Improved Cortisol Exposure-Time Profile and Outcome in Patients with Adrenal Insufficiency: A Prospective Randomized Trial of a Novel Hydrocortisone Dual-Release Formulation.

Johannsson, G; Nilsson, A G; Bergthorsdottir, R; Burman, Pia; Dahlqvist, P; Ekman, B; Engström, B E; Olsson, T; Ragnarsson, O; Ryberg, M; Wahlberg, J; Biller, B M K; Monson, J P; Stewart, P M; Lennernäs, H; Skrtic, S

Published in: The Journal of clinical endocrinology and metabolism

DOI: 10.1210/jc.2011-1926

2011

Link to publication

Citation for published version (APA):

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
Improved Cortisol Exposure-Time Profile and Outcome in Patients with Adrenal Insufficiency: A Prospective Randomized Trial of a Novel Hydrocortisone Dual-Release Formulation


Departments of Endocrinology (G.J., A.G.N., R.B., O.R.) and Clinical Pharmacology (S.S.), Sahlgrenska Academy, University of Gothenburg, SE-413 45 Gothenburg, Sweden; Department of Endocrinology (P.B.), Skånes University Hospital Malmö, SE-205 02 Malmö, Sweden; Department of Public Health and Clinical Medicine (P.D., T.O., M.R.), Umeå University, SE-901 87 Umeå, Sweden; Division of Cardiovascular Medicine (B.E., J.W.), Department of Medical and Health Sciences Faculty of Health Sciences, Linköping University, SE-581 83 Linköping, Sweden; Department of Endocrinology, Diabetes, and Metabolism (B.E.E.), University Hospital, and Department of Pharmacy (H.L.), Uppsala University, SE-751 85 Uppsala, Sweden; Neuroendocrine Clinical Center (B.M.K.B.), Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114; Centre for Clinical Endocrinology (J.P.M.), St. Bartholomew’s Hospital, Queen Mary University of London, London EC1A 7BE, United Kingdom; and College of Medical and Dental Sciences (P.M.S.), University of Birmingham, Birmingham B15 2TT, United Kingdom

Context: Patients with treated adrenal insufficiency (AI) have increased morbidity and mortality rate. Our goal was to improve outcome by developing a once-daily (OD) oral hydrocortisone dual-release tablet with a more physiological exposure-time cortisol profile.

Objective: The aim was to compare pharmacokinetics and metabolic outcome between OD and the same daily dose of thrice-daily (TID) dose of conventional hydrocortisone tablets.

Design and Setting: We conducted an open, randomized, two-period, 12-wk crossover multicenter trial with a 24-wk extension at five university hospital centers.

Patients: The trial enrolled 64 adults with primary AI; 11 had concomitant diabetes mellitus (DM).

Intervention: The same daily dose of hydrocortisone was administered as OD dual-release or TID.

Main Outcome Measure: We evaluated cortisol pharmacokinetics.

Results: Compared with conventional TID, OD provided a sustained serum cortisol profile 0–4 h after the morning intake and reduced the late afternoon and the 24-h cortisol exposure. The mean weight (difference: −0.7 kg, \( P = 0.005 \)), systolic blood pressure (difference: −5.5 mm Hg, \( P = 0.0001 \)) and diastolic blood pressure (difference: −2.3 mm Hg; \( P = 0.03 \)), and glycaemia (absolute difference: −0.1%, \( P = 0.0006 \)) were all reduced after OD compared with TID at 12 wk. Compared with TID, a reduction in glycaemia by 0.6% was observed in patients with concomitant DM during OD (\( P = 0.004 \)).

Conclusion: The OD dual-release tablet provided a more circadian-based serum cortisol profile. Reduced body weight, reduced blood pressure, and improved glucose metabolism were observed during OD treatment. In particular, glucose metabolism improved in patients with concomitant DM (J Clin Endocrinol Metab 97: 473–481, 2012)
The importance of glucocorticoids for survival was well known before their availability for therapeutic use when the 2-yr mortality rate in patients with Addison’s disease (AD) exceeded 80% (1). Although glucocorticoid replacement has been available for over a half-century, there have been few new developments in the oral preparations for treatment of patients with adrenal insufficiency (AI). Oral hydrocortisone in daily divided doses is the most widely used glucocorticoid in cortisol replacement therapy (2, 3), but no formal studies of its safety and efficacy have been performed in patients with AI.

