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A Phase 2 Study of Chronocort®, a Modified-release Formulation of Hydrocortisone, in the Treatment of Adults with Classic Congenital Adrenal Hyperplasia

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Abstract

Context: Treatment of congenital adrenal hyperplasia (CAH) is suboptimal. Inadequate suppression of androgens and glucocorticoid excess are common and current glucocorticoid formulations cannot replace the cortisol circadian rhythm.

Objectives: The primary objective was to characterize the pharmacokinetic profile of Chronocort®, a modified-release hydrocortisone formulation, in adults with CAH. Secondary objectives included examining disease control following 6 months of Chronocort® with dose titration.

Design, Setting and Patients: Sixteen adults (8 females) with classic CAH participated in an open label, non-randomized, Phase 2 study at the National Institutes of Health Clinical Center. 24-hour blood sampling was performed on conventional glucocorticoids and following 6 months of Chronocort®. Chronocort® was initiated at 10mg (0700h) and 20mg (2300h). Dose titration was performed based on androstenedione and 17-hydroxyprogresterone (17-OHP) levels and clinical symptomatology.

Main Outcome Measures: Cortisol pharmacokinetics of Chronocort® and biomarkers of CAH control (androstenedione and 17-OHP).

Results: In CAH patients, Chronocort® cortisol profiles were similar to physiologic cortisol secretion. Compared to conventional therapy, 6 months of Chronocort® resulted in a decrease in hydrocortisone dose equivalent (28 ± 11.8 *vs.* 25.9 ± 7.1mg/day), with lower 24-hour (P = 0.004), morning (0700h - 1500h; P = 0.002), and afternoon (1500h - 2300h; P = 0.011) androstenedione area under the curve (AUC) and lower 24-hour (P = 0.023) and morning (0700h - 1500h; P = 0.02) 17-OHP AUC.

Conclusions: Twice daily Chronocort® approximates physiologic cortisol secretion, and was well tolerated and effective in controlling androgen excess in adults with CAH. This novel hydrocortisone formulation represents a new treatment approach for patients with CAH.

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is characterized by cortisol and aldosterone deficiency and androgen excess (1). Goals of treatment are to replace deficient hormones and control excess androgen, while avoiding the adverse effects of exogenous glucocorticoid excess. Physicians caring for CAH patients often face management challenges. Thrice daily immediate-release short-acting hydrocortisone is the recommended therapy in growing children (2). However, there are no standard clinical guidelines for glucocorticoid therapy in adults. Several regimens using short or long acting glucocorticoid formulations are commonly used in practice, given once to thrice daily as a fixed, or weight adjusted-dose (3-5).

In addition to the lack of management consensus, it is difficult to achieve satisfactory outcome with conventional glucocorticoid formulations (6). These regimens are suboptimal as they cannot replace the normal cortisol circadian rhythm, and inadequate suppression of adrenal androgens and glucocorticoid excess are common (3,7). New hydrocortisone formulations are being produced. Plenadren®, marketed in Europe, is an immediate-release tablet with sustained-release hydrocortisone core taken first thing in the morning and provides once daily treatment but does not address the overnight rise in adrenocorticotrophic hormone(ACTH) (8). Chronocort®, a modified-release formulation of hydrocortisone in clinical development, aims to mimic the cortisol circadian rhythm and address the overnight ACTH rise driving the increase in androgens in CAH (9).

We previously compared conventional immediate-release hydrocortisone administered thrice daily (10, 5 and 15mg) to a pilot tablet modified-release hydrocortisone formulation (30mg at night) (Phoqus pharmaceuticals, UK) (10). This pilot modified-release hydrocortisone tablet was able to achieve physiologic cortisol levels and good control of ACTH and androgens overnight and in the early morning, but failed to provide adequate cortisol in the afternoon and evening leading to a rise in adrenal androgens.

Pharmacokinetic modeling suggested twice daily dosing would achieve better hormonal control, but further studies using this formulation were not possible due to manufacturing issues (11).

