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

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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 glycated hemoglobin (absolute difference = −0.1%, $P = 0.0006$) were all reduced after OD compared with TID at 12 wk. Compared with TID, a reduction in glycated hemoglobin 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**)

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Abbreviations: AD, Addison's disease; AE, adverse event; AI, adrenal insufficiency; AUC, area under the curve; DBP, diastolic blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; ITT, intention to treat; OD, once daily; PINP, N-terminal propeptide of type I procollagen; PK, pharmacokinetic; QoL, quality of life; SAE, serious AE; SBP, systolic blood pressure; S-cortisol, serum cortisol; TID, thrice daily.

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 tables 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

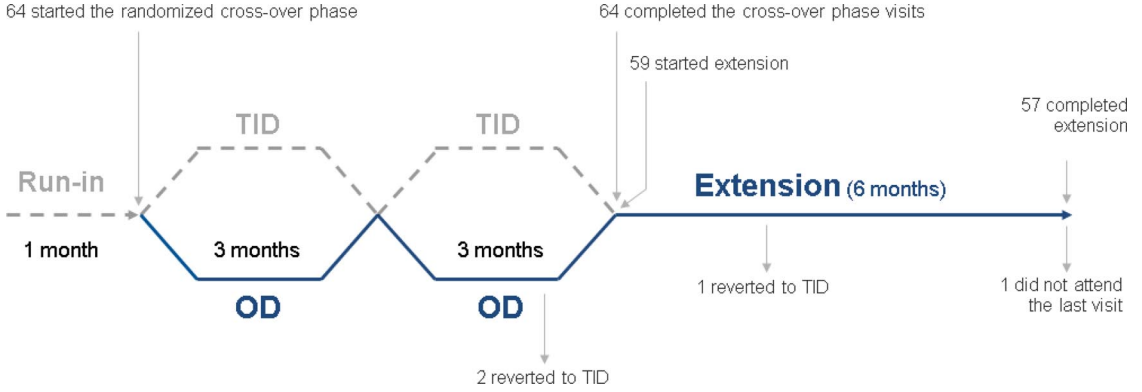

FIG. 1. Study design and patient disposition. A comparison between OD oral modified-release tablet and conventional tablets TID followed by an extension on OD. All 64 patients received at least one dose of study medication and are included in the safety population. All 64 patients completed the study visits of the randomized crossover phase, but two patients reverted to conventional treatment during the OD period. The ITT population includes 63 patients (excluding one patient with failed needle insertion); among these, 59 had complete OD and TID PK data for the analysis of the primary variable. Fifty-nine patients (92%) entered the 6-month extension. Fifty-seven patients completed the extension phase.

at the clinical trial unit on PK sampling days receiving standardized 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 dispensation, adverse event (AE) assessment, and collection of patient 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 extension study on OD therapy.

Study participants

Males and females aged at least18 yr with primary AI diagnosed 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, hepatobiliary, or pancreatic disease, renal dysfunction, gastrointestinal emptying, or motility disturbances and underlying disease that could necessitate treatment with glucocorticoids. Any medication or agents that could interfere with cortisol metabolism within 14 d before study start and ongoing treatment with dehydroepiandrosterone or oral estrogens were not allowed. Mineralocorticoid or L-T_4 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 between August 21, 2007, and January 28, 2009.

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 hydrocortisone 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 dispensed tablets − number of returned tablets)/(number of days during the study period × daily number of hydrocortisone tablets when taking the ordinary daily dose).

Analytical methods

Serum cortisol was assayed by a competitive immunoassay using direct chemiluminescent technology (ADVIA Centaur; Bayer Diagnostics, Femwald, Germany). The sensitivity of the assay was 5.5 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 immunoradiometric 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; Amersham Pharmacia Biotech, Uppsala, Sweden). Serum cortisol, lipids, 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 $(AUC)_{0-24\ h}$ (multiple dose) between OD and TID, log $AUC_{0-24\ h}$, was analyzed using the SAS procedure PROC GLM with sequence, subject (sequence), period, and treatment as class variables. $AUC_{0\text{-}t}$ was calculated by the linear/logarithmic trapezoidal rule. $AUC_{0\text{-}t}$ was extrapolated to infinity ($AUC_{0\text{-infinity}}$) by adding $AUC_{t\text{-infinity}}$ (where t is time), calculated as the last predicted concentration divided by the terminal rate constant λ_z using WinNonlin software 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) population 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 population 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 L-T_4. Treatment compli-

TABLE 1. Demographics and baseline characteristics of patients with primary AI: ITT population and patients with concomitant DM

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

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

[a] DM type 1, n = 9; DM type 2, n = 2.

ance was similar between OD (105%; SD = 8%) and TID (103%; SD = 13.2%).

