An *in silico* PBPK-PD coupled approach to assess Zolpidem effect on pre-clinically and clinically measured cardiac repolarisation parameters in the absence and presence of a circadian model of plasma ion concentration.

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Introduction

Zolpidem is administered nocturnally [1] and its potential to prolong the Q-T interval is a concern [2-4]. Diurnal fluctuations in plasma ion concentrations (K^+, Na^{2+} and Ca^{2+}) have been observed [9].

Using an *in silico* PBPK-PD coupled approach [5, 6] Zolpidem effects on cardiac repolarisation in a virtual population were examined in the absence and presence of a circadian model of variation in plasma ion concentration.

Methods

Zolpidem (10 mg, τ=24 h, @21:00) concentration - time profiles were simulated (Simcyp Simulator v13) for 2 (acute) or 10 (chronic) days in a North-European Caucasian (Sim-NEC) population (Male=51/100). Post-dose (total concentration) C_{max} (day (d) 1, 9) and C_{trough} (d 2, 10) were input parameters to the Cardiac Safety Simulator (CSS; v1.0) for AP and ECG waveform simulations in the absence and presence of a model of plasma ion circadian variability [7, 8].

Simulations were conducted in single left ventricular, mid-myocardial myocytes (O'Hara *et al.*, 2011) from the Sim-NEC cohort. Zolpidem block of I_{Kr} (hERG = 65.5 μM) was assumed to be equal to its potency at hERG. NCA was conducted in Phoenix WinNonLin.

Results

Pharmacokinetics

Pharmacokinetic (PK) non-compartmental analysis (NCA) revealed a marginal difference in the median apparent volume of distribution (Vz_F) between male and female subjects (72.5 (IQR: 53.8 – 98.4), N=51 and 60.0 (IQR: 45.4 – 80.4), N=49, p=0.049) respectively (Fig 1). Otherwise all PK parameters examined were not different (Fig 2).

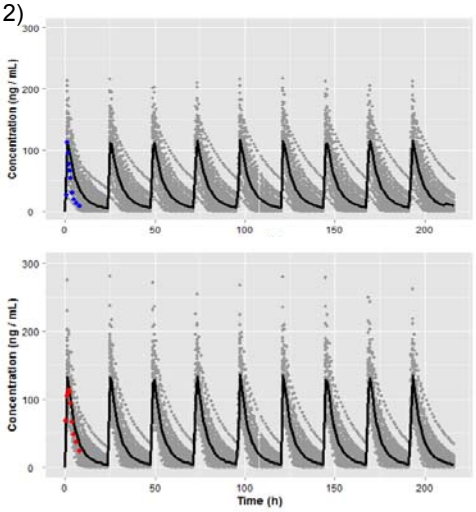

Fig 1. Male (top) and female (bottom) predicted individual (grey data) and observed (blue=male, red = female) concentration-time curves after Zolpidem administration (10mg, τ=24 h).

Results cont…

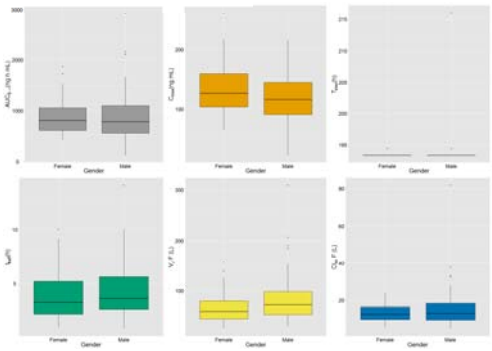

Fig 2. Selected PK parameters for virtual male (N=51) and female (N=49) virtual subjects receiving Zolpidem (10mg, τ=24h for 10 days).

Non-circadian cardiovascular pharmacodynamics (CVPD)

Acute administration of Zolpidem shortened action potential duration at 90 % but not 50 % repolarisation in both genders (Fig 3).

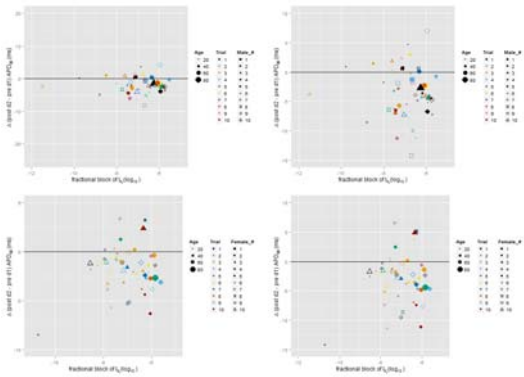

Fig 3. Individual Delta Action Potential Duration at 50 % (ΔAPD_{50}) (left plots) and 90 % (ΔAPD_{90}) (right plots) of repolarisation in North-European Caucasian Male (N=51; upper plots) and Female subjects (N=49; lower plots) by fractional block of an individuals' I_{Kr} current after administration of Zolpidem (10 mg, q.d).