Studies in patients with AD have shown a more than double the standardized mortality rate (4, 5) despite contemporary optimal glucocorticoid replacement therapy. Also, patients with hypopituitarism have a doubled standardized mortality rate (6, 7), and young adults with AI as part of their hypopituitarism have a 7-fold excessive mortality rate (8). Likely explanations are the supraphysiological maintenance doses (2), poor diurnal glucocorticoid exposure-time profile (9), and inadequate rescue therapy in response to intercurrent illnesses (10). Patients with AI also have increased cardiovascular risk factors, reduced health-related quality of life (QoL), and decreased bone mineral density (2, 11–13).

In an attempt to improve patient outcome, studies in which both the dose and the dosing strategies were adjusted have been performed (14–16). Weight reduction and increase in bone formation markers were observed when the hydrocortisone dose was decreased by 50 and 30%, respectively (14, 16). However, the blood pressure was unaffected when the dose of hydrocortisone was decreased from 30 to 15 mg (15). Glucose metabolism was not affected in these trials, suggesting that a dose reduction alone is not enough for reducing blood pressure and improving glucose metabolism. Other studies in AI patients have shown improved well-being by better mimicking the normal serum cortisol (S-cortisol) profile by increasing the frequency of dosing of oral immediate-release tablets or using a hydrocortisone infusion pump system (17, 18). The pattern of hydrocortisone delivery and the S-cortisol exposure-time profile may therefore be as crucial for patient outcome as the total daily dose.

A novel once-daily (OD) dual-release hydrocortisone tablet, based on an immediate-release coating together with an extended-release core, was developed to obtain a more physiological circadian-based S-cortisol exposure-time profile (19). The primary objective of this study was to compare the S-cortisol exposure-time profile of the OD dual-release tablet and a conventional thrice-daily (TID) replacement therapy in patients with primary AI. Secondary objectives were to compare metabolic outcome, QoL, and safety of the different treatment regimens. The rationale for using TID as the comparator was based on previous data indicating improved outcome of using hydrocortisone TID as compared with twice-daily dosing (16, 17) and its common use in Europe (2, 3).

Patients and Methods

This was an open, controlled, randomized, two-armed, two-period, 12-wk crossover, multicenter trial with a 24-wk extension on the OD therapy (Fig. 1). Patients were on a stable hydrocortisone dose (for at least 3 months before entering the study), which was kept constant throughout the study. Before randomization, all patients entered a 4-wk run-in period during which patients on twice-daily therapy were transferred to a TID oral regimen, with the same total daily dose. Eighteen patients underwent full single/multiple-dose standardized in-house pharmacokinetic (PK) sampling during 24 h at randomization and at the end of each 12-wk period (multiple-dose PK). A reduced PK sampling scheme of single-dose PK on d 1–2 and multiple-dose PK sampling on d 7–8 was performed in 46 patients in both of the 12-wk periods. The patients remained...
at the clinical trial unit on PK sampling days receiving standard-
ized meals. Blood samples for full PK (S-cortisol) analysis were
collected at 0, 5, 10, 15, 20, 25, 30, 45, 60, and 90 min and 2,
3, 4, 5, 6, 8, and 24 h during reduced PK sampling and in addition
at 10, 12, 14, 16, and 18 h during full PK sampling. Serum
samples were stored at −20°C until the analysis, which was
performed in one run.

Patients returned to the clinic every 4 wk for study drug dis-
pensation, adverse event (AE) assessment, and collection of pa-
tient questionnaires. The patients were admitted for full clinical
and biochemical examination (fasting lipids, glucose, glycated
hemoglobin (HbA1c), insulin, and bone markers) at the 12-week
visit. Except for PK sampling, the same evaluations as in the
controlled phase were performed after 12 and 24 wk in the ex-
tension study on OD therapy.