To address this shortcoming, Chronocort®, a novel modified-release hydrocortisone formulation using scalable technology was developed (Diurnal Ltd, UK). This new multi-particulate formulation has an enteric coat which has a pH trigger of 6.8, allowing small bowel dissolution. Phase 1 pharmacokinetic analysis showed that a twice daily regimen (10mg at 0700h and 20mg at 2300h) approximated physiologic cortisol rhythm (12).

The aim of this study was to evaluate the pharmacokinetics of Chronocort® in adults with CAH and test the hypothesis that providing near-physiologic cortisol replacement will improve control of androgenic precursors - androstenedione and 17-hydroxyprogresterone (17-OHP).

Patients and Methods

Patients

Sixteen adult patients (8 females) with classic CAH participated in this open label, single center, phase 2 study (www.clinicaltrials.gov identifier no. NCT01735617). Diagnosis of classic 21-hydroxylase deficiency was established based on medical records and genotype (13). All patients were on stable glucocorticoid and mineralocorticoid dosage for ≥ 3 months, in good general health and had laboratory evaluation within 12weeks of enrollment with plasma renin activity (PRA) < 1.5 times the upper normal range. Exclusion criteria included pregnancy, lactation, taking spironolactone or glucocorticoids (oral, inhaled or nasal) apart from treatment of CAH, significant medical or psychiatric illness, receiving medications that induce hepatic enzymes or interfere with glucocorticoid metabolism, history of bilateral adrenalectomy, or participation in a clinical trial within 3 months.

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

Study Design

The primary objective was to characterize the pharmacokinetic profile of short-term Chronocort® treatment in adults with CAH. Secondary objectives included examining the effect of Chronocort® on hormone control following 6 months of dose titration.

Patients were screened for eligibility up to 12 weeks prior to the first visit. All patients were admitted to the National Institutes of Health (NIH) Clinical Center every 2-months for a total of 6 months of treatment (Figure 1). Prior to Chronocort® administration at visit 1, a 24-hour hormonal profile (2300h - 2300h, 2-hourly) was obtained while on conventional therapy.

Patients received their last dose of conventional therapy until 2300 of Day #2 and were started on twice daily Chronocort® (2300h: 20mg; 0700h: 10mg) following completion of sampling on conventional therapy. This initial starting dose was chosen based on data from a prior Phase 1 study in healthy subjects (12). On Day #4 (48 hours post-dose initiation), 24-hour (2300h - 2300h) serial sampling (2-hourly from 2300h - 0500h; 1-hourly from 0600h - 1600h and 2-hourly from 1700h - 2300h) was performed to evaluate Chronocort® pharmacokinetics. 2-hourly serum samples (2300h - 2300h) were also drawn to evaluate ACTH, androstenedione and 17-OHP. Serial sampling was repeated after two, four and six months. Telephone contact was made within 2-weeks of each visit for dose adjustments and adverse event monitoring. After 6-months of Chronocort® treatment, patients were discharged to home on their prior conventional regimen with telephone follow-up.

Body composition was measured by Dual Energy X-ray Absorptiometry (DXA) prior to study medication administration at visit 1 and at the end of the study. Following breakfast at every visit, four questionnaires

were administered to assess fatigue (MAF, Multidimensional Assessment of Fatigue), health-related quality-of-life (SF-36, AddiQoL) and signs and symptoms of adrenal insufficiency.

Study medication and dose modification

Chronocort®, a modified-release capsule formulation of hydrocortisone, consists of uniform multi-particulate beads which have an inert core, a hydrocortisone drug layer, and a delayed-release enteric outer coat (12). Chronocort® was designed to mimic physiologic cortisol circadian rhythm through a delayed-release and sustained absorption profile of hydrocortisone after administration. Chronocort® was available in 20mg, 10mg, and 5mg capsules for this study.

Dose adjustments were made in 5mg increments based on clinical symptoms of adrenal insufficiency or cortisol excess, and androstenedione and 17-OHP levels. Hormone levels obtained between 0100h and 0900h and between 1100h and 1900h were considered to reflect the 2300h and the 0700h Chronocort® doses respectively. Dose adjustments were made if three or more of the 5 sample times showed out of range values for androstenedione and 17-OHP. Optimal androstenedione levels were based on the normal range (men: 40-150, women: 30-200 ng/dL); 17-OHP levels were categorized optimal: 300-1200 ng/dL; suppressed: $\leq$ 300 ng/dL; elevated: $\geq$ 1200 ng/dL.