However, chronic administration of Zolpidem shortened action potential duration at both 90 % and 50 % repolarisation in both genders, although males were more sensitive than female subjects.

Circadian CVPD

Increases in the ***basal*** (pre-dose) APD_x parameters between the non-circadian and circadian model were observed for both male and female subjects (Table 1). In Zolpidem naïve subjects (i.e. Day 1 pre-dose) the range of median APD_x increased from 1 – 11 ms between the non-circadian and circadian models respectively (Day 1 APD_x parameters alone). In respect of the circadian model, striking increases in both APD_{50} and APD_{90} parameters were observed in both male and female subjects when comparing day 1 pre-dose and day 9 pre-dose measurements (Table 1).

Results cont…

Table 1. Comparison of basal (pre-dose) median APD_x (25th and 75th percentile of the IQR given in parentheses) parameters (ms) between non-circadian and circadian models of plasma ion concentration

Dose Administration	Model	Non-Circadian				Circadian			
	Gender of Subjects	Male		Female		Male		Female	
	N	51		49		51		49	
	APD, Parameter (ms)	APD_{50}	APD_{90}	APD_{50}	APD_{90}	APD_{50}	APD_{90}	APD_{50}	APD_{90}
ACUTE	Pre-dose, Day 1	132 (114 – 141)	284 (280 – 288)	126 (112 – 142)	281 (278 – 284)	137 (133 – 141)	285 (281 – 290)	137 (133 – 142)	283 (281 –285)
	Pre-dose, Day 2	129 (112 – 140)	280 (276 – 284)	126 (112 – 140)	277 (274 – 283)	134 (130 – 137)	282 (279 – 286)	134 (127 – 139)	280 (276 –282)
CHRONIC	Pre-dose, Day 9	132 (113 – 141)	284 (279 – 287)	126 (112 – 142)	280 (276 – 284)	325 (319 – 334)	363 (357 – 369)	321 (317 – 326)	358 (356 - 363)
	Pre-dose, Day 10	129 (112 – 140)	278 (275 – 282)	126 (112 – 140)	276 (274 – 282)	327 (322 – 332)	363 (358 – 367)	321 (317 – 324)	358 (355 –360)

Zolpidem effects on clinically evaluated cardiac repolarisation parameters

There was no affect of Zolpidem on the QRS complex in either acute (d1 vs. d2) or chronic (d1 vs. d10) dose regimens. Acute administration of Zolpidem yielded prolongation of QTcF in male but not female subjects.

Delta (Δ) QTcF (d1 pre-dose vs. d10 post-dose) in males was 16.1 (IQR: 6.2 – 28.2) ms and in female subjects 10.2 (IQR: -0.8 – 20.2) ms (Fig 5).

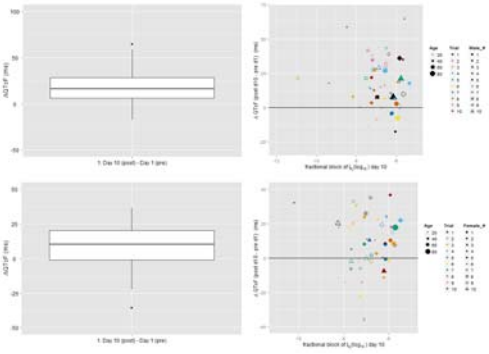

Fig 5. Comparison of Delta (Δ) QTcF in the male (n=51, upper plots) and female (n=49, lower plots) Sim-NEC population (left plots) and as individuals (right plots) between Day 10 post-dose and Day 1 pre-dose after administration of Zolpidem (10 mg q.d).

Conclusion

Chronic administration of Zolpidem to a Sim-NEC population in the presence of a circadian model of plasma ion concentration reveals prolongation of QTcF. Incorporating Zolpidem's chrono-pharmacological effect is important to its cardiovascular safety assessment. Further work will reveal to what extent this is true for other compounds too.

References

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