ACHIEVING A PHYSIOLOGICAL CORTISOL PROFILE WITH GLUCOCORTICOID REPLACEMENT THERAPY: A PHARMACOKINETIC STUDY OF ONCE-DAILY DUAL-RELEASE HYDROCORTISONE

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INTRODUCTION

- Conventional glucocorticoid replacement therapy has demonstrated efficacy in adrenal insufficiency (AI) but long-term clinical outcomes remain unsatisfactory.[1–4]
- Failure to normalize the cortisol time–exposure profile and glucocorticoid overexposure can have important clinical implications, including increased cardiovascular risk, metabolic disturbances and altered sleep patterns.[5–8]
- A once-daily, dual-release hydrocortisone (DR-HC) tablet has been developed for oral glucocorticoid replacement therapy in AI.[9–10] This formulation was developed to provide cortisol exposure that closely resembles the physiological serum cortisol profile.[11]

AIMS

- To characterize the single-dose plasma pharmacokinetics (PK) of DR-HC across the dose range of 5–20 mg in healthy volunteers and to assess intra-subject variability.

METHODS

- This was a randomized, open-label, four-period crossover, single-dose PK study of oral DR-HC tablets in healthy men and women (aged 20–55 years, body mass index [BMI] 18–30 kg/m²) who were either of Japanese descent or non-Hispanic Caucasian.
- After screening, there was a baseline 24-hour assessment of endogenous cortisol secretion and four 3-day treatment periods (separated by wash-out periods of ≥ 72 h).
- For each treatment period:
  - Oral dexamethasone 1 mg was administered at specific timepoints on Days 1 and 2 to suppress endogenous cortisol secretion during PK sampling.
  - Single doses of DR-HC 5 mg, 15 mg, 20 mg (test site) and 20 mg (reference site) were administered orally at 8 am on Day 2 after overnight fast.
  - Blood samples for PK assessments were collected at 15, 30, 45, 60, 90, 120 and 150 min, hourly from 3–10 hours, and at 12, 15 and 24 hours after dosing with study drug.
- Plasma cortisol concentrations were analyzed using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method (assay range 1–500 ng/mL).

Statistical analyses

- The intent-to-treat (ITT) population included all subjects who received the study drug, while the PK population included all subjects with at least one evaluable concentration–time profile.
- PK analyses were determined by non-compartmental analysis using WinNonlin version 6.2 or higher (Pharsight Corp., St Louis, MO).
  - All area under the concentration–time curve (AUC) parameters were calculated using linear/logarithmic trapezoidal method.
- Dose-proportionality of baseline corrected and uncorrected PK parameters over the dose range was examined using the power model method, with ethnicity as a potential covariate.

RESULTS

Baseline characteristics

- Thirty-one patients were randomized and included in the intent-to-treat and PK analysis populations (Table 1).

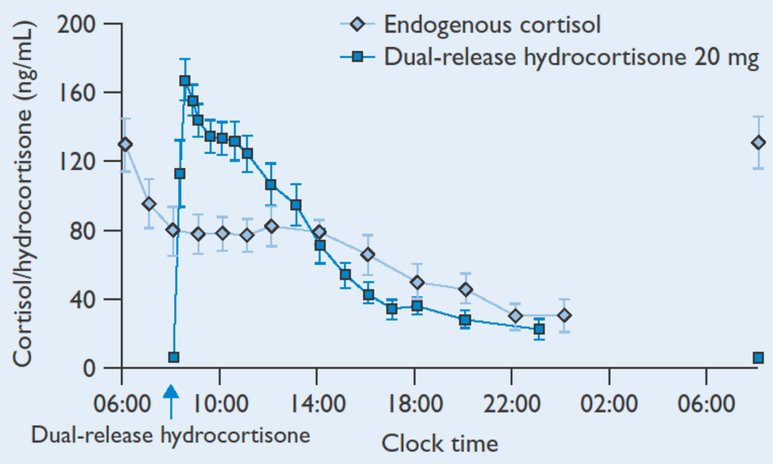
Comparison of replacement hydrocortisone with endogenous cortisol profile

- Replacement treatment with DR-HC 20 mg provided higher than endogenous cortisol plasma concentrations 0–4 hours post dose but similar concentrations later in the profile (Figure 1).

Plasma PK parameters for DR-HC

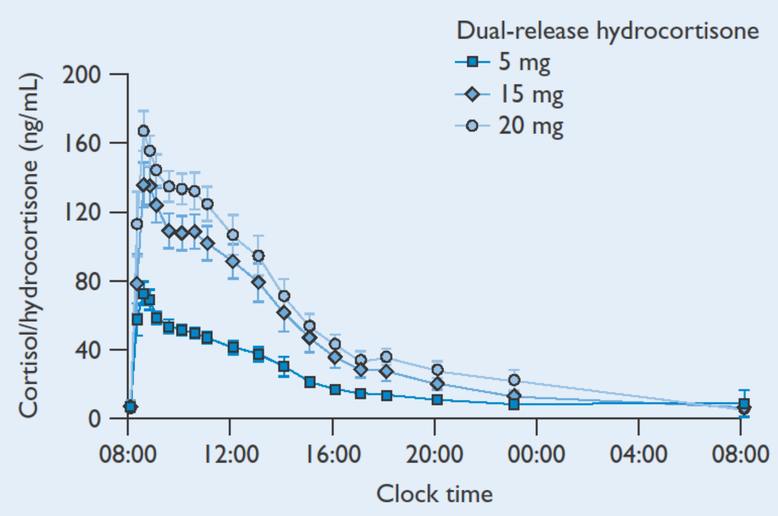
- Cortisol plasma concentrations increased with increasing doses of DR-HC (Figure 2). The maximal plasma concentration (C_{max}) occurred within 1 hour post dose for most subjects and concentrations remained above baseline levels for at least 15 hours after the 20 mg dose.