When androstenedione and 17-OHP showed inconsistent trends, androstenedione took precedence in directing dose adjustment since androstenedione levels are less variable (6). Daily Chronocort® dosage was not to exceed 50mg or be less than 10mg. Dose adjustments were made within 2-weeks following visits by telephone. Patients were re-contacted within 1-week after each dose change.

Compliance was assessed at each visit by accounting for number of capsules dispensed and number returned.

Hormonal assays

Serum concentrations of cortisol (Simbec Research Limited, UK), 17-OHP and androstenedione (Mayo Medical Laboratories, Rochester, MN) were determined by high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS). The cortisol assay had an analytical sensitivity of 0.05 µg/dL, inter-assay coefficient of variation (CV) of 2.6%, 4.5%, 2.4%, intra-assay CV of 3.7%, 1.1%, 1.9% at mean concentration of 0.8, 7.9 and 19.7 µg/dL respectively. The androstenedione assay had a sensitivity of 15 ng/dL, inter-assay CV of 7.9%, 7.2%, 8.7%, intra-assay CV of 13.9%, 5.9%, 2.6% at mean concentration of 112, 916 and 2281 ng/dL respectively and normal range of 40-150 ng/dL for males and 30-200 ng/dL for females. The 17-OHP assay had an analytical sensitivity of 40 ng/dL, inter-assay CV of 9.7%, 8.7%, 6.8%, intra-assay CV of 6.8%, 2.9%, 4.4% with a mean concentration of 111, 751 and 2006 ng/dL respectively and normal range of ≤ 220 ng/dL for males and ≤ 285 ng/dL for females.

Plasma ACTH was measured using a chemiluminescence immunoassay on Siemens Immulite 2000 XPi analyzer (NIH Clinical Center), with a sensitivity of 5 pg/mL, intra- and inter-assay CVs of 2.5% and 3.6% respectively, and normal range of 0 - 46 pg/mL.

Statistical analyses

Data are presented as mean ± SD, unless otherwise indicated, and were analyzed using SAS v9.2 (SAS Institute, Inc, Cary, NC). All *P* values were two sided and < 0.05 was considered significant. Pharmacokinetic parameters for cortisol were calculated via non-compartmental analysis using Phoenix WinNonlin software (v6.3, Pharsight Corp., Mountain View, CA). The area under the curve (AUC) was computed using the linear-up, log-down trapezoidal rule for 24-hour (2300h - 2300h) and three 8-h time intervals (night: 2300h - 0700h; morning: 0700h - 1500h; afternoon: 1500h - 2300h) chosen to approximate physiologic periods of low, high and intermediate cortisol respectively. Peak concentration (C_{max}) and time to peak concentration (T_{max}) were determined using actual collection time-points. 24-hour

hormonal exposure was also evaluated based on the number of time-points that androgens were within elevated, optimal and suppressed ranges according to the categorization used for dose adjustments.

Pharmacokinetic parameters from this Phase 2 study were compared to prior Phase I study results in healthy volunteers and to cortisol profiles (using LC-MS/MS,) obtained in healthy controls not receiving any medication (n = 28) who underwent every 20min cortisol sampling over 24-hours as an approximation of normal circadian rhythm (12,14).

SF-36 score was computed using SF-36v2 OptumInsight software as norm-based score, which employs a linear T-score transformation with mean of 50 and standard deviation of 10 (15). AddiQoL, a disease specific questionnaire developed for patients with adrenal insufficiency, has scores ranging from 30 (worst possible) to 120 (best possible) (16). Global Fatigue Index (GFI) score was calculated using the MAF data and GFI scores range from 1 (no fatigue) to 50 (severe fatigue) (17).

Depending on the data distribution, parametric (paired *t*-test) and non-parametric (Wilcoxon signed rank) tests were used to compare changes in AUCs, biomarkers and metabolic indices from baseline (conventional treatment) to 6-months of Chronocort® therapy. Categorical data between these intervals were compared using McNemar's test.

