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

P1-P010

J. Melin (1,2), N. Hartung (1,3), Z.P. Parra-Guillen (1,4), M.J. Whitaker (5), R.J. Ross (6), C. Kloft (1)

(1) Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany;
(2) and Graduate Research Training program PharMetrX, Germany;
(3) Institute of Mathematics, Universität Potsdam, Germany;
(4) Pharmacometrics and Systems Pharmacology, University of Navarra, Pamplona, Spain;
(5) Diurnal Limited, Cardiff, UK;
(6) The University of Sheffield, UK;

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 interassay 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. 1-3.

$$CIRC24 = amp_{24} \cdot cos\left(\frac{2 \cdot \pi \cdot (time - shift_{24})}{24}\right) \quad \text{(Eq. 1)}$$

$$CIRC12 = amp_{12} \cdot cos\left(\frac{2 \cdot \pi \cdot (time - shift_{12})}{12}\right) \quad \text{(Eq. 2)}$$

$$CBG = CBG_{baseline} \cdot (1 + CIRC24 + CIRC12) \quad \text{(Eq. 3)}$$

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 (C_{max})) 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, $AUC_{0\text{-}8h}$ and C_{max} 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).

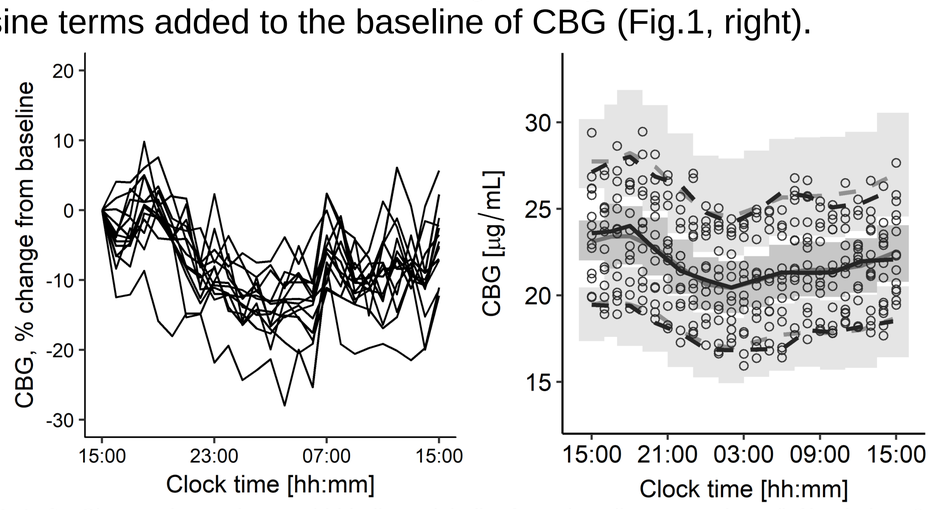

Fig. 1 Left: Change in corticosteroid-binding globulin from baseline over time (left), during 24 h (n=14). Right: Visual predictive check for the circadian corticosteroid-binding globulin model during 24 h (15:00 day 1-15:00 day 2). Lines correspond to the 5th, 50th and 95th percentile of observed (black) and simulated (n=1000, grey) 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%).

Table 1. PK parameter estimates of circadian corticosteroid-binding globulin model.

Parameter	Parameter estimate (95% CI)
Fixed-effects	
$Baseline_{CBG}$ [µg/mL]	21.8 (20.3, 23.3)
Amp_{24} [%]	5.53 (4.80, 6.20)
$Shift_{24}$ [h]	1.77 (1.33, 2.27)
Amp_{12} [%]	2.87 (2.21, 3.42)
$Shift_{12}$ [h]	15.7 (15.4, 16.0)
Interindividual variability	
ωBaseline,CBG [%CV]	11.9 (7.76, 14.0)
Residual variability	
σprop* [%CV]	3.90 (3.46, 4.32)

95% confidence interval (95% CI). amplitude for 24 h cosine function (Amp_{24}), time shift for 24 h cosine function ($Shift_{24}$), amplitude for 12 h cosine function (Amp_{12}), time shift for 12 h cosine function ($Shift_{12}$), variance of log-normally distributed interindividual variability (ω), variance or proportional residual variability (σprop).