Figure 1. Mean (95% CI) plasma concentration–time profiles for endogenous cortisol[a] and DR-HC 20 mg (test site) in the PK population.



[a]Endogenous cortisol concentrations were not assessed after 00:00 on Day 1 until 08:00 on Day 2.
CI, confidence interval; DR-HC, dual-release hydrocortisone; PK, pharmacokinetic.

Figure 2. Mean (95%CI) plasma concentration–time profiles for DR-HC in healthy subjects after single oral doses of 5, 15 and 20 mg (test site) in the ITT population.



CI, confidence interval; DR-HC, dual-release hydrocortisone; ITT, intent-to-treat.

Table 1. Demographic and baseline characteristics: ITT population.

	ITT (n = 31)
Age (years)	38.5 (10.1)
Sex	
Male	26 (83.9%)
Female	5 (16.1%)
BMI (kg/m²)	
Male	23.7 (1.7)
Female	21.9 (2.6)
Race	
Non-Hispanic Caucasian	15 (48.4%)
Japanese	16 (51.6%)
Clinically relevant disease	10 (32.3%)

Results are presented as n (%) for categorical variables and mean (SD) for continuous variables.
ITT, intent-to-treat; SD, standard deviation.

- Hydrocortisone PK exposure parameters increased with increasing doses of DR-HC (Table 2). Mean PK parameters were similar if corrected or uncorrected.
- Within-subject variability was low and below 15% for all examined PK parameters (evaluated for the two 20 mg tablets; Table 3).

Dose-proportionality

- Exposure PK parameters (uncorrected and baseline corrected) were found to be less than dose-proportional, i.e. AUC_{∞} with a 0.78 slope (95% CI: 0.70–0.85) in the 5–20 mg dose range.
- There were no differences between the two ethnic groups.

Impact of ethnicity on PK parameters for DR-HC

- DR-HC PK parameters were generally similar for Caucasian and Japanese subjects.
- Marginal significant differences in C_{max} due to ethnicity were further analysed and shown to be explained by differences in body weight between the groups.

Table 2. Plasma pharmacokinetic variables for DR-HC in healthy subjects in the PK population.

Parameter	5 mg[a]	15 mg[a]	20 mg[a]	20 mg[b]
C_{max} (ng/mL)	82.0 (18.2)	148.8 (29.3)	177.1 (25.5)	178.0 (28.1)
AUC_{∞} (h*ng/mL)	562.8 (141.0)	991.6 (162.0)	1180.8 (213.8)	1162.1 (175.7)
AUC_{12h} (h*ng/mL)	371.8 (75.8)	770.4 (209.0)	947.7 (174.2)	919.5 (169.7)
T_{max} (h)	0.51 (0.22)	1.75 (4.35)	1.05 (1.28)	0.96 (1.04)
Terminal half-life (h)	13.72 (8.03)	8.27 (5.14)	6.02 (2.87)	6.65 (3.58)
% extrapolated AUC (%)[c]	17.4 (10.8)	7.5 (6.7)	4.3 (2.6)	5.7 (4.9)

[a]Test site; [b]reference site; [c]percentage of the AUC resulting from extrapolation after the last measurable concentration. All pharmacokinetic variables are uncorrected and presented as mean (SD).
AUC, area under the concentration–time curve; AUC_{∞}, total area under the concentration–time curve; AUC_{12h}, area under the concentration–time curve to the last sample taken at 12 hours after dosing; C_{max}, maximal serum concentration; DR-HC, dual-release hydrocortisone; PK, pharmacokinetic; SD, standard deviation.

Table 3. Within-subject variability for DR-HC the two 20 mg tablets (reference and test sites) in the PK population

Parameter	Geometric LSMs		Within-subject %CV	LSM ratio (test/reference)	90% CI
	20 mg (reference site)	20 mg (test site)			
C_{max} (ng/mL)	175.42	175.56	8.8%	100.1%	96.2–104.1
AUC_{12h} (h*ng/mL)	905.05	933.37	10.9%	103.1%	98.3–108.2
AUC_{t} (h*ng/mL)	1088.35	1113.89	11.4%	102.3%	97.3–107.7

AUC, area under the concentration–time curve; AUC_{12h}, area under the concentration–time curve to the last sample taken at 12 hours after dosing; AUC_{t}, area under the concentration–time curve through to the last measurable concentration; C_{max}, maximal serum concentration; CV, coefficient of variation; DR-HC, dual-release hydrocortisone; LSM, least-squares mean; PK, pharmacokinetic.

Adverse events

- DR-HC at all doses was generally well tolerated. AEs were reported in 3/31 healthy volunteers (10%).

CONCLUSIONS

- Once-daily DR-HC demonstrates a plasma cortisol exposure profile that closely resembles the endogenous serum cortisol profile during the day, producing high exposure for the first 4 hours followed by gradual reduction.
- Within-subject, day-to-day variability in cortisol exposure with DR-HC was less than 15%, indicating the reliability of this formulation and the minimal risk for any absorption failure.
- PK exposure parameters for DR-HC were less than dose proportional, similar to conventional hydrocortisone,[12] which should be considered during intercurrent illness in the management of AI.
- As well as confirming previous findings,[9–10] this study has expanded the PK data to an additional dose and into a different ethnic group.
- This new formulation of hydrocortisone has the potential to improve clinical outcomes for patients with AI.

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