

A Phase 2 Study of Continuous Subcutaneous Hydrocortisone Infusion in Adults With Congenital Adrenal Hyperplasia

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Context: Classic congenital adrenal hyperplasia (CAH) management remains challenging, given that supraphysiologic glucocorticoid doses are often needed to optimally suppress the ACTH-driven adrenal androgen overproduction.

Objective: This study sought to approximate physiologic cortisol secretion via continuous subcutaneous hydrocortisone infusion (CSHI) and evaluate the safety and efficacy of CSHI in patients with difficult-to-treat CAH.

Design: Eight adult patients with classic CAH participated in a single-center open-label phase I–II study comparing CSHI to conventional oral glucocorticoid treatment. All patients had elevated adrenal steroids and one or more comorbidities at study entry. Assessment while receiving conventional therapy at baseline and 6 months following CSHI included: 24-hour hormonal sampling, metabolic and radiologic evaluation, health-related quality-of-life (HRQoL), and fatigue questionnaires.

Main Outcome Measures: The ability of CSHI to approximate physiologic cortisol secretion and the percent of patients with 0700-hour 17-hydroxyprogesterone (17-OHP) \leq 1200 ng/dL was measured.

Results: CSHI approximated physiologic cortisol secretion. Compared with baseline, 6 months of CSHI resulted in decreased 0700-hour and 24-hour area under the curve 17-OHP, androstenedione, ACTH, and progesterone, increased osteocalcin, c-telopeptide and lean mass, and improved HRQoL (and SF-36 Vitality Score), and fatigue. One of three amenorrheic women resumed menses. One man had reduction of testicular adrenal rest tissue.

Conclusions: CSHI is a safe and well-tolerated modality of cortisol replacement that effectively approximates physiologic cortisol secretion in patients with classic CAH poorly controlled on conventional therapy. Improved adrenal steroid control and positive effects on HRQoL suggest that CSHI should be considered a treatment option for classic CAH. The long-term effect on established comorbidities requires further study. (*J Clin Endocrinol Metab* 101: 4690–4698, 2016)

Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders of adrenal steroidogenesis with 21-hydroxylase deficiency accounting for 95% of cases (1). In the classic form, 21-hydroxylase enzyme function is lacking and deficient cortisol and aldosterone biosynthesis results in excess ACTH-driven adrenal steroid production. Conventional cortisol replacement

with oral glucocorticoids once, twice, or thrice daily remains suboptimal, and often fails to effectively suppress adrenal steroid production without supraphysiologic

Abbreviations: 17-OHP, 17-hydroxyprogesterone; ALT, alanine aminotransferase; A₄, androstenedione; AddiQoL, adrenal insufficiency-specific HRQoL; AST, aspartate aminotransferase; AUC, area under the curve; BMD, bone mineral density; BMI, body mass index; CAH, congenital adrenal hyperplasia; CSHI, continuous subcutaneous hydrocortisone infusion; CTX, cross-linked telopeptide; CV, coefficient of variation; DXA, dual-energy x-ray absorptiometry; GFI, Global Fatigue Index; GI, gastrointestinal; HOMA-IR, homeostasis model assessment–insulin resistance; HRQoL, health-related quality of life; LC-MS/MS, HPLC-tandem mass spectrometry; MAF, Multidimensional Assessment of Fatigue; NIH, National Institutes of Health; PCOS, polycystic ovary syndrome; SF-36, 36-Item Short Form Health Survey; TART, testicular adrenal rest tissue.

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doses (2–5). Patients with difficult-to-treat CAH typically present with a combination of CAH-related (hyperandrogenemia, testicular adrenal rest tissue [TART], amenorrhea, and adrenal tumors) and glucocorticoid overtreatment-related (iatrogenic Cushing's syndrome, obesity, visceral adiposity, insulin resistance, and low bone mineral density [BMD]) complications (2, 3).

Physiologic cortisol secretion demonstrates a distinct circadian rhythm, characterized by nadir cortisol level shortly after midnight, peak secretion early in the morning, (6) and variable, although declining levels during the day. Exogenous glucocorticoid replacement is unable to replicate this pattern given that post-dose peaks are typically followed by troughs before the next dose (7, 8). New oral hydrocortisone formulations (9) and alternative hydrocortisone delivery systems (continuous subcutaneous hydrocortisone infusion [CSHI]) (10–15) are being studied with the aim of mimicking the cortisol circadian rhythm and suppressing the overnight ACTH-driven steroid production. Two recent randomized multicenter clinical trials of CSHI in Addison's disease demonstrated morning ACTH and cortisol levels similar to the normal circadian secretion, unlike conventional oral hydrocortisone (11, 13). Case reports of CSHI in CAH have shown improved adrenal steroid control at doses similar or lower than conventional glucocorticoid therapy (10, 14, 15); however, no clinical trials have been performed to systematically investigate this hypothesis.

The aim of this study was to evaluate cortisol replacement via CSHI compared with conventional oral glucocorticoid therapy in patients with difficult-to-treat classic CAH. We aimed to mimic the normal diurnal cortisol rhythm and hypothesized that near-physiologic cortisol replacement via CSHI would improve CAH control and related comorbidities in difficult-to-treat patients compared with conventional oral glucocorticoid therapy.

