP_x \cdot t})}{e^{-KP_x \cdot \frac{LOG(\frac{KAP_x}{KP_x})}{KAP_x - KP_x}}}$$

Placebo effect ($Plac_x$) No placebo effect

Drug effect ($DRUG_x$) $DRUG_u = \frac{E_{max} \cdot C_p^{\gamma}}{EC_{50}^{\gamma} + C_p^{\gamma}}$

$$DRUG_v = SLP \cdot LOG(C_p + C_0)$$

Results

- A two-compartment PK model with first order elimination and lagged first order absorption described the PK data adequately (data not shown).
- The observed and simulated number of patients being awake *vs.* time after start of PSG assessment at Nights 13 and 14 per treatment group are similar indicating the adequate model performance of the two-state Markov model (Figure 2). The model parameters were estimated with adequate precision (Table 1).
- Plasma AZD5213 concentrations inhibited transitions to sleep more markedly than transitions to wakefulness.
- Simulations for various doses (low to high) at steady-state (Week 2) demonstrated that overall time awake increased with increasing dose with a minimal effect at low doses. Clinically important sleep disturbances were associated with receptor occupancies above 70% during the entire night (Figure 3).[2]

Table 1: Parameter estimates from two-state Markov model

		Acquisition of sleep (u) Value [CV[a]]	Clearance of sleep (v) Value [CV[a]]
Baseline intensity	x_0	-5.86 [-0.5]	-4.37 [-4.7]
Maximum increase in baseline intensity	TGM_x	1.28 [-2.9]	-2.17 [-9.6]
Half-life increase in baseline intensity[b]	$HLKA_x$ (s)	7560 [1.4]	435 [11.4]
Half-life clearance in baseline intensity	$HLKP_x$ (s)	Equal to HLKA	50100 [12.6]
Drug effect	E_{max}	-0.813 [-3.8]	
	EC_{50} (nM)	4.33 [3.4]	
	γ	5.41 [18.2]	
	SLP (1/nM)		-124 [-7.2]

[a]*Coefficient of variation, calculated as SE/Value*100%*
[b]*HLKA and HLKP are defined as ln(2)/KA_x and ln(2)/KP_x, respectively*

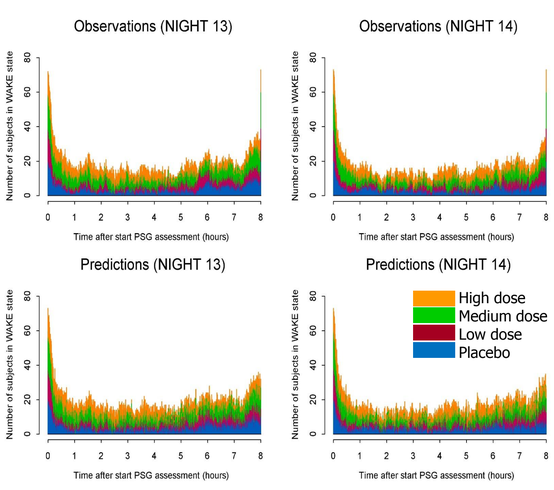

Figure 2: Observed and simulated number of patients being awake vs. time after start of PSG assessment (at Nights 13 and 14) per treatment group
Plots are stacked.

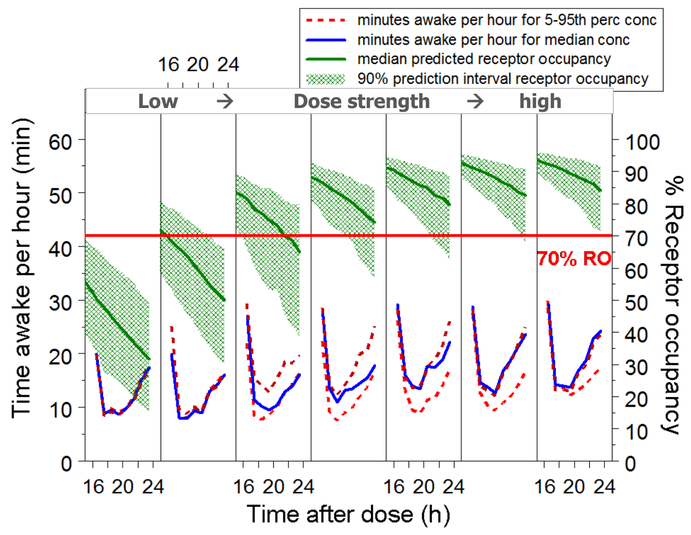

Figure 3: Simulations (100 replicates) of time course of time awake during the night (left y-axis) and receptor occupancy (right y-axis) at steady-state following QD administration of different doses AZD5213. *Presented is the time course of the time awake for a typical 90kg patient (median: blue line; 5-95th percentile: red dotted line) and the time course of the median receptor occupancy (green line) and 90% prediction area (green striped area)*

Conclusions & Perspectives

A two-state Markov model was successfully applied to describe the influence of placebo and AZD5213 on the sleep-wake pattern in patients with AD and MCI.

Plasma AZD5213 concentrations inhibited directly the transitions to sleep and the transitions to wakefulness with a stronger inhibition of transition to sleep.

Simulations demonstrated doses at or below medium strength are not expected to affect sleep to a great extent.

References

[1] Diack C., Ackaert O., Ploeger B.A., van der Graaf P.H., Gurrell R., Ivarsson M., Fairman D. A hidden Markov model to assess drug-induced sleep fragmentation in the telemetered rat. *Journal of Pharmacokinetics and Pharmacodynamics*, 38(6):697–711, 2011.

[2] Jucaite A. et al. AZD5213: a novel histamine H3 receptor antagonist permitting high daytime and low nocturnal H3 receptor occupancy, a PET study in human subjects. *International Journal of Neuropsychopharmacology,* 16(6):1231–1239, 2013.