Optimal design of a reduced sampling schedule for the characterization of prolactin dynamics in healthy male volunteers and its evaluation to describe the pharmacodynamic effect of a prolactin antagonist in a single rising dose study

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Objectives

To optimize a constrained sampling design for the estimation of the diurnal cycle of prolactin in the absence of drug in healthy male subjects and evaluate the design performance to describe the pharmacodynamic (PD) effect of a prolactin antagonist in a clinical single rising dose (SRD) study.

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Introduction

- Prolactin is involved in dopaminergic pathways and typical and atypical antispsychotics can cause hyper- or hypo-prolactinemia.
- While an adverse affect of these drugs, the prolactinemia may be utilized as a marker of brain target engagement, enabling early proof of pharmacological principle.
- Accurately measuring prolactin levels to estimate a drug effect is challenging due to the high inter-individual variability (IIV) as well as circadian variability (manifest as a diurnal cycle of prolactin) which must be considered in the study design.

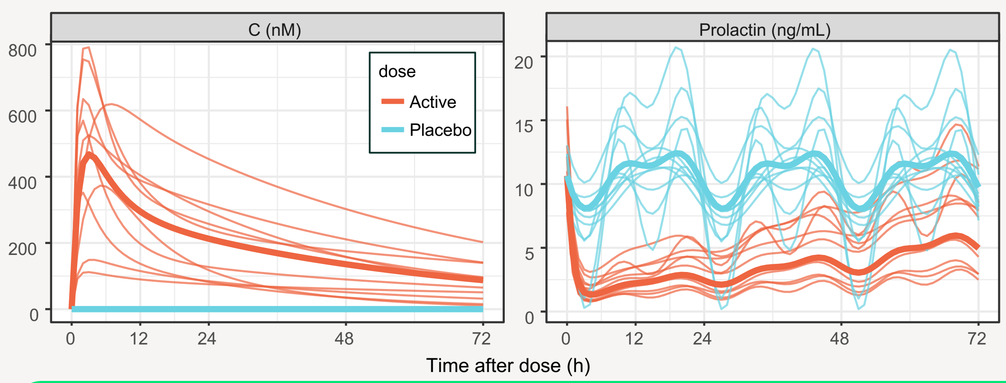

Figure 2. Illustration of PK and prolactin typical profiles (thick line) and 10 randomly sampled healthy males (thin lines) after placebo (blue) and active treatment (red) based on the Esdonk model) [1] . Time 0 corresponds to 08:00 in the morning.

Methods

- A prolactin antagonist model of a somatostatin-dopamine chimera in healthy male volunteers after single or multiple dose administration, and with extensive sampling, (Esdonk model[1]) was implemented using mrgsolve[2] and the PopED[3,4] optimal design package. The Esdonk model features a pool model with two cosine functions of 12h and 24h periods respectively to describe the diurnal pattern of prolactin. In the absence of drug, the model was verified to result in similar description of prolactin levels over a day as circadian agonist-antagonist interaction models for remoxipride, and risperidone and paliperidone.[5]
- A sampling schedule optimization of four samples between 08:00 and 20:00 (i.e., no night sampling, see Figure 1) was performed with the aim of characterizing the prolactin diurnal pattern in the absence of drug (representing a screening visit, day -1) with only the prolactin formation rate, the phase shifts and amplitudes of the 12 and 24h cosine functions, the residual variability and the associated IIV variances as unfixed parameters.

