



Pool Model versus Agonist-Antagonist Interaction Model for the Remoxipride Effect on Prolactin

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Objectives

The pool model [1] has previously been shown to be inferior to an agonist-antagonist interaction (AAI) model [2, 3] to describe prolactin response following administration of two antipsychotic drugs [3]. This study aimed to compare the pool model and the agonist-antagonist interaction (AAI) model to describe prolactin concentrations after administration of the antipsychotic drug remoxipride, i.e. the same data set as the pool model was originally developed from.

Methods

The remoxipride and prolactin concentration data were from 8 healthy male volunteers [1]. There were 5 study occasions and on each occasion two 0.5 h infusions of remoxipride were administered. The intervals between the first dose and the second dose on the 5 occasions were 2, 8, 12, 24 and 48 hours.

Five models were compared in NONMEM and by visual predictive checks; (1) the original pool model [1], (2) a pool model with enforced mass balance, (3) a pool model with enforced mass balance and a circadian rhythm function for prolactin release [Figure 1], (4) the AAI model [2], and (5) the AAI model with circadian rhythm [3] [Figure 2].

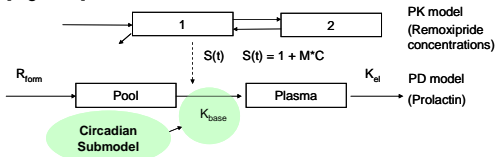


Figure 1. The circadian pool model. R_{om} is the prolactin synthesizing rate; k_{base} is the rate constant describing prolactin release from the pool compartment to the plasma compartment; k_{el} is the prolactin elimination rate constant; $S(t)$ is a function to describe the relationship between the drug concentration and the release rate of prolactin.

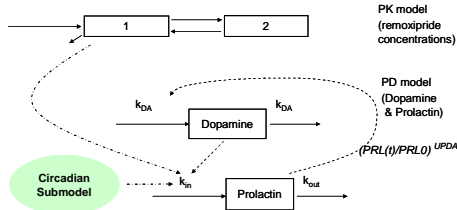


Figure 2. The circadian agonist-antagonist interaction (AAI) model. k_{in} is the generation rate and k_{out} is the elimination rate constant of prolactin, respectively; k_{DA} is the turnover rate constant of the dopamine system; $(PRL(t)/PRL0)^{UPDA}$ is a feedback component; $UPDA$ is a feedback parameter; $PRL(t)$ is the prolactin concentration in plasma; $PRL0$ is the baseline value of prolactin concentration.

Results

The AAI model had 85 units lower OFV than the pool model with mass balance, while the pool model had 1 less THETA and 1 less ETA than the AAI model. Addition of a circadian sub-model improved the OFVs of both the pool model and the AAI model. A VPC revealed that the circadian pool model was inferior to adequately predict the prolactin profile after remoxipride administration [Figure 3].

The pharmacodynamic parameters estimated by the circadian AAI model were in line with previous studies and current understanding about prolactin [Table 1]. The prolactin rhythm predicted by the circadian AAI model was close to reports in the literature [Figure 4].

Table 1. Estimated pharmacodynamic parameters for the evaluated prolactin models. For the AAI model the relative standard errors (RSE) could be estimated.

| | TV | CPRL ($\mu\text{g/L}$) | CPool ($\mu\text{g/L}$) | M (L/mg) | R _{form} ($\mu\text{g/L/h}$) | k_{base} (h^{-1}) | K_{el} (h^{-1}) | KL (mg/L) | k_{out} (h^{-1}) | k_{DA} (h^{-1}) | UPDA | AMP ₁ | PHS ₁ (h) | AMP ₂ | PHS ₂ (h) | OFV |
|----------------------|-------------|--------------------------|---------------------------|----------|---|--------------------------------|------------------------------|-----------|-------------------------------|------------------------------|-----------|------------------|----------------------|------------------|----------------------|--------|
| Circadian Pool Model | TV | 14.2 | 198 | 5.62 | 30.5 | 0.154 | 2.15 | | | | | 0.0956 | 19.2 | -0.336 | -0.468 | 1513.3 |
| | IIV% (RSE%) | 24 | - | 12 | - | - | - | | | | | - | - | - | - | |
| Circadian AAI Model | TV | 8.80(3.3) | | | | | | 11.1(7.9) | 1.19(4.9) | 0.145(4.2) | 1.86(4.9) | -0.192(21) | 0.8(0.8) | -0.32(12) | 5.5(0.7) | 1498.6 |
| | IIV% (RSE%) | 12(26) | | | | | | 54(23) | 25(29) | - | - | - | - | - | - | |

