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.1,5 A once-daily dual-release hydrocortisone (DH-C) tablet has been developed for oral glucocorticoid replacement therapy in AI.6,7 This formulation was developed to provide cortisol exposure that closely resembles the physiological serum cortisol profile.7

AIMS

To characterize the single-dose plasma pharmacokinetics (PK) of DH-C 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 DH-C 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 dehydrocortisone 1 mg was administered at specific timepoints on Days 1 and 2 to suppress endogenous cortisol secretion during PK sampling.
- Single doses of DH-C 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 performed by non-compartmental analysis using WinNonlin version 6.2 or higher (Pharsight Corp, St Louis, MO).

All areas under the concentration-time curve (AUC) parameters were calculated using linear/logarithmic trapezoidal method.

Dose-proportionality of baseline corrected and uncorrected PK parameters across 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 DH-C 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 DH-C

Concentration-time profiles were developed with increasing doses of DH-C (Figure 2). The maximal plasma concentrations (Cmax) 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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>5 mg</th>
<th>15 mg</th>
<th>20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>175.47</td>
<td>175.66</td>
<td>8.8%</td>
</tr>
<tr>
<td>AUIC (ng/mL h)</td>
<td>77.44</td>
<td>77.36</td>
<td>10.3%</td>
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<tr>
<td>AUIC (ng/mL h)</td>
<td>217.50</td>
<td>217.73</td>
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<tr>
<td>AUIC (ng/mL h)</td>
<td>74.95</td>
<td>75.09</td>
<td>10.6%</td>
</tr>
<tr>
<td>AUIC (ng/mL h)</td>
<td>17.54</td>
<td>17.54</td>
<td>10.6%</td>
</tr>
</tbody>
</table>

Adverse events

- DH-C at all doses was generally well tolerated AE were reported in 33% healthy volunteers (10%).

CONCLUSIONS

- Once-daily DH-C demonstrates a plasma cortisol exposure profile that closely resembles the endogenous cortisol serum 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 DH-C was less than 15%, indicating the reliability of this formulation and the minimal risk for any absorption failure.

- PK exposure parameters for DH-C were less than dose proportional, similar to conventional hydrocortisone, which should be considered during intercurrent illness in the management of AI.

- As well as confirming previous findings,8,9,10 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.

REFERENCES


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