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

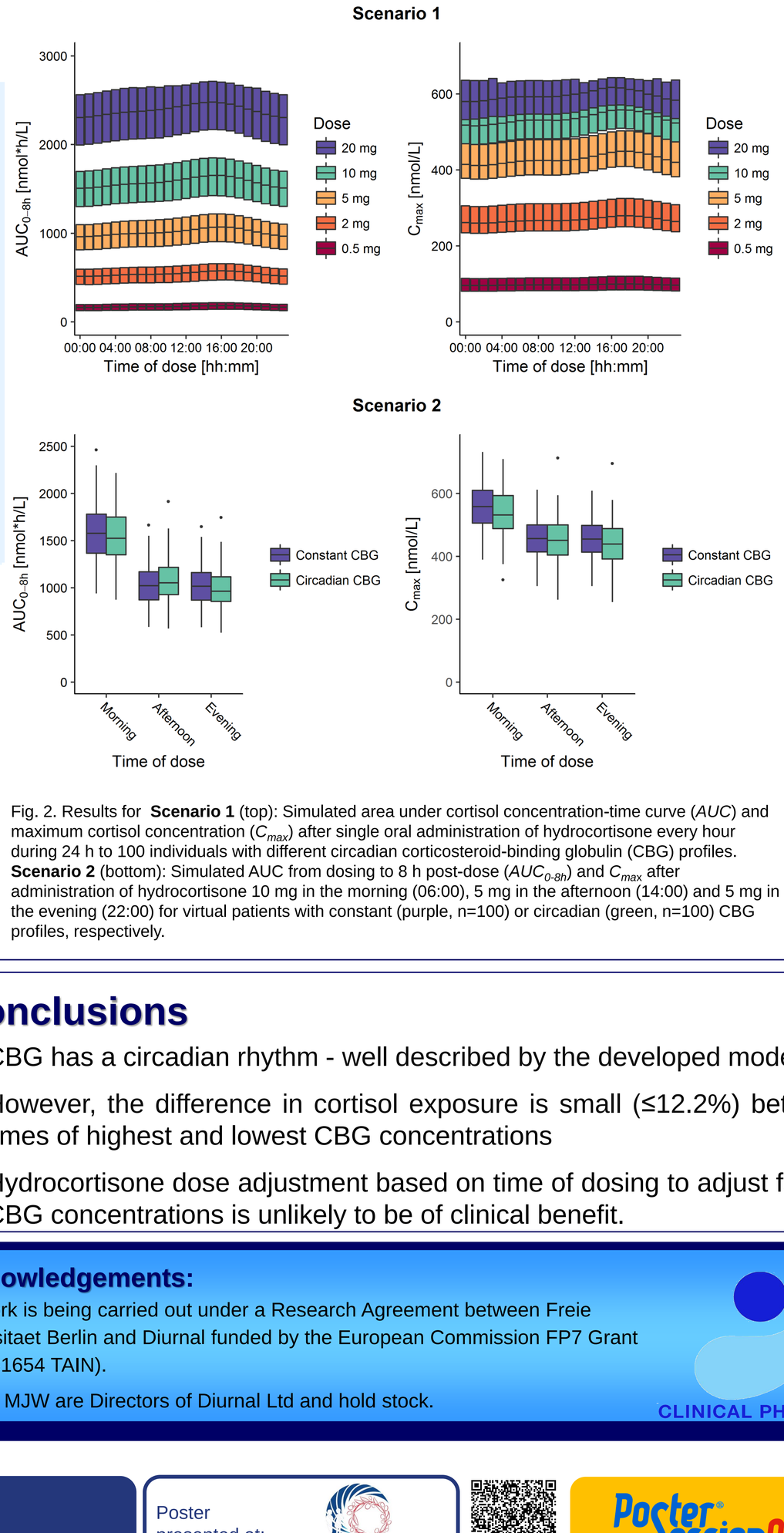

Fig. 2. Results for **Scenario 1** (top): Simulated area under cortisol concentration-time curve (*AUC*) and maximum cortisol concentration (C_{max}) after single oral administration of hydrocortisone every hour during 24 h to 100 individuals with different circadian corticosteroid-binding globulin (CBG) profiles. **Scenario 2** (bottom): Simulated AUC from dosing to 8 h post-dose ($AUC_{0\text{-}8h}$) and C_{max} after administration of hydrocortisone 10 mg in the morning (06:00), 5 mg in the afternoon (14:00) and 5 mg in the evening (22:00) for virtual patients with constant (purple, n=100) or circadian (green, n=100) CBG profiles, respectively.

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 unlikely to be of clinical benefit.

References:

[1] EGWM Lentjes, FHTPM Romijn, J Clin Endocrinol Metab 84: 682-687 (1999)
[2] M Debono, RF Harrison, J Clin Endocrinol Metab 101: 1469-1477 (2016)
[3] JG Lewis, MG Lewis, Clinica Chimica Acta 328: 121-128 (2003)
[4] S Beal, LB Sheiner, NONMEM User's guides (1989-2009)
[5] J Melin, ZP Parra-Guillen, Clin Pharmacokinet 57: 515-527 (2018)
[6] SR Bornstein, B Allolio, J Clin Endocrinol Metab 101: 364-389 (2016)

Acknowledgements:

The work is being carried out under a Research Agreement between Freie Universitaet Berlin and Diurnal funded by the European Commission FP7 Grant (No. 281654 TAIN).

RJR & MJW are Directors of Diurnal Ltd and hold stock.