Results

Twenty one patients were screened. Four patients failed to meet the inclusion criteria for PRA level and one patient was eligible but chose not to participate due to time constraints. Sixteen adults (8 females; median age: 24 years, range 18 - 60 years) with classic CAH (12 salt-wasting, 4 simple virilizing) participated. Patients were on a variety of glucocorticoid regimens (Table 1).

Medication accountability revealed that one patient was noncompliant with taking the study medication. Results were similar when analyses were repeated excluding this patient. At study completion, 75% of patients expressed an interest in continuing Chronocort® if it were available.

Pharmacokinetic Profile of Chronocort®

The cortisol pharmacokinetic profile 48-hours post Chronocort® initiation and following 6 months of therapy was similar to the normal circadian rhythm of cortisol observed in healthy subjects and the pharmacokinetic profile of Chronocort® observed in a Phase 1 study (Table 2) (12,14).

Ten patients required Chronocort® dose adjustments (decrease in 8, increase in 2) resulting in an overall decrease in glucocorticoid dose (glucocorticoid equivalent dose: conventional *vs.* 6 months: 28 ± 11.8 *vs.* 25.9 ± 7.1mg/day). After 6 months of Chronocort®, there was no evidence of dose accumulation or nonlinear pharmacokinetics. Overall exposure to cortisol (AUC) over 24-hours was similar following the first Chronocort® dose and at 6 months (dose-normalized to 10 mg). However, peak cortisol levels were lower by approximately 10% at 6 month therapy (90% CI, 0.742 - 1.057), which was expected due to reduced doses following dose titration.

Biomarkers of Disease Control

On conventional therapy, ACTH levels began to rise at 0500h, plateaued between 0700h - 1500h, and declined after 1700h. 6 months Chronocort® therapy resulted in lower ACTH levels throughout the day; however changes in ACTH were not significant (Figure 2).

The majority of patients had elevated androstenedione and 17-OHP during the day while receiving conventional therapy. In comparison to baseline, androstenedione at 6 months showed a decrease in the

percent of time-points with elevated levels (33.7% *vs.* 12.0%, $P < 0.0001$) and a higher percent of time-points in the normal range (55.8% *vs.* 73.1%, $P < 0.0001$). Likewise compared to baseline, 17-OHP at 6 months showed a decrease in the percent of timepoints with elevated levels (33.2% *vs.* 12.0%, $P < 0.0001$) and an increase in the number of timepoints in the suppressed range (46.2% *vs.* 69.2%, $P < 0.0001$). In fact, the majority (59%) of patients had 17-OHP values in the normal range (males: 40-220 ng/dL, females: 40-285 ng/dL) following 6 months of Chronocort® therapy.

Similarly, at 6 months, Chronocort® resulted in lower 24-hour ($P = 0.003$), morning (0700h - 1500h; $P = 0.0008$) and afternoon (1500h - 2300h; $P = 0.009$) AUC androstenedione and lower 24-hour ($P = 0.021$) and morning (0700h - 1500h; $P = 0.018$) AUC 17-OHP compared to conventional therapy.

Disease related metabolic indices and quality-of-life estimates

Following 6 months of Chronocort®: there were no significant changes in body mass index (BMI) but there was an increase in lean mass ($P = 0.003$); homeostasis model assessment-estimated insulin resistance (HOMA-IR) measured in the morning (2300h – 0700h) increased (1.91 ± 0.7 *vs.* 2.98 ± 1.7; $P = 0.02$); and the bone turnover marker osteocalcin, increased ($P = 0.01$) (Table 3).

Sex differences were observed in some measurements of body composition. Although body composition showed an overall increase in lean mass ($P = 0.003$) and no changes in fat mass, subgroup analysis revealed that an increase in lean mass occurred in females only ($P = 0.006$) and males experienced a decrease in fat mass ($P = 0.036$). Whole body bone mineral density (BMD) showed a slight decrease ($P = 0.007$), and subgroup analysis by sex showed a decrease in BMD in females only ($P = 0.015$) (Table 3).

