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ABSTRACT

Objectives: To develop a population kinetic-pharmacodynamic (kPD) model that describes the pattern of sleep and quantifies the sleep changes in Wistar rats after different oral doses of citalopram.

Methods: Citalopram was administered orally (PO) to 91 Wistar rats at different doses: vehicle (n=17), 0.3 (n=8), 1 (n=11), 2.5 (n=8), 5 (n=11), 10 (n=10), 30 (n=18) and 60-mg/kg (n=8). Citalopram and n-desmethylcitalopram concentration measurements were not available in this study, therefore simulated profiles were used derived from a previously published PK model by Velez de Mendizabal et al. [1] for Wistar and Sprague-Dawley rats and used as input to the PD model. No Inter-subject variability was included in those profiles, although weight was taken into account to adjust parameters. Three dependent variables (DV) were defined for estimation. They represent the accumulated minutes in AWAKE, NREM and REM stage. These three DVs were simultaneously modelled during both the baseline (no treatment) and the citalopram/vehicle treatment period. This model was developed in three steps: (i) baseline, (ii) handling effect and (iii) drug effect. The analyses were performed using NONMEM version 7.2 (Icon Development Solutions, Hanover, Maryland). The First Order Conditional Estimation method with the INTERACTION option was used for parameter estimation.

Results: The accumulated number of minutes in AWAKE, NREM and REM stages were described using a 3-compartment model, one per stage, defined by three inter-related zero order rate functions (minutes per hour). Administration of citalopram produced changes in those rates resulting in a new dynamic re-distribution of the accumulated minutes in AWAKE, NREM and REM stages. However, REM sleep is the more affected stage by means of a strong inhibition.

Conclusions: The kPD model developed here describes sleep architecture with and without citalopram treatment, and quantifies the strong REM inhibition effect at multiple dose levels in rats. This population analysis was carried out with the lack of the actual citalopram and n-desmethylcitalopram concentrations. The PD model part of the model (baseline, handling effect) can be also applied for drug effect evaluations of other sleep changing compounds.

INTRODUCTION

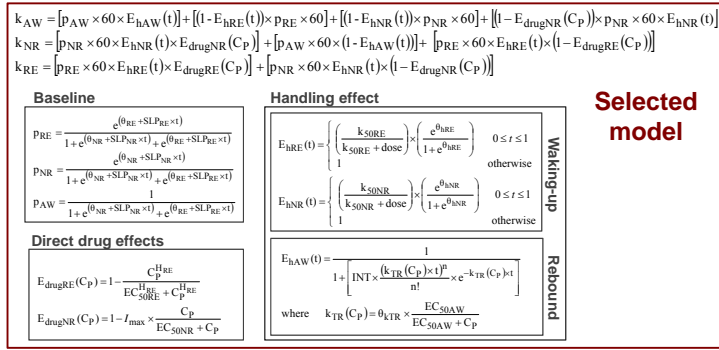
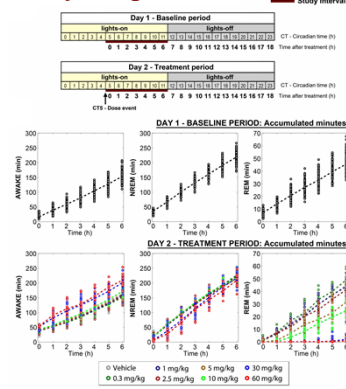
Citalopram has been observed to affect sleep architecture, specifically decreasing REM sleep, in rats and human healthy volunteers and patients. As effects are observed both preclinically and clinically, these objective sleep measures present an excellent opportunity to explore the possibility of quantitative translation of pharmacological effects from rats to humans.

METHODS

Study Design & Data Analysis. Day 1, baseline (no intervention). Day 2: Treatment (citalopram or vehicle) was administered at the circadian time (CT) 5. The study interval corresponds to the 7 hours following treatment, and the corresponding during the baseline. Citalopram and n-desmethylcitalopram concentrations were not available in this study, therefore simulated profiles that were derived from a previously published PK model by Velez de Mendizabal et al. [1] were used as input to the PD model. No between subject variability (BSV) was included in the PK parameters and in the drug effect PD parameters. All analyses were performed using NONMEM 7.2. This kPD model is designed based on three concepts: (i) baseline, (ii) handling effect during vehicle/drug administration and (iii) drug effect. Model development was performed in two consecutive steps: (i) No BSV included, (ii) Population parameters fixed and BSV estimated.