Study participants

Males and females aged at least 18 yr with primary AI diag-
nosed more than 6 months before study entry and with a total
daily hydrocortisone dose of 20, 25, 30, or 40 mg were eligible
for the study. Exclusion criteria included clinical or laboratory
signs of significant cerebral, cardiovascular, respiratory, hepa-
tobiliary, or pancreatic disease, renal dysfunction, gastrointes-
tinal emptying, or motility disturbances and underlying disease
that could necessitate treatment with glucocorticoids. Any med-
ication or agents that could interfere with cortisol metabolism
within 14 d before study start and ongoing treatment with de-
hydroepiandrosterone or oral estrogens were not allowed. Min-
eralocorticoid or T4 replacement therapy was stable for at least
3 months before the trial. Pregnant or lactating women were not
eligible for the trial.

All patients received oral and written study information and
signed informed consent before entering the study. The study
protocol (EudraCT:2006-0007084-83; www.ClinicalTrials.gov
ID NCT00915343) was approved by the Ethics Committee at
the Sahlgrenska Academy, Gothenburg, and by the Swedish
Medical Product Agency. The study was performed according to
the principles of Good Clinical Practice (CPMP/ICH/135/95)
and the Declaration of Helsinki. The trial was conducted be-

Intervention

The dual-release tablets (20 and 5 mg) were administered
orally OD in the fasting state in the morning (at 0800 h on PK
sampling days) (19). The reference drug was a hydrocortisone
10-mg tablet administered TID (at 0800, 1200, and 1600 h on
PK sampling days). For example, a daily dose of 30 mg hy-
drocortisone was delivered as 20 + 5 + 5 mg for OD, all at
0800 h, and as 15 + 10 + 5 mg for TID. The patients were
instructed to double the dose during an intercurrent illness.
For OD, a second dose 8 ± 2 h after the first morning dose was
added.

By counting the number of dispensed and returned tablets,
compliance could be calculated as the actual consumption in
percentage of expected consumption: 100 × (number of dis-
pensed tablets − number of returned tablets)/(number of days
during the study period × daily number of hydrocortisone tab-
lets when taking the ordinary daily dose).

Analytical methods

Serum cortisol was assayed by a competitive immunoassay
using direct chemiluminescent technology (ADVIA Centaur;
Bayer Diagnostics, Fenwold, Germany). The sensitivity of the
assay was 5.3 nmol/liter, and the total coefficient of variation
was less than 8%.

Osteocalcin (CIS Bio International, Gif-sur Yvette, France)
and intact N-terminal propeptide of type I procollagen (PINP)
(Orion Diagnostica, Espoo, Finland) were measured using im-
munoradiometric assay methods.

Serum lipids were measured using enzymatic methods, serum
insulin by a RIA and plasma glucose by a photometric method (all
Roche Diagnostics, GmbH, Mannheim, Germany). HbA1c was
analyzed using a chromatographic method (Kolon Mono-S; Am-
sham Pharmacia Biotech, Uppsala, Sweden). Serum cortisol, lip-
ids, insulin, and bone markers were analyzed in a central laboratory.

Patient questionnaires

Three validated QoL instruments were used: Fatigue Impact
Scale (20), Short Form Survey (21), and Psychological General
Well-Being index (22). Treatment preference was also collected
by patient questionnaires.

Statistical analyses

The study was designed as a two-period crossover study. For
analysis of the quotient of area under the curve (AUC0–24 h
(multiple dose) between OD and TID, log AUC0–24 h
was analyzed using the SAS procedure PROC GLM with sequence,
subject (sequence), period, and treatment as class variables. AUC0–4
was calculated by the linear/logarithmic trapezoidal rule. AUC0–t
was extrapolated to infinity (AUC0–infty) by adding AUC0–t
(where t is time), calculated as the last predicted concentration
divided by the terminal rate constant λ, using WinNonlin soft-
ware version 5.2 (Pharsight Corp., Mountain View, CA).

For analyses of other PK endpoints, preference, QoL, and
biochemical and safety variables, the differences between the
period 1 and period 2 were calculated for each patient. These
differences were then compared between patients who started on
OD and those who started on TID using Fisher’s nonparametric
two-sample permutation test or Wilcoxon signed rank test for
continuous variables and sign test for ordinal and dichotomous
variables. Post hoc analyses were performed of the subgroup of
patients with concomitant diabetes mellitus (DM) and of AE vs.
exposure. Data from the safety and intention-to-treat (ITT) pop-
ulation are presented. All significance tests were two sided and
conducted at a significance level of 0.05.