There are two periods, 24 and 12 hours, in the circadian sub-model. AMP₁ and AMP₂ are the amplitudes of each cosine functions. PHS₁ and PHS₂ are the phase shifts.

Conclusions

As previously observed for other antipsychotic drugs [3], the circadian AAI model was superior to the other investigated models in describing the prolactin response. The AAI model appears to work well across drugs and for a range of different types of administration schedules.

Acknowledgement

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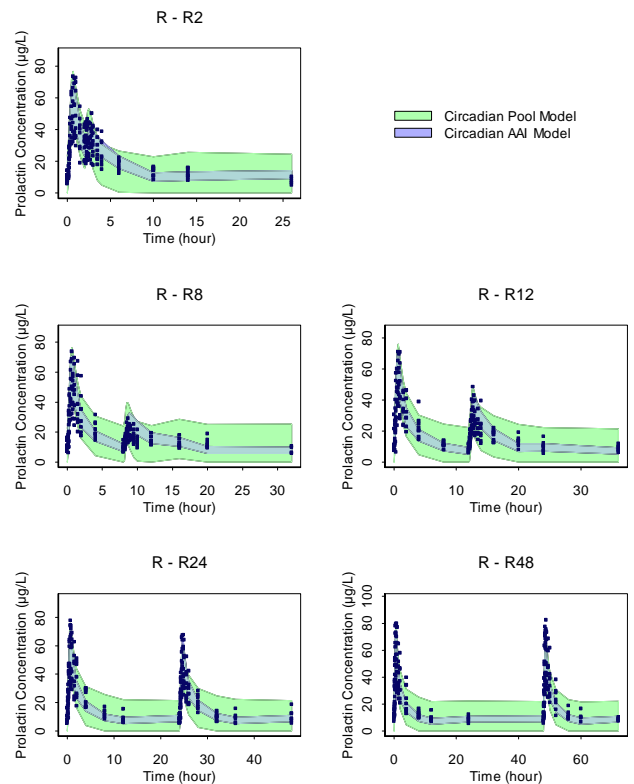


Figure 3. Visual predictive check for the circadian pool model and the circadian agonist-antagonist interaction (AAI) model with 50% prediction interval (PI). R-R2 to R-R48 are the five different occasions. R is first dose; R2, R8, R12, R24, and R48 indicate that second doses were given on 2, 8, 12, 24, and 48 hours, respectively. 0 is 8 a.m.

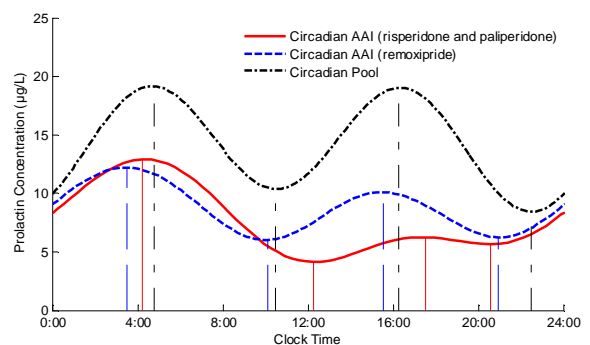


Figure 4. Daily variations in placebo prolactin concentrations predicted by the circadian agonist-antagonist interaction (AAI) models and the circadian pool model.

References

- [1] Movin Osswald, G. and M. Hammarlund Udenaes. J Pharmacol Exp Ther; 1995; 274: 921-7.
- [2] Bagli, M., et al. J Pharmacol Exp Ther; 1999; 291: 547-54.
- [3] Friberg, L.E., et al. PAGE. 2006.