Materials and Methods

Patients

Eight adult patients (five females, age 19–42 y, and three males, age 25–43 y) with classic CAH due to 21-hydroxylase deficiency participated in this open label phase I–II study (NCT01859312). Four patients were recruited from a pool of 147 adult patients with CAH enrolled onto the National Institutes of Health (NIH) Natural History Study (NCT00250159). The remaining four patients were recruited through advertisements.

The diagnosis of classic CAH due to 21-hydroxylase deficiency was confirmed by hormonal and genetic testing. All patients had difficult-to-treat CAH, defined as the coexistence of elevated adrenal biomarkers (17-OHP >1200 ng/dL or/and androstenedione above the normal range at approximately 0700 h and prior to medication), and one or more glucocorticoid-related

comorbidities: obesity (body mass index [BMI] >30.0 kg/m²), fatty liver disease [aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio <1 (16) and/or steatosis per liver ultrasound (17)], low insulin sensitivity [homeostasis model assessment–insulin resistance (HOMA-IR) >2.6, where HOMA-IR = [insulin (μU/mL) × glucose (mmol/L)]/22.5 (18, 19)], osteopenia or osteoporosis (BMD T-score <−1), or glucocorticoid-related gastrointestinal (GI) adverse effects. Exclusion criteria included pregnancy, lactation or use of an estrogen-containing medication (women), use of medications that induce hepatic enzymes or interfere with glucocorticoid metabolism, use of glucocorticoids for reasons other than CAH, history of bilateral adrenalectomy, or comorbid conditions that could interfere with protocol compliance. All patients were on unchanged fludrocortisone and glucocorticoid (five prednisone, one dexamethasone, two combination) therapy for at least 3 months prior to study entry.

The study was approved by the Eunice Kennedy Shriver National Institute of Child Health & Human Development Institutional Review Board. All patients provided written informed consent.

Study design

Our objective was to safely achieve near-physiologic cortisol replacement with CSHI and describe the efficacy of CSHI, compared with conventional oral glucocorticoid therapy, based on changes in adrenal steroid production and comorbidity status following 6 months of therapy.

The primary efficacy endpoint was the percent of patients with early-morning 0700-hour 17-OHP ≤1200 ng/dL. Secondary endpoints included changes in: 1) 17-OHP, androstenedione, ACTH, progesterone (0700 h, area under the curve [AUC]-24 h, AUC daytime [0700–1500 h], AUC midday [1500–2300], AUC nighttime [2300–0700]); 2) fasting insulin; 3) HOMA-IR; 4) weight and BMI; 5) body composition and BMD; 6) bone turnover markers (cross-linked telopeptide [CTX] and osteocalcin); 7) waist and hip circumference; 8) percent of patients with hypertensive blood pressure; 9) liver steatosis and AST/ALT ratio; 10) adrenal gland size and morphology; 11) fatigue and health-related quality-of-life (HRQoL); 12) daily glucocorticoid dose based on glucocorticoid equivalencies; and 13) signs and symptoms of adrenal insufficiency.

All patients underwent a screening visit for eligibility two to three months prior to study entry. Patients were evaluated every 2 months over a 6-month period (Figure 1). All patients underwent a history and physical (by A.A.N or A.M.), and fasting laboratory evaluation of electrolytes, liver and renal function, complete blood count, lipids, insulin, bone turnover markers, and pregnancy test (women only), along with 24-hour sampling. Questionnaires to evaluate fatigue (Multidimensional Assessment of Fatigue [MAF] Scale) (20), HRQoL [adrenal insufficiency-specific HRQoL (AddiQoL) (21), SF-36v2 Health Survey/Four-Week Recall (22)], and symptoms of adrenal insufficiency or glucocorticoid overtreatment were administered. A hydrocortisone clearance study was performed at baseline. An iv bolus injection of 100 mg hydrocortisone (Solucortef) was given followed by cortisol measurements every 10 minutes for a total of 150 minutes (23). After a washout period (12 h for hydrocortisone and prednisone, 36 h for dexamethasone), CSHI was initiated. Pump infusion was adjusted prior to discharge based on cortisol sampling approximately 24 and 36 hours after pump