No significant changes were noted in quality-of-life or fatigue (baseline *vs.* 6 months: SF-36: 54.2 ± 4.6 *vs.* 53.7 ± 5.5; AddiQoL: 96.1 ± 10.9 *vs.* 97.4 ± 12.5; GFI: 14.3 ± 8.8 *vs.* 12.6 ± 9.3. Of note, at baseline, mean SF-36 score across all domains was greater than 50, the mean of a healthy population (15). Similarly, AddiQoL and GFI scores were similar to a healthy population (16,17) .

Adverse Events

Chronocort® was well tolerated. No serious adverse events occurred. Common short-term adverse events resolved and may have been associated with changes in glucocorticoid medication and/or the frequent blood sampling (Table 4). Six patients received stress dosing for acute viral illnesses of short duration. Two patients received stress dosing related to incidental surgical diagnosis and treatment (inguinal hernia, benign breast nodule). One patient experienced symptoms of adrenal insufficiency one week after starting the study and received stress dosing for a few days followed by an increase in Chronocort® dose. One patient was diagnosed with tenosynovitis and one patient had worsening of trigger finger.

Three patients had unexpected carpal tunnel syndrome, but two had a prior history. In one patient, symptoms self-resolved while still receiving Chronocort®. The other two patients had symptomatic improvement with wrist splints. Changes in PRA were not observed.

Discussion

Our study is the first to demonstrate that it is possible to safely replace cortisol in a near physiologic manner using Chronocort®, an oral modified-release hydrocortisone formulation, in patients with CAH. This novel hydrocortisone formulation was well tolerated and effective in controlling androgen excess in adults with CAH when administered twice daily.

Chronocort® is a multi-particulate modified-release capsule formulation of hydrocortisone, developed in attempt to overcome the challenges observed with conventional glucocorticoid therapy, such as inability to adequately control androgen secretion without the complications of supraphysiologic glucocorticoids (12). At baseline, while receiving conventional glucocorticoid therapy, 24-hour sampling revealed inadequate androgen control throughout the day in the majority of our patients, despite receiving long-acting glucocorticoids. Although all of our CAH patients were on stable glucocorticoid doses for at least three months prior to study entry, inclusion criteria was not based on level of hormonal control. Overall, our patients tended to have mildly elevated androgens on their conventional treatment, none were grossly over treated and none had hypothalamic-pituitary-adrenal axis suppression. Large cohort studies report that only about one third of adult patients with classic CAH have hormones within target ranges (3,18).

Based on the data obtained in our study of classic CAH patients, Chronocort® provides a stable peak to trough ratio of plasma cortisol concentrations that more closely mimics the normal circadian rhythm over a 24 hour period than conventional glucocorticoid replacement therapy. In particular, overnight cortisol rise (2300h - 0700h) and cortisol peak after awakening into the early afternoon (0700h - 1500h) had the most confluence with estimated physiologic cortisol secretion. However, even with the twice daily regimen of Chronocort®, cortisol levels were low in the evening hours but the ACTH and androgen levels remained in an acceptable range and all patients exhibited persistence of an endogenous diurnal variation in their hormone levels. This supports the concept that less cortisol replacement is needed at this time of the day as naturally cortisol and ACTH levels are low (10,19,20).

As the cortisol profile approximated physiologic cortisol secretion, Chronocort® therapy effectively controlled the androgen excess characteristic of CAH. Compared to conventional therapy at baseline, Chronocort® at 6 months showed improved serial androstenedione levels with lower 24-hour, morning and afternoon androstenedione and improved 17-OHP levels over 24 hours and in the morning. Interestingly the majority of 17-OHP levels were within the normal range, rather than in the mildly elevated range typically used for management (3,21). Single time-point morning androgen measurement

is frequently used for monitoring treatment in CAH (22). An advantage of our study was our ability to perform 24 hour serial sampling and this lowering of androgens observed throughout the day was achieved with lower average daily glucocorticoid doses.