Serum PK of cortisol

The mean total S-cortisol $AUC_{0-24\ h}$ 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 $AUC_{0-4\ h}$ was 6.4% higher after OD than after TID treatment, whereas the mean $AUC_{4-10\ h}$ was 30.5% lower after OD, and $AUC_{10-24\ h}$ 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_{first} (first determined concentration) was similar between OD and TID treatment (Fig. 2). The mean terminal half-life (operational) of cortisol was 4.6 h ($t_{½}$ over 5–14 h) after OD and 1.8 h ($t_{½}$ over 5–24 h) after TID treatment. The longer terminal half-life after OD contributes to a later [T_{max1} (time to maximal serum concentration)] appearance of C_{max1} (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 over 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)

	OD, mean (SD)	TID, mean (SD)	Quotient OD/TID or difference OD − TID (95% CI)	*P* value
C_{max1} (nmol/liter)	690.7 (109.2)	802.8 (136.2)	Difference = −111.989 (−133.980 to −89.999)	<0.0001
n	61	61		
$C_{6\ h}$ (nmol/liter)	278.5 (134.9)	426.7 (135.2)	Difference = −148.015 (−189.469 to −106.561)	<0.0001
n	60	60		
$C_{7\ h}$ (nmol/liter)	214.1 (106.8)	322.4 (110.0)	Difference = −108.306 (−140.193 to −76.420)	<0.0001
n	60	60		
$AUC_{0-4\ h}$ (h · nmol/liter)	2053.7 (432.0)	1929.7 (409.9)	Quotient = 1.064 (1.032–1.097)	0.0002
n	61	61		
$AUC_{4-10\ h}$ (h · nmol/liter)	1334.7 (582.5)	1839.0 (599.0)	Quotient = 0.695 (0.632–0.765)	<0.0001
n	61	61		
$AUC_{10-24\ h}$ (h · nmol/liter)	465.0 (352.2)	1058.0 (752.4)	Quotient = 0.412 (0.338–0.504)	<0.0001
n	61	61		
$AUC_{0\text{-infinity}}$ (h · nmol/liter)	3972.6 (1125.9)	5162.8 (1777.2)	Quotient = 0.776 (0.714–0.843)	<0.0001
n	52	52		
$T_{200\ nmol/liter}$ (h)	0.262 (0.154)	0.213 (0.119)	Difference = 0.049 (0.006–0.093)	0.0280
n	62	62		
T_{max1} (h)	1.11 (0.84)	0.837 (0.388)	Difference = 0.270 (0.028–0.512)	0.0214
n	61	61		

P values are for comparisons of the difference between OD and TID (see *Subjects and Methods*). CI, Confidence interval; C_{max}, maximal serum concentration; C_{6h}, concentration at 6 h; T_{200}, time to reach 200 nmol/L; T_{max1}, time to maximal concentration.

Serum cortisol concentration (μg/liter) = S-cortisol concentration (nmol/liter)/27.59.

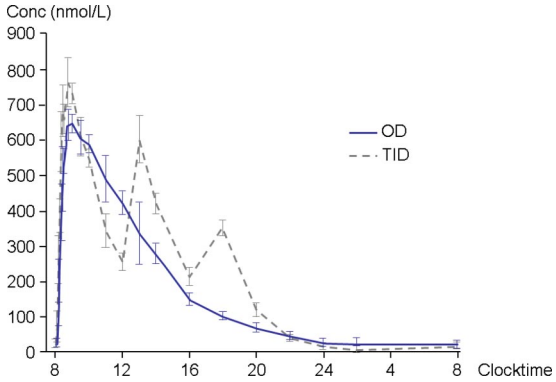

FIG. 2. Mean observed S-cortisol concentration after single and multiple dosing in 64 patients with primary AI. Mean values are from all dosing events (20–40 mg) during both OD and TID. The *error bars* demonstrate the 95% confidence interval.