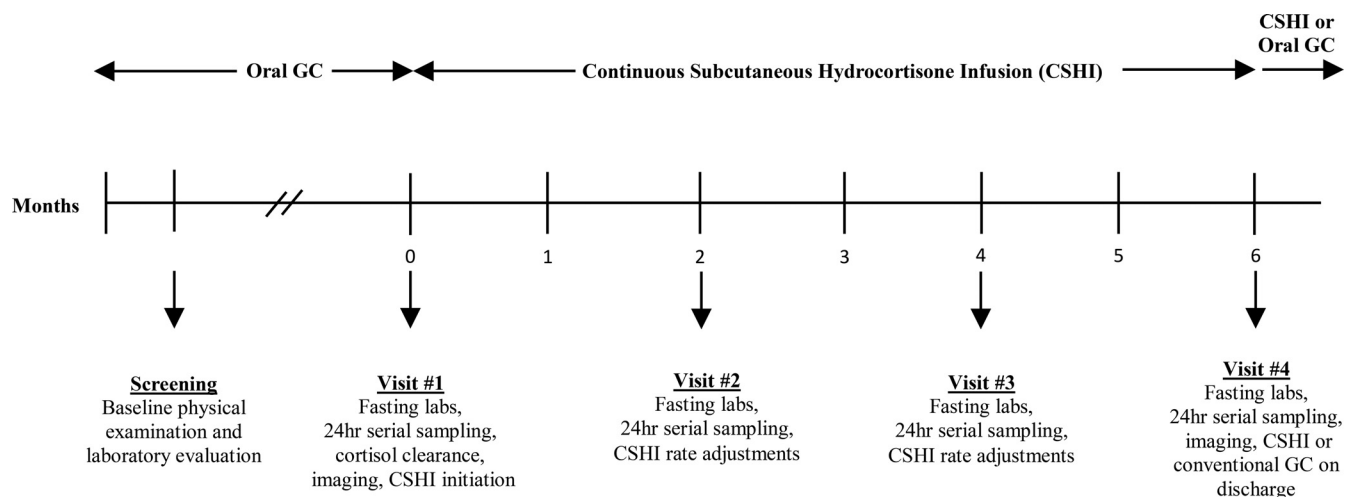


Figure 1. CSHI Study Design. Fasting labs were obtained on day 2 of visits 1–4 and included: Biochemistry and safety panels. Twenty-four hour (2300–2300 h) serial sampling included: ACTH, cortisol, 17-hydroxyprogesterone, androstenedione, progesterone, and T.

initiation. On the first and last visits, patients underwent dual-energy x-ray absorptiometry (DXA) to assess body composition and BMD, and radiological studies (pelvic or testicular ultrasound, abdominal magnetic resonance imaging with liver proton magnetic resonance spectroscopy) to evaluate for adrenal rest, visceral fat, hepatic steatosis, and adrenal hyperplasia or tumors. All patients continued to receive daily fludrocortisone throughout the study. At 6 months, patients were offered the option to continue CSHI or transition to their original glucocorticoid regimen.

CSHI intervention

Total daily hydrocortisone dose was calculated based on the patient's estimated cortisol clearance (10). Rates were es-

tablished to achieve peak and trough concentrations within the normal circadian cortisol range based on an estimate of the mean in healthy controls (6) and by using the formula [infusion rate (mg/d) = clearance (mL/d) × target cortisol concentration (mg/mL)]. Target cortisol levels used were: 0000–0259 hours: 4 mcg/dL; 0300–0459 hours: 5 mcg/dL; 0500–0859 hours: 14 mcg/dL; 0900–1159 hours: 10 mcg/dL; 1200–1759 hours: 7 mcg/dL; 1800–2359 hours: 4 mcg/dL. Infusion rates were selected and programmed an hour prior to the desired concentration peak, as previously described by Bryan et al (10); however, our calculations overestimated the desired daily hydrocortisone dose by approximately 30% and all patients subsequently required hydrocortisone dose reduction by 2 months.

Table 1. Baseline Characteristics and Hormone Levels of 8 Adult Patients with Classic Congenital Adrenal Hyperplasia

Pt	Age/Sex	Phen	GC Equiv Dose/Med ^a	17-OHP, ng/dL	A ₄ , ng/dL	BMI, kg/m ²	IR ^b	Fatty Liver ^c	Low BMD ^d	GI Intolerance to GC	TART/PCOS ^e	Adrenal Mass or Hypertrophy
1	43/M	SV	26.5/P	5972	458	28.8	+	–	–	–	+	+ ^f
2	25/M	SW	19.3/P	19 731	1003	34.8	+	+	–	+	+	+ ^g
3	19/F	SW	16/P	2999	268	51.8	+	+	–	–	–	–
4	38/F	SW	24.4/P	11 438	1711	39.8	+	+	–	–	–	+ ^{g,h}
5	32/F	SW	12.7/HC,P	5661	676	54.1	+	+	+	+	+	–
6	41/F	SW	8.8/HC,PI	6092	182	43	+	+	–	–	–	–
7	25/F	SV	13/P	6158	498	40.3	+	–	+	+	+	–
8	41/M	SW	21.2/D	7198	425	27.7	–	–	+	–	+	+ ^g

Abbreviations: +: present; –: not present. A₄, androstenedione; D, dexamethasone; GC Equiv Dose, glucocorticoid equivalent dose; F, Female; HC, hydrocortisone; GI intolerance to GC, gastrointestinal intolerance to glucocorticoid; IR, insulin resistance; M, Male; Med, medication; P, prednisone; Phen, phenotype; PI, prednisolone; Pt, patient; SV, simple virilizing; SW, salt-wasting.

^a Glucocorticoid equivalent dose (mg/m²/d): hydrocortisone × 1, prednisone and prednisolone × 5, and dexamethasone × 80 (3).

^b HOMA-IR >2.6.

^c AST/ALT <1 or steatosis by ultrasound.

^d DXA T-score <–1.

^e Twelve or more follicles 2–9 mm in diameter and/or an increased ovarian volume >10 ml by ultrasound (30).

