The circadian rhythm of cortisol binding globulin has little impact on cortisol exposure after hydrocortisone dosing

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Background
Optimisation of hydrocortisone replacement therapy remains challenging, due to complex pharmacokinetics as circulating cortisol is protein bound mainly to corticosteroid-binding globulin (CBG) [1] that has a circadian rhythm [2].

Objectives
A detailed analysis of the CBG circadian rhythm and its impact on cortisol exposure during hydrocortisone replacement therapy.

Methods
Study design and patient population
- CBG was sampled hourly over 24 h in 14 healthy individuals not using regular medication nor working night shift. The age (median (range)) was 28.5 years (22-60) and body weight of 82.9 kg (63.6-103) [2].
- CBG was quantified using an ELISA with lower limit of quantification of 3.13 ng/mL and intra- and inter-assay variability less than 3%CV and 6%CV, respectively [3]. No CBG concentrations were below quantifiable.

Circadian CBG model
- 350 CBG concentrations were used to establish the CBG model in NONMEM 7.3 [4]. Two cosine functions were added to the CBG baseline to accurately describe the circadian CBG concentrations over time, according to Eq. 1.

\[
\begin{align*}
\text{CIRC24} &= \text{amp}_{1,2} \times \cos (2\pi \times \text{time} - \text{shift}_{1,2}) / 24 \\
\text{CIRC12} &= \text{amp}_{1,2} \times \cos (2\pi \times \text{time} - \text{shift}_{1,2}) / 24 \\
\text{CBG} &= \text{CBG}_{\text{baseline}} - (1 - \text{CIRC24} + \text{CIRC12})
\end{align*}
\]

Simulations
An established semi-mechanistic hydrocortisone (HC) pharmacokinetic model [5] was combined with the circadian CBG model to assess the impact of hydrocortisone administration at different clock times and the changing CBG concentrations on cortisol exposure in two scenarios:

1. Single HC administration at different clock times
Individual CBG concentration-time profiles (n=100) and cortisol exposure (Area under concentration-time curve (AUC), maximum concentration ([Cmax]), and time to maximum concentration (tmax)) were simulated after administration of single hydrocortisone doses (0.5, 2, 5, 10 or 20 mg) every hour (5 doses at 24 different administration times)

2. Recommended three times daily dosing regimen
Circadian (n=100) or constant (n=100) CBG profiles, AUC_{\text{CIRC12}} and C_{\text{CIRC12}} for cortisol were simulated after a recommended thrice daily dosing for adults: 10 mg at 06:00, 5 mg at 14:00 and 5 mg at 22:00 [6].

Results
The circadian rhythm of CBG (Fig. 1, left) was well described with two cosine terms added to the baseline of CBG (Fig. 1, right).

Fig. 1: Change in corticosteroid-binding globulin from baseline over time (left), during 24 h (n=14). Right: Visual predictive check for the circadian corticosteroid-binding globulin model during 24 h (100 days 1:15:00 day 1-15:00 day 2). Lines correspond to the 5th, 50th and 95th percentile of observed (black) and simulated (n=1000, gray) data. The areas are the 95th confidence interval around the simulated percentiles and the circles the observations.

Results (cont.)

- Baseline CBG was 21.8 µg/mL with low interindividual variability (11.9%CV).
- The amplitude for the 24 and 12 h cosine functions were relatively small (24 h: 5.53%, 12 h: 2.87%) (Table 1).
- The highest and lowest CBG concentrations were determined at 18:00 and 02:00, respectively.
- The lowest and highest simulated cortisol exposure was observed for HC doses given at 23:00-02:00 and 15:00-18:00, respectively (Fig. 2, upper panels).
- However, the differences between the highest and lowest exposure were minor (≤12.2%).

No clinically relevant difference in AUC or C_{\text{max}} was observed for the three times daily dosing regimen considering circadian CBG rhythms or not (Fig. 2 lower panels).

Conclusions
- CBG has a circadian rhythm - well described by the developed model.
- However, the difference in cortisol exposure is small (≤12.2%) between times of highest and lowest CBG concentrations.
- Hydrocortisone dose adjustment based on time of dosing to adjust for the CBG concentrations is too be of clinical benefit.

References:

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