−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

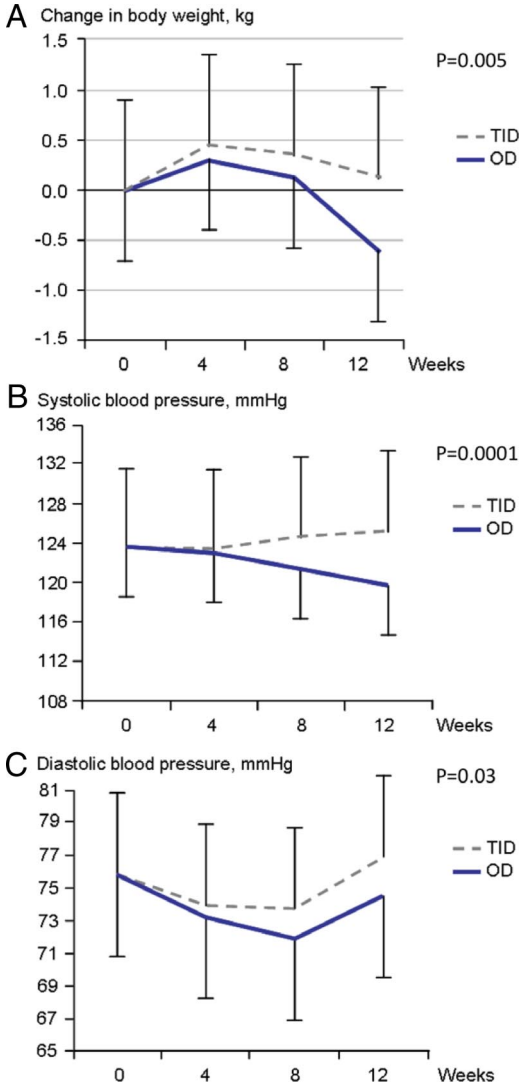

FIG. 3. Body weight and blood pressure in 64 patients with primary AI during 12 wk of OD and TID hydrocortisone replacement therapy. A, Mean (SD) change in body weight; B, mean (SD) systolic blood pressure; C, mean (SD) diastolic blood pressure. All *P* values are for the difference between OD and TID at 12 wk.

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

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

	Safety population					DM population	
Variable	Baseline, mean (SD)	12 wk OD, mean (SD)	12 wk TID, mean (SD)	OD minus TID at 12 wk	*P* value	OD minus TID at 12 wk	*P* value
HbA1c (%)	4.9 (1.1)	4.9 (0.9)	5.0 (1.1)	−0.1 (0.4)	0.0006	−0.6 (0.6)	0.0039
n	60	61	59	57		10	
Cholesterol (mmol/liter)	5.3 (1.1)	5.2 (1.0)	5.3 (0.9)	0.0 (0.4)	0.6729	−0.2 (0.2)	0.0938
n	63	57	57	51		8	
LDL-cholesterol (mmol/liter)	3.1 (1.0)	3.0 (0.9)	3.1 (0.9)	0.0 (0.3)	0.9131	−0.1 (0.1)	0.0625
n	63	57	57	51		8	
HDL-cholesterol (mmol/liter)	1.4 (0.4)	1.4 (0.4)	1.5 (0.4)	−0.1 (0.2)	<0.0001	−0.1 (0.1)	0.1875
n	63	57	57	51		8	
Triglycerides (mmol/liter)	1.5 (0.8)	1.6 (0.9)	1.4 (0.6)	0.2 (0.6)	0.0086	−0.2 (0.2)	0.0313
n	62	57	57	51		8	
PINP (μg/liter)	57.2 (28.3)	63.9 (34.8)	56.1 (29.2)	6.1 (15.5)	0.0036	5.8 (7.2)	0.0195
n	63	58	58	53		9	
Osteocalcin (μg/liter)	11.4 (5.6)	13.4 (6.5)	12.4 (5.4)	0.7 (4.5)	0.2337	0.5 (3.1)	0.6523
n	63	58	58	53		9	

P values are for comparisons of the difference between OD and TID (see *Subjects and Methods*).

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, two cases of acute AI induced by 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 $AUC_{0-24\ h}$, 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-

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.

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