^f Adrenal myelolipomas.

^g Adrenal hyperplasia.

^h Adrenal adenoma.

Overall, hydrocortisone dosing was primarily aimed at achieving a near-physiologic cortisol profile (6), with consideration of adrenal steroid suppression and the clinical symptoms of hyperandrogenism, glucocorticoid excess, or adrenal insufficiency. In the case of conflicting data, dose adjustments were based on clinical symptomatology (for details see [Supplemental Data–Appendix 1](#)).

The iv/im powder preparation of hydrocortisone sodium succinate (100 mg/2 mL Solu-Cortef ACT-O-VIAL, Pfizer Inc.) was reconstituted to a 50-mg/mL solution, resulting in 0.5 mg of hydrocortisone per pump-administered unit. The Paradigm REAL-Time (MMT-722) insulin pump, MMT-332A reservoir and Mio 9 mm/32" infusion set were used. Patients were asked to replace the hydrocortisone solution with every insert/tubing set change, every third day. Patients received on-site training and had technical assistance available upon request. All patients maintained a supply of oral hydrocortisone and im hydrocortisone for stress dosing and emergency use.

Hormonal assays

Hormonal assays were performed at the NIH Clinical Center (Bethesda, MD). Serum cortisol was analyzed by HPLC-tandem mass spectrometry (LC-MS/MS). Cortisol assay limit of quantitation was 0.6 $\mu\text{g/dL}$, interassay coefficient of variation (CV) ranged from 3.1–3.2% and intra-assay CV from 5.0–7.7%. Plasma ACTH was analyzed by chemiluminescent immunoassay on Siemens Immulite 2000 XPi analyzer; analytical sensitivity was 5 pg/mL, intra-assay CV, 2.5% and interassay CV, 3.6%. Androstenedione, 17-OHP, progesterone, and T were analyzed by LC-MS/MS (24, 25). Intra-assay CV ranged from 2.5–9.5% and interassay CV from 2.9–11.1%.

Statistical analysis

Sample size calculation was based on the hypothesis that CSHI therapy would achieve early-morning 17-OHP ≤ 1200 ng/dL in 80% of patients at 6 months. Taking into account a 10% dropout rate, the power analysis yielded a sample size of eight subjects with an 80% statistical power and at a significance level of 0.05.

Results were expressed as mean \pm SEM, unless otherwise noted. Data were analyzed by SPSS Statistics 21 and SAS version 9.4 (SAS Institute, Inc.). Comparisons of CSHI with conventional glucocorticoid therapy (at baseline) were made. Continuous data between baseline and 6 months were compared by paired *t* tests, and categorical data were compared by McNemar's test. Two-sample *t* tests were carried out for comparisons of data between independent groups (ie, normative data from healthy controls). Noncompartmental analysis (Phoenix WinNonlin software) was used to calculate the pharmacokinetic values. The linear-up log-down trapezoidal rule was used to calculate AUC for the entire 24-hour and three 8-hour time periods. Actual collection times were used to define peak plasma concentration (C_{max}) and time to peak plasma concentration (T_{max}). For all values less than the detection limit of the assay, the value at half of the lower limit was used in calculations. Logarithmic transformation was used as needed to achieve a normal distribution. Two-tailed tests were performed and *P*-values $< .05$ were considered statistically significant.

SF-36 score was calculated using the SF-36 OptumInsight software, which provides norm-based scores and applies a linear T-score transformation (mean 50, SD 10) (22, 26). AddiQoL

questionnaire scores range from 30 to 120, where higher scores indicate better HRQoL (21). MAF data was used to compute the Global Fatigue Index (GFI) score, which ranged from 1 (no fatigue) to 50 (severe fatigue), as previously described (20).

Results

Twenty-eight patients were screened. Eight adult patients with classic CAH participated in the study (Table 1). All patients completed the study but, according to medication and supply accountability, one patient was found to be partially noncompliant, with the pump being disconnected approximately 30% of the time. When this patient