Results

Baseline characteristics

Sixty-four patients were randomized, and the ITT pop-
ulation includes 63 patients (Fig. 1 and Table 1). The mean
age was 47 yr (range, 19–71 yr), the most common dose of
hydrocortisone was 30 mg/d (58.7%), and 45% had a
TID regimen before the run-in period. Eleven patients
(17.5%) had DM, and 11 had treated hypertension; 87.5% were on
fludrocortisone treatment, and 36.5% received replacement therapy with T4. Treatment compli-
TABLE 1. Demographics and baseline characteristics of patients with primary AI: ITT population and patients with concomitant DM

<table>
<thead>
<tr>
<th></th>
<th>ITT (n = 63)</th>
<th>DM&lt;sup&gt;a&lt;/sup&gt; (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47.3 (13.7)</td>
<td>50.6 (16.4)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37 (58.7%)</td>
<td>8 (72.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (41.3%)</td>
<td>3 (27.3%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.6 (14.3)</td>
<td>90.8 (16.4)</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>26.2 (4.0)</td>
<td>29.2 (4.4)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>123.6 (19.7)</td>
<td>131.7 (15.3)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>75.8 (11.5)</td>
<td>75.3 (10.6)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65.5 (10.4)</td>
<td>65.7 (10.6)</td>
</tr>
<tr>
<td>Normal ECG</td>
<td>56 (88.9%)</td>
<td>10 (90.9%)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>11 (17.5%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Replacement dose (mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>8 (12.7%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>25</td>
<td>6 (9.5%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>30</td>
<td>37 (58.7%)</td>
<td>5 (45.5%)</td>
</tr>
<tr>
<td>40</td>
<td>12 (19.0%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Regimen before run-in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BID</td>
<td>33 (55.0%)</td>
<td>7 (63.6%)</td>
</tr>
<tr>
<td>TID</td>
<td>27 (45.0%)</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (17.5%)</td>
<td>4 (36.4%)</td>
</tr>
</tbody>
</table>

Results are presented as n (%) for categorical variables and mean (SD) for continuous variables. BID, Twice daily; BMI, body mass index; ECG, electrocardiogram.

<sup>a</sup>DM type 1, n = 9; DM type 2, n = 2.

The mean total S-cortisol AUC<sub>0–24 h</sub> at multiple dosage was 19.4% lower with the OD formulation than with the conventional TID formulation (quotient OD/TID = 0.806, P < 0.0001). The mean AUC<sub>0–4 h</sub> was 6.4% higher after OD than after TID treatment, whereas the mean AUC<sub>4–10 h</sub> was 30.5% lower after OD, and AUC<sub>10–24 h</sub> was 58.8% lower after OD (Table 2).

The S-cortisol concentration-time profile demonstrated three peaks after TID treatment, whereas only one peak was observed for 87% of the patients on OD treatment. The time to C<sub>first</sub> (first determined concentration) was similar between OD and TID treatment (Fig. 2). The mean terminal half-life (operational) of cortisol was 4.6 h (t<sub>1/2</sub> over 5–14 h) after OD and 1.8 h (t<sub>1/2</sub> over 5–24 h) after TID treatment. The longer terminal half-life after OD contributes to a later [T<sub>max1</sub> (time to maximal serum concentration)] appearance of C<sub>max1</sub> (maximal serum concentration), but the accumulation ratio was similar during OD (1.11) and TID (1.03) treatment (P = 0.10; n = 55), showing no risk of dose accumulation. The mean extrapolated area was also small for both OD and TID.

**Body weight, blood pressure, and heart rate**

Body weight decreased over 12 wk with OD treatment, whereas a small increase was observed during TID treatment (difference of OD – TID at 12 wk = −0.7 kg, P = 0.005; Fig. 3). The mean body weight also decreased from randomization to the end of the 24-wk extension phase (−0.9 kg, P = 0.02).

Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) also decreased during 12 wk of OD treatment but increased during TID treatment (difference in SBP =

**TABLE 2. Secondary PK variables in patients with primary AI, OD vs. TID [average of single and multiple dosing (combined full and reduced PK)], in the ITT population (patients with both OD and TID measurements)**

<table>
<thead>
<tr>
<th></th>
<th>OD, mean (SD)</th>
<th>TID, mean (SD)</th>
<th>Quotient OD/TID or difference OD – TID (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max1&lt;/sub&gt; (nmol/liter)</td>
<td>690.7 (109.2)</td>
<td>802.8 (136.2)</td>
<td>Difference = −111.989 (−133.980 to −89.999)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C&lt;sub&gt;6h&lt;/sub&gt; (nmol/liter)</td>
<td>278.5 (134.9)</td>
<td>426.7 (135.2)</td>
<td>Difference = −148.015 (−189.469 to −106.561)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C&lt;sub&gt;7h&lt;/sub&gt; (nmol/liter)</td>
<td>214.1 (106.8)</td>
<td>322.4 (110.0)</td>
<td>Difference = −108.306 (−140.193 to −76.420)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0–4 h&lt;/sub&gt; (h·nmol/liter)</td>
<td>2053.7 (432.0)</td>
<td>1929.7 (409.9)</td>
<td>Quotient = 1.064 (1.032–1.097)</td>
<td>0.0002</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;4–10 h&lt;/sub&gt; (h·nmol/liter)</td>
<td>1334.7 (582.5)</td>
<td>1839.0 (599.0)</td>
<td>Quotient = 0.695 (0.632–0.765)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;10–24 h&lt;/sub&gt; (h·nmol/liter)</td>
<td>465.0 (352.2)</td>
<td>1058.0 (752.4)</td>
<td>Quotient = 0.412 (0.338–0.504)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0–infinity&lt;/sub&gt; (h·nmol/liter)</td>
<td>3972.6 (1125.9)</td>
<td>5162.8 (1777.2)</td>
<td>Quotient = 0.776 (0.714–0.843)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>T&lt;sub&gt;200&lt;/sub&gt; (nmol/liter)</td>
<td>0.262 (0.154)</td>
<td>0.213 (0.119)</td>
<td>Difference = 0.049 (0.006–0.093)</td>
<td>0.0280</td>
</tr>
<tr>
<td>T&lt;sub&gt;max1&lt;/sub&gt; (h)</td>
<td>1.11 (0.84)</td>
<td>0.837 (0.388)</td>
<td>Difference = 0.270 (0.028–0.512)</td>
<td>0.0214</td>
</tr>
</tbody>
</table>

P values are for comparisons of the difference between OD and TID (see Subjects and Methods). CI, Confidence interval; C<sub>max</sub> maximal serum concentration; C<sub>6h</sub> concentration at 6 h; T<sub>200</sub> time to reach 200 nmol/L; T<sub>max1</sub>, time to maximal concentration.

Serum cortisol concentration (µg/liter) = S-cortisol concentration (nmol/liter)/27.59.
−5.5 mm Hg, \( P = 0.0001 \); difference in DBP = −2.3 mm Hg, \( P = 0.03 \); Fig. 3). Mean heart rate increased over 12 wk OD treatment and decreased during TID treatment (difference = 2.2 beats/min, \( P = 0.003 \)). Reductions in blood pressure were predominantly observed in patients with normal to high blood pressure levels (data not shown). No further changes in blood pressure occurred during the extension phase.

**Glucose and lipid metabolism and bone markers**

No differences in fasting plasma glucose or insulin were observed between the treatments at 12 wk; however, a small but statistically significant reduction in HbA1c was observed during OD as compared with TID at 12 wk (Table 3). A small decrease in mean high-density lipoprotein (HDL) and a small increase in S-triglycerides were observed at 12 wk during OD (Table 3). From randomization to end of the 24-wk extension, total S-cholesterol decreased (−0.2 mmol/liter, \( P = 0.04 \)) and S-triglyceride concentration increased (0.2 mmol/liter, \( P = 0.049 \)).