RESULTS

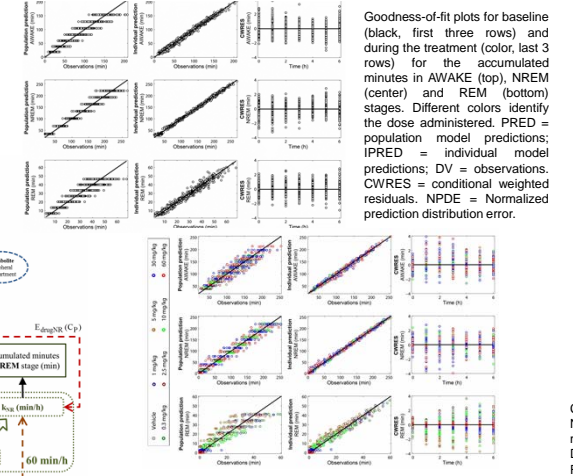
1 Study design & Data



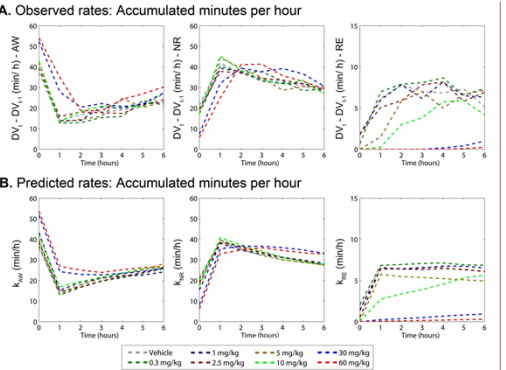
Parameters	Estimate (RSE)		BSV	
	Estimate (RSE)	ISV (RSE)	Estimate	BSV
θ_{PRE}	0.046 (5.90)	36.00 (12.46)	0.049 (13.70)	36.30 (14.11)
θ_{PRE}	0.999 (4.24)	44.6 (14.40)	-0.998 (1.07)	0.931 (4.22)
SLP_{AW}	-0.003 (9.90)	7.98 (13.30)	-0.001 (0.09)	-0.005 (7.47)
SLP_{NR}	-0.048 (19.17)	9.96 (18.30)	-0.005 (0.07)	-0.037 (9.96)
θ_{RE}	-0.663 (42.80)	345.55 (17.80)	-0.723 (1.13)	-0.182 (158.52)
θ_{RE}	-0.996 (26.48)	407 (10.97)	-0.928 (1.88)	-0.479 (446.52)
θ_{RE}	1.29 (15.97)	80.19 (28.20)	1.338 (0.97)	1.801 (80.55)
INT	2.1 (43.90)	54.95 (50.51)	2.46 (1.28)	4.12 (59.87)
EC_{50RE}	59.3 (32.30)	60.40 (45.64)	68.60 (45.64)	68.60 (45.64)
H_{RE}	1.9 (17.50)	1.91 (17.50)	1.98 (1.98)	2.49 (1.98)
EC_{50NR}	189 (32.2)	171.56 (35.96)	171.56 (35.96)	171.56 (35.96)
H_{NR}	0.42 (49.80)	0.42 (49.80)	0.386 (0.04)	0.626 (0.386)
k_{ONRE}	15.4 (103.6)	16.42 (10.90)	15.4 (103.6)	15.4 (103.6)
k_{ONNR}	0.778 (73.15)	0.859 (10.12)	1.965 (0.859)	1.965 (0.859)
k_{ONAW}	78.9 (49.42)	76.95 (13.30)	150 (76.95)	150 (76.95)
$cov(\theta_{PRE}, \theta_{PRE})$	0.152 (13.08)	0.152 (13.08)	0.026 (0.03)	-0.020 (0.026)
$cov(\theta_{PRE}, \theta_{RE})$	-0.026 (14.64)	-0.026 (14.64)	-0.029 (0.03)	-0.023 (0.029)
$cov(\theta_{PRE}, \theta_{NR})$	-0.029 (17.08)	-0.029 (17.08)	-0.031 (0.03)	-0.021 (0.031)
$cov(\theta_{PRE}, \theta_{AW})$	0.087 (17.80)	0.087 (17.80)	-0.038 (0.05)	-0.028 (0.038)
$cov(\theta_{RE}, \theta_{RE})$	0.005 (15.74)	0.005 (15.74)	0.006 (0.005)	0.006 (0.006)
$cov(\theta_{RE}, \theta_{NR})$	4.8 (44.84)	4.8 (44.84)	4.8 (44.84)	4.8 (44.84)
$cov(\theta_{RE}, \theta_{NR})$	0.18 (70.40)	0.18 (70.40)	0.23 (0.23)	0.67 (0.23)
$cov(\theta_{RE}, \theta_{NR})$	4.58 (8.80)	4.58 (8.80)	4.58 (8.80)	4.58 (8.80)
Prop. Res. Error NREM (%)	7.95 (40.52)	7.95 (40.52)	6.08 (5.05)	6.08 (5.05)
Add. Res. Error REM (%)	2.22 (13.90)	2.22 (13.90)	2.22 (13.90)	2.22 (13.90)