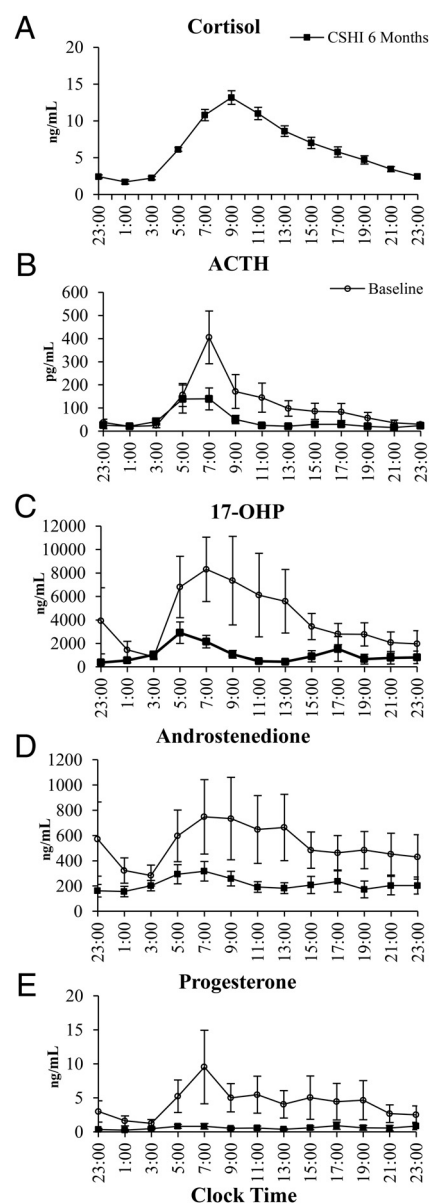


Figure 2. Twenty-four-hour serial measurement of (A) cortisol, (B) ACTH, (C) 17-OHP, (D) androstenedione, and (E) progesterone (mean \pm SEM) at baseline while receiving conventional oral glucocorticoid (open circles) and following 6 mo of CSHI (solid squares).

was excluded, analysis yielded similar results. Of the eight patients, 6 (75%) expressed the desire to continue CSHI, two patients found the pump incompatible with their lifestyle.

Pharmacokinetics

CSHI pharmacokinetic cortisol profile approximated physiologic secretion (Figure 2A). CSHI therapy at 6 months compared with a prior study of healthy volunteers (6) resulted in similar time to peak cortisol concentration (CSHI vs healthy: T_{max} [mean, 95% confidence interval]: 0845 [0810–0920] h vs 0832 [0759–0905] h) and exposure to cortisol (24-h AUC [$h \times \mu\text{g/dL}$]: 153.5 [127.3–179.8] vs 160.2 [148.6–171.6]), but peak cortisol concentration (C_{max}) was lower (13.2 [11.0–15.4] $\mu\text{g/dL}$ vs 16 [14.6–17.4] $\mu\text{g/dL}$; $P = .020$). Efforts to increase C_{max} were undertaken, but were limited by symptoms of early-morning awakening. Glucocorticoid dose in hydrocortisone equivalents at baseline (on oral glucocorticoid) and following 6 months of CSHI were similar (conventional vs CSHI: 17.7 ± 1.9 vs 17.5 ± 1.3 $\text{mg/m}^2/\text{d}$).

Biomarkers of disease control

At 6 months, the primary efficacy endpoint, the percent of patients with early-morning 0700-hour 17-OHP less than or equal to 1200 ng/dL, was not different than baseline (only three patients achieved this goal); however, 0700-hour 17-OHP ($P = .021$), ACTH ($P = .024$), an-

drostenedione ($P = .015$), and progesterone ($P = .007$) significantly decreased (Table 2). Similarly, 6 months of CSHI resulted in lower 24-hour AUC of ACTH ($P = .031$), 17-OHP ($P = .027$), and androstenedione ($P = .009$). This was mostly due to lower daytime and midday (0700–2300 h) levels (Table 2; Figure 2, B–E). T and plasma renin activity concentration remained unchanged.

Glucocorticoid-related comorbidities, metabolic indices and HRQoL assessment

Although weight increased (107 ± 9 vs 112 ± 9 kg, $P = .004$), no significant changes were observed in HOMA-IR, C-peptide, leptin, C-reactive protein, lipids, and waist/hip circumference. Only one patient had elevated systolic blood pressure at baseline, and this did not change during the study. Osteocalcin (16.6 ± 1.8 vs 22.6 ± 2.0 ng/mL; $P = .004$) and CTX (379.1 ± 50.6 vs 460.0 pg/mL ± 69.8 ; $P = .013$) increased.

Whole-body BMD and total fat mass by DXA did not change, but lean mass increased (60.7 ± 3.7 vs 64.3 ± 4.4 kg; $P = .016$). AST/ALT ratio and visceral fat (as fraction of total fat) remained unchanged. At baseline, a moderate to large degree liver fat was noted in five of eight patients. At the 6-month visit, a 5% or more increase in measurable liver fat was observed in two patients, one of whom was also noted to have the largest weight gain. Adrenal imaging demonstrated multiple fatty tumors compatible with myelolipomas

Table 2. Comparison of Early Morning and 24-hour Hormone Levels on Conventional Glucocorticoid Therapy at Baseline and Following 6 Months of CSHI