Mean concentrations of S-PINP increased over 12 wk OD as compared with TID treatment (Table 3). A similar trend was seen for osteocalcin. Bone markers were unchanged during the extension phase. No statistically or clinically relevant changes were observed in hematology parameters, electrolytes, liver function tests, or TSH.

**QoL and treatment preference**

In the Fatigue Impact Scale questionnaire, the difference between OD and TID treatment in psychosocial functioning (\( P = 0.04 \); \( n = 60 \)), cognitive functioning (\( P = 0.054 \)), and the total score (\( P = 0.08 \)) were in favor of OD at 12 wk. In the Psychological General Well-Being questionnaire, the difference between OD and TID treatment, with regard to the total score (\( P = 0.06 \)) and positive well-being (\( P = 0.03 \)) at 12 wk was in favor of OD treatment. No differences were observed between OD and TID treatment at 12 wk in the Short Form Survey questionnaire.

The preference of OD vs. TID treatment was assessed as large or very large by 85% of the patients at 12 wk (\( P < 0.0001 \); \( n = 58 \)). Also, 59 of 64 randomized patients (92%) chose to continue into the extension phase of the trial.

**Adverse events**

In the crossover phase, 47 of the 64 patients (73.4%) reported a total of 103 AE on OD treatment, and 42 patients (65.6%) reported 75 AE on TID treatment. The most commonly reported AE were nasopharyngitis (seven patients on OD vs. 15 on TID), fatigue (eight vs. three), gastroenteritis (eight vs. two), and influenza (eight vs. two). The frequency of AE belonging to the system organ...
class infections and infestations was 43.8% on OD and 39.1% on TID treatment. Five AE were of severe intensity: two in patients on OD (both gastroenteritis) and three in patients on TID treatment (one case of each of gastroenteritis, streptococcal infection, and headache). AE were more commonly reported during the first 8 wk of the OD period (0–4 wk, 33 AE; 4–8 wk, 31 AE) than during wk 8–12 (24 AE).

During the 6-month extension, 30 patients (50.8%) reported 37 AE during the first 3-month period, and 31 patients (54.4%) reported 50 AE during the second 3-month period.

No deaths occurred during the study. Eight serious adverse events (SAE) occurred in the crossover phase, six SAE occurring during OD, and two during TID treatment. All SAE were caused by infectious disorders, and the patients were hospitalized (a common routine in Sweden) to prevent/treat a state of acute AI (OD, two cases of gastroenteritis, one case of bacterial bronchitis, and one case of pneumonia; TID, two cases of gastroenteritis). During the 6-month extension, two patients (3.4%) reported SAE during the first and four patients (7.0%) during the second 3-month period. These were all assessed as serious due to hospitalization and included one case of each of gastroenteritis, pancreatitis, nephrolithiasis, cholelithiasis, planned surgery (hysterectomy), and varicella.

No withdrawals due to AE were reported. No association was detected between occurrence of SAE and daily dose, extent of exposure measured as AUC0–24 h, preceding intercurrent illness, concomitant disease, concomitant medication, age, gender, or study site.

**Rescue therapy**

The percentage of days when increased hydrocortisone use was reported was low (mean, 3.8% on OD and 1.9% on TID; median, 0.0% on both treatments); i.e. a majority of the patients had no increase of hydrocortisone use during a 3-month period. Intercurrent illness use constituted 1.7% of the total dose during OD treatment and 1.1% of the total dose during TID in the randomized part of the trial. Increased hydrocortisone use due to physical or mental stress constituted 0.4% of the total dose during OD treatment and 0.2% of the total dose during TID.

**Patients with concomitant DM**

The PK profile was essentially the same in the subgroup of 11 patients with concomitant DM, as in patients without DM (data not shown). The mean HbA1c (OD – TID = −0.6%, P = 0.004), S-triglycerides, and SBP were lower on OD than on TID treatment at 12 wk, and mean PINP values were higher on OD than on TID treatment also in patients with DM (Table 3). Preference data showed that 91% of the DM patients preferred OD treatment to conventional treatment. The following changes and trends were observed over the 24-wk extension in DM patients: body weight, −0.6 kg, P = 0.43; total S-cholesterol, −0.3 mmol/liter, P = 0.02; HbA1c, −0.4%, P = 0.31; SBP, −4.2 mm Hg, P = 0.20; and DBP, −2.0 mm Hg, P = 0.39.