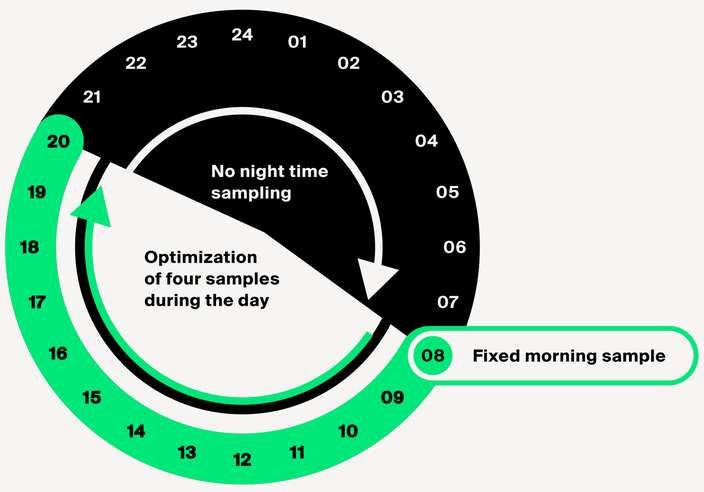

Figure 1. Illustration of sampling schedule optimization.

- The optimized sampling times were then evaluated on a hypothetical SRD study where the same sampling pattern was repeated at day 1 (drug administration assumed at 08:00) in addition to a morning sample at screening, day 1, 2 and 6. The hypothetical PK used to drive the PD is illustrated in Figure 2. In the evaluation all parameters in the Esdonk prolactin model were unfixed, 10 active dose groups were assumed in addition to placebo with 6 subjects per dose group, and maximum suppression of prolactin release was observed within the dose range.

Results

- With the addition of two fixed morning samples at 08:00 and the same time the following day, a schedule with four samples at 10:30, 14:00, 18:00 and 20:00 (Figure 3) was found to yield acceptable precision in the prolactin diurnal model in the absence of drug (highest RSE predicted for the amplitude of the 24h cosine at less than 42% for typical and 45% for IIV variance).
- When the sampling design was repeated on the hypothetical SRD study, all parameters in the Esdonk prolactin model were predicted to be estimable (highest RSE again predicted for the amplitude of the 24h cosine at 36% for both typical and IIV variance). However, the actual performance of the design is highly dependent on the PK/PD properties of the study drug.
- The relatively poor precision in the amplitude of the 24h cosine function is not surprising given the limitation of no sampling during half of the time interval but could be improved by the addition of a single night sample at the screening day at the cost of convenience.

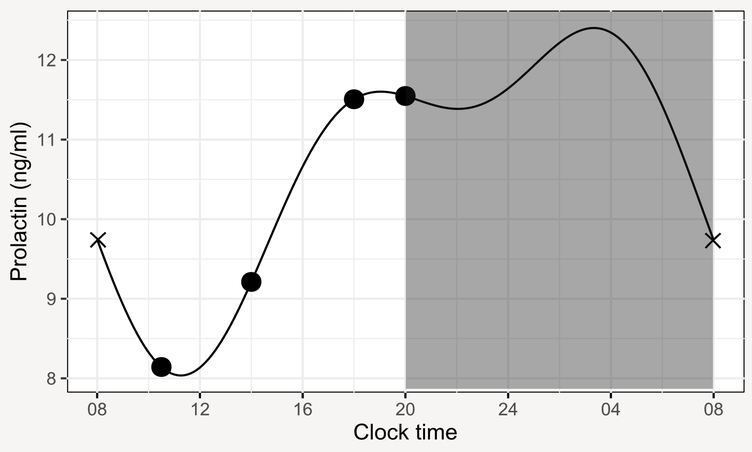

Figure 3. Optimized sampling schedule for determination of pre-dose prolactin circadian components (dots) along with fixed morning sample (cross). The shaded area represents the "no night time" sampling (20:00 to 08:00).

Conclusions

We suggest a practical sampling design for capturing prolactin diurnal dynamics without night time sampling. The same sampling design when applied in a hypothetical SRD study allows estimation of all system and PD parameters of a prolactin antagonist, demonstrating the practicability of the design for prolactin biomarker analysis in early clinical studies.

Abbreviations
IIV, inter individual variability; OD, Optimal design; PD, pharmacodynamic(s); PK, pharmacokinetic(s); PoPP, Proof of pharmacological principle; RSE, relative standard error; SRD, single rising dose

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