	Baseline	CSHI at 6 Mo	P Value
17-OHP			
0700 h, ng/dL	8313 \pm 2748	2150 \pm 531	.021
AUC-24 h, $h \times \mu\text{g/dL}$	98.5 \pm 39.3	25.7 \pm 9.5	.027
AUC 0700–1500 h, $h \times \mu\text{g/dL}$	48.6 \pm 22.4	6.8 \pm 1.8	.008
AUC 1500–2300 h, $\mu\text{g} \times \text{h/dL}$	20.5 \pm 6.8	7.5 \pm 4.9	.012
AUC 2300–0700, $h \times \mu\text{g/dL}$	29.5 \pm 11.1	11.4 \pm 3.0	.157
A_4			
0700 h, ng/dL	748 \pm 295	317 \pm 77	.015
AUC-24 h, $h \times \mu\text{g/dL}$	12.7 \pm 4.5	5.2 \pm 1.4	.009
AUC 0700–1500 h, $h \times \mu\text{g/dL}$	5.3 \pm 2.1	1.8 \pm 0.4	.008
AUC 1500–2300 h, $h \times \mu\text{g/dL}$	3.7 \pm 1.1	1.6 \pm 0.6	.009
AUC 2300–0700, $h \times \mu\text{g/dL}$	3.7 \pm 1.3	1.8 \pm 0.4	.043
ACTH			
0700 h, pg/mL	405 \pm 114	139 \pm 47	.024
AUC-24 h, $h \times \text{pg/mL}$	2538 \pm 743	1087 \pm 359	.031
AUC 0700–1500 h, $h \times \text{pg/mL}$	1239 \pm 402	340 \pm 107	.005
AUC 1500–2300 h, $h \times \text{pg/mL}$	458 \pm 179	183 \pm 55	.004
AUC 2300–0700, $h \times \text{pg/mL}$	841 \pm 233	564 \pm 216	.524
Progesterone			
0700 h, ng/mL	9.5 \pm 5.4	0.8 \pm 0.4	.007
AUC-24 h, $h \times \text{ng/mL}$	101.1 \pm 48.8	13.7 \pm 4.6	.084
AUC 0700–1500 h, $h \times \text{ng/mL}$	42.2 \pm 20.0	4.2 \pm 1.6	.057
AUC 1500–2300 h, $h \times \text{ng/mL}$	30.7 \pm 17.7	5.5 \pm 3.2	.103
AUC 2300–0700, $h \times \text{ng/mL}$	28.2 \pm 12.5	4.0 \pm 0.5	.070

Means \pm SEM. P values $< .05$ are indicated with bold typeface.

in one patient and minimal bilateral hyperplasia in three patients. The patient with poor compliance had an increase in myelolipoma size (5 cm to 6.4 cm maximum dimension), whereas no other adrenal changes were appreciated following 6 months of CSHI in the other seven patients. All three men had TART, which decreased by approximately 40% in the youngest male patient (age 27 y) and remained stable in the other two. Three of five women presented with secondary amenorrhea; one had resumption of menses during CSHI. Two women had sonographic findings compatible with polycystic ovaries (>25 follicles in one or both ovaries) with no observed changes over time.

Compared with baseline, HRQoL (SF-36 Vitality Score: 32 ± 5 vs 64.8 ± 6 ; $P = .001$; AddiQoL: 72.4 ± 4 vs 86.8 ± 4 ; $P = .004$), and fatigue, (GFI: 25.8 ± 2 vs 12.3 ± 2 ; $P = .001$) improved at 6 months on CSHI (Figure 3). In addition, both symptoms of adrenal insufficiency ($P = .014$) and symptoms of glucocorticoid overtreatment ($P = .003$) also improved.

Adverse events

CSHI was well tolerated. Serious adverse events did not occur (Table 3). No pump failure or hydrocortisone infusion set blockage was reported. All skin reactions were self limited apart from one case, requiring oral antibiotics, and

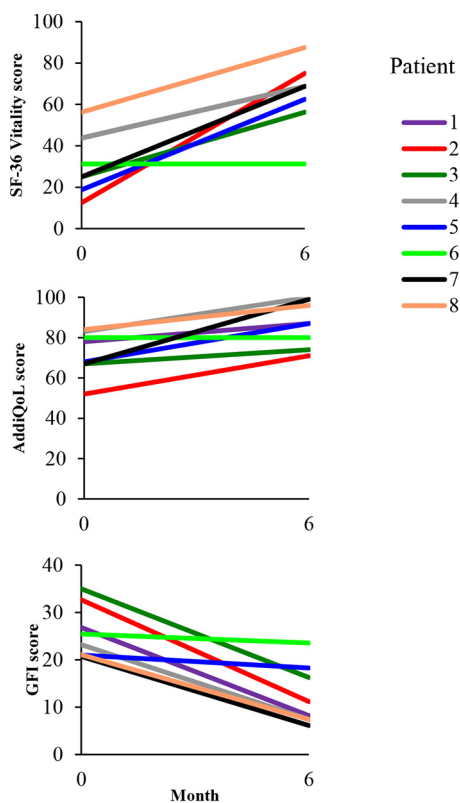


Figure 3. Measurements of subjective health status and fatigue at baseline and following 6 mo of CSHI. Abbreviations: SF-36, 36-Item Short Form Health Survey (36); AddiQoL, adrenal insufficiency-specific health-related quality-of-life (20–22, 26); GFI, General Fatigue Index. Patient 1 and Patient 4 had the same SF-36 Vitality score.

incision and drainage. Poor skin hygiene was reported or observed in all cases of local skin infection. Early-morning symptoms resolved following dose adjustments. Two patients reported early-morning awakening that resolved following rate adjustments aimed at producing a later cortisol increase. Symptoms of dizziness and lightheadedness resolved after increasing early-morning dose. Two patients received stress dosing for minor procedures (molar extraction, endoscopic carpal tunnel release) and four for illness.

Discussion

This is the first clinical trial to systematically evaluate CSHI in comparison with conventional oral glucocorticoid therapy in patients with classic CAH. We demonstrate that CSHI can safely and easily achieve a cortisol profile similar to physiologic cortisol secretion. We also show that near physiologic cortisol replacement via CSHI controls adrenal steroid production and improves HRQoL and fatigue in patients with difficult-to-treat classic CAH suffering from hyperandrogenism and glucocorticoid-related comorbidities.