**Discussion**

A novel oral dual-release formulation of hydrocortisone was developed to obtain a more physiological circadian-

### Table 3. Glucose, lipid, and bone metabolism in patients with primary AI during 12 wk OD and TID: safety population and the patients with concomitant DM

<table>
<thead>
<tr>
<th>Variable</th>
<th>Safety population</th>
<th>DM population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline, mean (SD)</td>
<td>12 wk OD, mean (SD)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.9 (1.1)</td>
<td>4.9 (0.9)</td>
</tr>
<tr>
<td>n</td>
<td>60</td>
<td>61</td>
</tr>
<tr>
<td>Cholesterol (mmol/liter)</td>
<td>5.3 (1.1)</td>
<td>5.2 (1.0)</td>
</tr>
<tr>
<td>n</td>
<td>63</td>
<td>57</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/liter)</td>
<td>3.1 (1.0)</td>
<td>3.0 (0.9)</td>
</tr>
<tr>
<td>n</td>
<td>63</td>
<td>57</td>
</tr>
<tr>
<td>Triglycerides (mmol/liter)</td>
<td>1.4 (0.4)</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>n</td>
<td>63</td>
<td>57</td>
</tr>
<tr>
<td>PINP (µg/liter)</td>
<td>15.2 (28.3)</td>
<td>16.9 (34.8)</td>
</tr>
<tr>
<td>n</td>
<td>63</td>
<td>58</td>
</tr>
<tr>
<td>Osteocalcin (µg/liter)</td>
<td>11.4 (5.6)</td>
<td>13.4 (6.5)</td>
</tr>
</tbody>
</table>

P values are for comparisons of the difference between OD and TID (see Subjects and Methods).
targeted S-cortisol concentration-time profile and improve outcome of glucocorticoid replacement therapy. The once-a-day administration also reduces the day-to-day variation in exposure and thereby increases the robustness of the achieved profile. Compared with TID, the OD profile increased S-cortisol exposure in the morning, reduced exposure in the afternoon and evening, and reduced 24-h exposure by approximately 20%. These differences may explain the reductions in body weight and blood pressure and the improved glucose metabolism observed with the OD treatment.

Total 24-h S-cortisol exposure was reduced while still providing a higher exposure during the first 4 h in the morning and then gradually lower levels throughout the day with a cortisol-free nighttime interval. Moreover, daytime troughs and the last two peaks during the day with TID were not observed with OD. These features of the S-cortisol exposure-time profile, together with the lower total AUC\(_{0-24}\) h is likely to improve efficacy and safety outcomes.

There is a delicate balance between the short-term benefits on well-being and the long-term adverse metabolic and cognitive impact of slight cortisol overexposure as seen in subclinical Cushing’s syndrome (23) and in users of moderate doses of synthetic glucocorticoids (24). Low cortisol exposure during the evening and a night-free interval were considered to be important to prevent dose accumulation and additional overexposure. Available data do not suggest that low cortisol exposure in the late evening and night constitutes a safety issue (25). On the other hand, elevated cortisol levels between 2200 and 0400 h may have detrimental effects on sleep quality and thereby well-being in AI patients (26). When targeting a physiological S-cortisol profile, it should also be considered that although collection of normative data has been done with care (27), there is still a concern that nighttime cortisol levels might be falsely high due to an arousal effect (stress) (28).

No previous patient studies have demonstrated the importance of the S-cortisol exposure-time profile on metabolic factors. In this study, reductions in body weight, HbA1c, and blood pressure and improvements in bone formation markers occurred during OD as compared with TID. In contrast, a small increase in S-triglycerides and a small decrease in HDL-cholesterol concentrations occurred. Previous studies using similar doses of hydrocortisone (14–16) have been unable to demonstrate changes in glucose metabolism and blood pressure, although the doses were reduced by 30–50%. Studies in rodents have, however, shown that changing from a diurnal exposure pattern to a more continuous exposure using the same glucocorticoid dose leads to weight gain and insulin resistance (9). This clearly indicates the importance of the cortisol time-exposure profile for the improved outcome seen in this study, in particular the reduced exposure during the afternoon and evening.