Our findings need to be considered within the context of the population of patients being studied and may be confounded by the multiple hormonal imbalances characteristic of CAH. On Chronocort®, there was a decrease in overall glucocorticoid dose based on hydrocortisone dose equivalency, increase in lean body mass, decrease in fat mass (males only), and insulin resistance assessed by morning HOMA-IR increased. The increase in HOMA-IR was observed after the first dose of Chronocort® and therefore is unlikely to reflect a change in body composition and might be due to a rise in early morning cortisol which does not occur with conventional glucocorticoid therapy. In healthy individuals insulin sensitivity falls before awakening associated with the physiological cortisol increase. Patients with adrenal insufficiency on hydrocortisone have low concentrations of metabolic fuels throughout the night, related to decreased overnight cortisol levels, and this might play a role in non-specific symptoms such as fatigue, early morning headache, and risk of hypoglycemia (23). Exogenous glucocorticoids in pharmacologic doses have negative effects on the bone and decrease osteocalcin, a marker of bone formation (24).We observed an increase in osteocalcin reflecting lower glucocorticoid exposure during 6months of Chronocort® therapy. Conversely, we observed a slight decrease in whole body BMD, significant in females only. This finding is possibly due to a decrease in androgen exposure. Region specific BMD changes were not assessed. Future studies of Chronocort® therapy in CAH patients should involve more detailed assessments of metabolic parameters and BMD.

Patients with CAH have increased morbidity which in part is due to the limitations of current available glucocorticoid therapy (3,7,25-27). As a result, novel therapies are being developed and studied by our group and others in an attempt to improve patient outcomes. (10,28,29). Short-term proof of concept studies and case reports have demonstrated promising results using continuous subcutaneous hydrocortisone infusion to achieve circadian cortisol replacement in CAH patients (28,30-32). In patients

with primary autoimmune adrenal insufficiency, once daily Plenadren®, the dual-release hydrocortisone, achieved normal morning cortisol levels but resulted in lower cortisol exposure over 24 hours and lack of normalization of early morning cortisol levels prior to awakening (33). Thus it is doubtful that this type of hydrocortisone formulation would improve androgen excess in CAH patients because it does not provide overnight cortisol replacement. In contrast, the pharmacokinetic profile of cortisol on twice daily Chronocort® showed good 24hour bioavailability resulting in lowering androgens in CAH patients.

Although Chronocort® overall achieved a near-physiological 24-hour cortisol profile, cortisol secretion exhibits a distinct circadian and ultradian rhythm which is influenced by the sleep-wake cycle and cannot be replicated with oral glucocorticoid replacement (11,34,35). The clinical significance of this is unknown. The hypothalamic-pituitary axis has a significant role in the sleep-wake cycle (36,37), and a subset of our patients experienced sleep disturbances while receiving Chronocort®. Dose adjustments helped with early awakening in both patients but complaints of odd dreams persisted in one patient. Qualitative or quantitative assessments of sleep were not part of our study. We did not find any changes in quality-of-life, which was not surprising given the small sample size, short study duration and relatively normal baseline quality-of-life scores.

There were no serious adverse events. Three patients had the unexpected adverse event of carpal tunnel syndrome. Two of these patients had a history of similar complaints in the past. The etiology of these three cases of median nerve entrapment syndrome is not clear. Although increased mineralocorticoid activity of Chronocort® compared to pre-study treatments (prednisone, dexamethasone) is a possibility, all three patients were receiving fludrocortisone and no changes were seen in PRA.

In addition to the small sample size, our study had a few important limitations. First, the study was an open label, non-randomized design. Although majority of patients were being followed at the NIH prior to study enrollment and were known to be compliant on their conventional medication, it is possible that improved compliance occurred secondary to the close scrutiny characteristic of being enrolled in a

clinical trial. Moreover, an additional potential advantage during Chronocort® therapy was the frequent dose adjustments to optimize treatment. These potential biases are due to the nonrandomized study design. Second, although the study design allowed dosage adjustments, the options were limited as the smallest available dose was 5mg. Having smaller dose formulations would allow for more flexible and precise dose adjustments.

It is anticipated that the ability of Chronocort® therapy to mitigate the drastic fluctuations in cortisol levels observed with conventional glucocorticoid therapy while more closely mirroring physiologic diurnal variation will result in improved patient outcome. This newly-developed modified-release oral hydrocortisone formulation regimen given as a twice daily dosing represents a new treatment approach for patients with CAH. Further studies, and studies including children, are necessary to determine the long-term outcomes of Chronocort® therapy.

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