Management of classic CAH with conventional oral glucocorticoids remains challenging given that optimal suppression of adrenal steroids is difficult to achieve without supraphysiologic glucocorticoid doses (5, 6). We chose to treat an especially challenging subset of patients with CAH with CSHI, those with hyperandrogenism and other treatment-related comorbidities, because ultimately these types of patients might be the best candidates for pump therapy. CSHI is expensive and complex, requiring much patient commitment and might be best reserved for those who are not easily managed with oral therapy.

Initially, we started patients on a basal infusion rate using calculations provided by Bryan et al (10), but this overestimated the total daily hydrocortisone dose by approximately 30%. This may be attributed to the nonlinearity of cortisol clearance at higher hydrocortisone concentrations due to the saturable binding of hydrocortisone to plasma proteins. Using a lower dose of hydrocortisone in the clearance study might have avoided this issue. In addition, obesity coupled with weight fluctuations throughout the study (potentially altering the volume of distribution and half-life of hydrocortisone), as well as patient differences in hydrocortisone metabolic rates likely contributed to the observed cortisol clearance variability. Despite this initial dose miscalculation, we safely and easily approximated a physiologic cortisol profile by using 24-hour sampling and multiple infusion rates throughout the day. An alternative approach to using cor-

Table 3. Adverse Events During CSHI Therapy

Adverse Event	No. of Patients	Outcome (n)
Skin erythema with pruritus at the infusion set site	3	Self limited (n = 3).
Local skin infection at the infusion set site	5	Self limited (n = 4), resolved after oral antibiotics and incision and drainage (n = 1).
Dizziness	5	Resolved 2 mo following CSHI (n = 1), resolved after increasing early morning and decreasing 0900–1100 h dose (n = 1), intermittent (n = 2).
Lightheadedness	5	Resolved 2 to 4 mo following CSHI (n = 2), resolved after increasing early morning and decreasing 0900–1100 h dose (n = 1), intermittent (n = 2).
Weakness	3	Resolved 2 mo following CSHI (n = 2), intermittent (n = 1).
Fatigue	7	Resolved 2 mo following CSHI (n = 2), intermittent (n = 5).
Nausea	2	Resolved 2 mo following CSHI (n = 1), resolved after dose increase (n = 1).
Headache	7	Resolved by 4 mo of CSHI (n = 3), intermittent (n = 4).
Carpal tunnel	1	Resolved after surgical procedure (n = 1).
Knee pain when walking	1	Intermittent (n = 1).
Tinnitus	1	Mild, prior diagnosis Meniere's disease, resolved at 6 mo (n = 1).
Decreased appetite	2	Resolved 2 mo following CSHI (n = 1), while on CSHI (n = 1).
Increased appetite	6	Resolved 2 mo following CSHI (n = 2), resolved spontaneously (n = 2), intermittent (n = 1).
Difficulty falling asleep or frequent wakening	5	Resolved 2 mo following CSHI (n = 3), resolved after dose adjustments (n = 1), intermittent (n = 1).
Early morning wakening	3	Resolved 2 months following CSHI (n = 1), resolved after dose adjustments (n = 2).
Increased acne	2	Resolved spontaneously (n = 2).
Weight gain	5	Weight stable following dose reduction (n = 4).

tisol clearance data to estimate starting rates might be to use an average starting dose of hydrocortisone of 15 mg/m²/d, with subsequent dose adjustments based on 24-hour sampling. This approach would have sufficed in half of our patients, who had a final rate within 20% of this estimate. However, this approach might extend the time required to approximate a physiologic cortisol profile in some patients and would delay identification of patients who are fast metabolizers.

New ways of replacing glucocorticoid aim to improve the outcome of patients with adrenal insufficiency by mimicking physiologic circadian rhythm. In our study, CSHI approximated the mean physiologic cortisol profile in all patients, but ACTH was not fully suppressed resulting in mildly elevated adrenal steroids in some patients. Interestingly, the cortisol levels necessary to suppress the early morning ACTH increase were not tolerated by all patients because of early or frequent awakening. Our inability to fully suppress ACTH might also be due to CAH-specific alterations in the hypothalamic-pituitary-adrenal axis. Intrauterine glucocorticoid deficiency might affect postnatal sensitivity to feedback inhibition, thus blunting the central effect of treatment. Other factors known to affect ACTH secretion, such as CRH, neurotransmitters, arginine vasopressin, and angiotensin II may have played a role. This requires further study.