A. Study design. Treatment (citalopram or vehicle) was administered at the circadian time (CT) 5. The study interval corresponds to the 7 hours following treatment, and the corresponding during the baseline (maroon solid line). **B. Data.** Accumulated minutes in AWAKE, NREM and REM stages during the baseline (black) and treatment (color). Circles – individual observations | dashed lines – observed median.

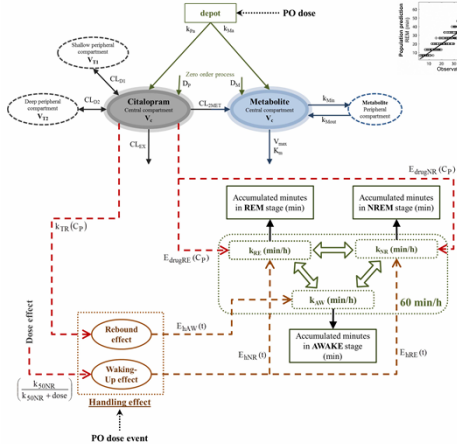
3 Goodness-of-fit plots for baseline & treatment



4 Comparison – Accumulated rates

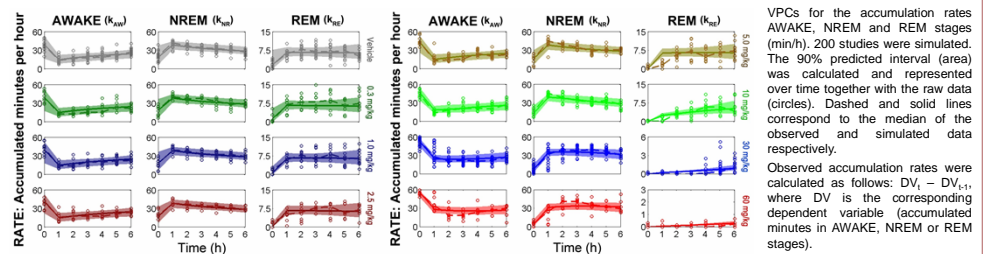


2 Selected k-PD Model



The concentration input to the PD model was derived from a PK model developed previously [1]. The accumulated minutes in AWAKE, NREM and REM were modeled with 3 ODE governed by the 3 zero order input rates: k_{AW} , k_{NR} and k_{RE} (min/h). These rates vary with time (i.e. Circadian rhythms) and vary with changes produced by the animal and citalopram plasma concentration. The handling effect was modeled as the sum of two signals: (i) the initial waking-up effect, which reduces the sleep rates (k_{NR} and k_{RE}), and (ii) the posterior rebound effect which inhibits the AWAKE rate (k_{AW}). Citalopram inhibits the sleep rates (k_{NR} and k_{RE}) and also influences the impact of the animal manipulation. Note, the sum of the three rates should be 60 min/h, so changes in one rate imply changes in one or both other rates (green double arrows).

5 Visual Predictive check – Accumulation rates



Conclusions

- A population kPD model was developed to describe changes in AWAKE, NREM and REM sleep stages simultaneously in Wistar rats after administration of 0.3-60mg/kg oral doses of citalopram - during the baseline period (no perturbations) as well as during the treatment period (citalopram/vehicle).
- Drug/vehicle administration produced an important handling effect that was modelled as a wake promoting effect occurring in the first hour followed by rebound NREM sleep in subsequent hours.
 - These effects were drug/dose dependent, with a reduced impact of the handling effect apparent at the higher citalopram doses
- Citalopram was shown to directly inhibit the accumulation rates for the effect that was more pronounced on REM sleep where there was close to complete inhibition at the highest doses as reflected in the model parameters
 - $[EC_{50RE} = 59.3 \text{ ng/mL} (R_{max} = 0)] \parallel [EC_{50NR} = 183 \text{ ng/mL} (R_{max} = 0.42)]$.
- This kPD model, specifically baseline and vehicle treatment (handling effect) models can be used in the development of models for other compound effects .