The results achieved by the dual-release hydrocortisone treatment in patients with DM may be of particular benefit because patients with both AD and type 1 DM have a 2-fold higher mortality rate than patients with AD alone (5). A clinically significant reduction in HbA1c and favorable effects on body weight, serum lipids, and blood pressure were obtained by changing from TID to OD. Current glucocorticoid replacement results in large fluctuations in the cortisol levels directly influencing glucose homeostasis and, consequently, making accompanying insulin treatment difficult to manage. This is supported by data showing increased insulin requirement and a tendency of increased frequency of severe hypoglycemia in patients with both AD and type 1 DM as compared with patients with type 1 DM alone (29).

This prospective study recording the incidence of intercurrent illnesses in AI patients found that days when it was necessary to take extra doses of hydrocortisone due to illness were very infrequent. Approximately 20% of the patients, however, required emergency medical care for any reason during a 1-yr period. This may be higher than reported in a previous cross-sectional survey (10) studying the frequency of adrenal crises only. There was an initial increase in number of AE during OD treatment. The reasons for this transient increase could be an effect of the open-study design leading to an increased initial awareness of symptoms and signs that could reflect glucocorticoid deficiency merely by changing the treatment regimen because these patients have been educated to recognize such symptoms. Another explanation is the marked change in the cortisol exposure time.

The compromised QoL in AI patients (11, 12) emphasizes the need for studying QoL during a new therapeutic approach. The three questionnaires used demonstrated a consistent pattern. After a small nonsignificant initial deterioration in QoL (data not shown), significant improvements were observed in some of the QoL domains at 12 wk of OD treatment, particularly in those reflecting fatigue. Although the open design of the study is a limitation, the initial deterioration strongly suggests that the observed changes are not placebo effects. The strong patient preference for the new treatment and the high rate of participation through the extension phase support these data.

In the absence of a reliable biomarker of hydrocortisone efficacy, serum cortisol AUC\(_{0-24}\) h, (a measure of bioavailability) was chosen as the primary endpoint considered to reflect both safety and efficacy. An open-trial
design was selected because a blinded trial using a double-dummy design was considered a safety hazard. The concern is that an AI patient who is at risk for rapid development of adrenal crisis in certain acute situations may mix up the emergency medication with dummies (placebo) with serious outcome. Also, because the hydrocortisone dose–response relationship is poor (30), a crossover design was chosen to minimize the large and well-known between-individual variation in cortisol responsiveness. Because no true washout is possible because AI patients cannot be left untreated for safety reasons, carryover effects may occur. The randomized study design and the 3-month duration of each treatment arm will, however, reduce such effects. Interpretation of the metabolic data and QoL should therefore take the study design into consideration.

In conclusion, the cortisol time-exposure profile achieved using the OD dual-release hydrocortisone treatment improved cardiovascular risk factors, glucose metabolism, and QoL in comparison with conventional treatment. The OD dosing achieved a high and reliable bioavailability and consistent-exposure S-cortisol profile more resembling normal physiology, avoiding the last two peaks during TID, all of which may be of importance for improving outcome in AI patients.

Acknowledgments

We thank the study personnel for their skillful support during this study and the patients who so willingly participated. We also thank Karin Gewert and Maria Fors for the assistance in preparing this manuscript, Statistiska Konsultgruppen for their statistical expertise, and Professors Thomas Hedner and Bengt-Åke Bengtsson for their contribution to this work.

Address all correspondence and requests for reprints to: Gudmundur Johannsson, M.D., Ph.D., Department of Endocrinology, Gröna stråket 8, Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden. E-mail: Gudmundur.Johannsson@gu.se.

DuoCort Pharma AB financially supported the trial. G.J. received a mobility grant from the Swedish Foundation of Strategic Research.

Disclosure Summary: G.J., H.L., and S.S. have equity interests in DuoCort AB. P.M.S., J.P.M., and B.M.K.B. have acted as Consultants for DuoCort Pharma AB.

References