Prior case reports of CSHI suggested that patients achieved a 17-OHP in the target range within 3 months of

intervention (10, 12, 15). Thus, we hypothesized that CSHI intervention would result in a 17-OHP less than or equal to 1200 ng/dL in 80% of the subjects within 6 months. However, this was only achieved in three of eight patients (38%). Our failure to achieve target range 17-OHP in most patients could be related to the population studied (difficult-to-treat patients with established comorbidities including polycystic ovary syndrome [PCOS] with a possible gonadal contribution), and to the way in which we adjusted pump settings. Our inability to fully suppress early morning ACTH peak also probably contributed. Although an earlier increase in cortisol effectively suppressed morning ACTH and 17-OHP in two patients, this was not tolerated and led to early-morning awakenings. When the profile was adjusted to prevent early awakening, adrenal steroids were not as well controlled. Despite that shortcoming, and although total daily glucocorticoid dose remained similar to baseline, all patients demonstrated significantly improved adrenal steroid control and six of the eight patients achieved decreases of 17-OHP levels to 10–50% of their baseline levels. Of those six patients, all reported improved sleep, four had improved fatigue; three had improved acne, hirsutism and anorexia; and two had decreased skin pigmentation.

Our patients reported remarkable improvements in HRQoL and fatigue and this was the primary reason why most patients wished to continue CSHI at the conclusion of the trial. Similarly, a 3-month CSHI multicenter cross-

over randomized trial of 33 patients with Addison's disease reported improved HRQoL (13). This is in contrast with the Chronocort study (9) and a double blind placebo-controlled trial of CSHI vs oral glucocorticoid therapy in 10 patients with Addison's disease (11), but both of these studies had participants with relatively good HRQoL at study entry. Our patients were all suffering from multiple comorbidities with poor HRQoL at baseline, making improvement more likely to be achieved.

Longstanding morbidities such as fatty liver, insulin resistance, adrenal hypertrophy, and polycystic ovaries did not change in this 6-month study. Similarly, TART did not change in our older males, possibly because longstanding late-stage TART may become fibrotic and irreversible despite improved disease control (27). However, a decrease in TART size in one male patient and resumption of menses in one previously amenorrheic female patient did occur.

Overall, decreased cortisol exposure was suggested by the observed increase in osteocalcin (marker of bone formation) after 6 months of CSHI. An increase in CTX (marker of bone resorption) was also observed, possibly related to decreased androgens. The significance and potential benefit of this is unclear. Whole-body BMD changes were not observed, although lumbar BMD was not assessed. Weight gain (in the order of 2–9 kg) occurred in all but one patient, and it was more pronounced during the first 2 months of the study (2–6 kg); interestingly weight gain was also noted prior to study enrollment (1–6 kg between the screening and first study visits), implicating an influence of dietary/lifestyle habits. Increased cortisol exposure during the first 2 months of CSHI treatment and postintervention improvement of adrenal insufficiency symptoms may have promoted food intake; the increase in lean mass may have also accounted for a portion of the weight gain. A tendency for weight gain was similarly reported in a CSHI study of Addison's patients (13), although it was not as pronounced as in our study. Nevertheless, and despite the weight changes, insulin resistance (HOMA-IR) remained stable. In addition, whereas lean mass increased, fat mass remained unchanged; findings in agreement with the Chronocort study (9). Physiologic cortisol exposure with nadir levels in the evening may have been responsible for the above findings. Decreased fatigue may have resulted in increased physical activity, contributing to the lean mass increase (28). Progestin-only oral contraceptives have been associated with a decrease in lean mass (29), suggesting that changes in the adrenal hormone milieu may have contributed, but little is known about the effect of progesterone or other adrenal steroids on lean mass.

This exploratory study has several limitations derived

from its small sample size, lack of blinding and randomization, lack of placebo-control design, and heterogeneity of the study population (diverse comorbidities, small numbers of men and women). We aimed to achieve cortisol levels approximating the mean of a representative sample of healthy controls, which may not be ideal for the management of patients with CAH. In addition, although CSHI was able to approximate a normal cortisol circadian secretion profile, it was not able to mimic its ultradian rhythm. It is unknown whether patients would have benefited from lower or higher cortisol concentrations during the 24-hour period. As expected, management of CSHI was more time consuming and intensive than clinical management with oral therapy. Extensive teaching was necessary and proper hygiene with pump use took months to establish. However, local skin pruritus, erythema, and infection occurred at rates similar to insulin pump users (30). It is unknown whether Chronocort, an oral modified-release hydrocortisone aimed at mimicking physiologic cortisol secretion, is comparable to CSHI therapy. However, the ability to fine tune the cortisol profile with a continuous infusion allows for more individualized therapy, which might be beneficial in a subset of patients. In addition, CSHI is the optimal route of hydrocortisone delivery for patients with GI conditions that interfere with oral therapy.

In summary, CSHI was a well-tolerated and safe modality of hydrocortisone replacement. A physiologic cortisol profile was achieved, resulting in improved adrenal steroid control and positive effects on HRQoL and fatigue in patients with CAH poorly controlled with oral glucocorticoid therapy. Longstanding morbidities such as fatty liver, insulin resistance, adrenal and testicular tumors, and polycystic ovaries remained mostly unchanged following 6 months of CSHI, suggesting that earlier (childhood) intervention and preventative strategies are needed. The long-term effect of near physiologic cortisol replacement has yet to be determined, but is also being studied with a novel modified-release oral preparation, Chronocort (9). Adverse outcomes in CAH are due to a combination of disease-related and treatment-related adverse effects. Long-term studies of physiologic cortisol replacement starting in childhood would help unravel the role glucocorticoids play in the development of comorbidities and advance preventative management strategies.

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