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Clinical Study

Nocturnal Dexamethasone versus Hydrocortisone for the Treatment of Children with Congenital Adrenal Hyperplasia

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Classic congenital adrenal hyperplasia affects approximately 1 in 15,000 children. Current treatment strategies using multiple daily doses of hydrocortisone lead to suboptimal outcomes. We tested the hypothesis that nocturnal administration of dexamethasone will suppress the hypothalamic-pituitary-adrenal axis more effectively than standard hydrocortisone treatment by blocking the inherent diurnal secretion of ACTH. We performed a pilot study of five prepubertal patients comparing CAH control during two 24-hour hospitalizations, one on hydrocortisone and the other on dexamethasone. The patterns of adrenal suppression differed markedly between hydrocortisone and nocturnal dexamethasone, with significant suppression of the morning rise in ACTH, 17-hydroxyprogesterone, and androstenedione while on dexamethasone. On hydrocortisone therapy, there is a marked variation in ACTH and adrenal hormones depending on time of day and timing of hydrocortisone administration. Longer-term studies are needed to investigate the lowest effective dose and potential toxicity of nocturnal dexamethasone to determine its utility as a therapy for CAH.

1. Introduction

Congenital adrenal hyperplasia results from a defect in the adrenal steroid biosynthetic pathway leading to hypocortisolemia, resultant elevated ACTH levels and hyperandrogenism. In theory, glucocorticoid replacement should restore normocortisolemia, thus inhibiting excess ACTH secretion and correcting the hyperandrogenic state. In reality, however, adequate adrenal androgen suppression is difficult to achieve as, even in the face of ACTH levels in the normal range, adrenal steroid precursors proximal to the enzymatic defect will still accumulate and maintain the hyperandrogenic state [1]. Supraphysiologic doses of glucocorticoids may be needed to suppress excess androgen production at the risk of impaired linear growth [2, 3]. On the other hand, suboptimal adrenal androgen suppression with inadequate hydrocortisone therapy may accelerate linear growth, resulting in premature closure of the epiphyses and an impaired final adult height [4]. There is no consensus as to the optimal treatment or monitoring regimen for congenital adrenal hyperplasia.

Our study is an open-labeled pilot study comparing the efficacy of nocturnal dexamethasone versus standard hydrocortisone therapy in the control of the hypothalamic-pituitary-adrenal axis in prepubertal subjects with classic salt-wasting congenital adrenal hyperplasia. We hypothesize that the administration of a long-acting glucocorticoid, dexamethasone, being given at night will more effectively suppress the pituitary gland diurnal secretion of ACTH, most of which occurs during the night. There is much debate in the literature as to the dose equivalency between hydrocortisone and dexamethasone with ratios ranging from 17 : 1 to 80 : 1 [5–8]. As our study was intended as an initial proof of principle pilot study, we chose a dose equivalency of 50 : 1 in order to ensure our ability to detect a difference in hormonal profiles on the two medication regimens, prior to exploring the lowest effective dose and potential toxicities of dexamethasone in a subsequent, longer-term study.

2. Materials and Methods

Subjects were eligible for enrollment if they had classic salt-wasting 21-hydroxylase-deficient congenital adrenal hyperplasia with a bone age below 8 years of age and a chronological age above two years of age. This age group was chosen as this study was designed as a pilot study with the intention of eventually performing further studies examining long-term outcomes such as growth velocity. Therefore, we limited enrollment to prepubertal children so as to avoid the growth promoting effects of sex steroids. Diagnosis was confirmed by reviewing the medical record. Subjects were excluded if they required glucocorticoid therapy for another medical indication besides CAH. Subjects were also excluded if they were taking any medications that interfered with the metabolism or bioavailability of glucocorticoids.

Subjects were recruited from the outpatient Endocrinology clinic at Children's Hospital Boston. This study was approved by the Children's Hospital Boston Committee on Clinical Investigation. Informed consent was obtained from both parents of all subjects. The trial was registered at http://clinicaltrials.gov/, identifier # NCT00621985.

There were 16 subjects who met the study inclusion criteria. Six subjects consented to inclusion in the study. IV access could not be obtained in one subject, and the remaining five subjects (2 females) were included in the study. Four completed the entire protocol while the fifth only completed the baseline admission due to intravenous access difficulties. Subjects' ages ranged from 2 to 7 years with bone ages between 1 year 9 months and 7 years 10 months. Four of the subjects received hydrocortisone three times per day and Subject 3 received it twice per day as baseline therapy. Total daily hydrocortisone doses ranged from 6.94 to 18.52 mg/m^2/day. All subjects were on Fludrocortisone for mineralocorticoid replacement with doses ranging from 0.05 mg to 0.1 mg (See Table 1 in supplementary material available online at doi: 10.1155/2010/347636; it includes detailed demographic information).

Subjects were admitted to the Clinical and Translational Science Unit for two 24-hour inpatient hospitalizations, the first on standard hydrocortisone therapy and the second on dexamethasone therapy. During each admission, subjects were admitted to the hospital at noon on day 1. They had a drawing IV placed, and the study commenced with the first blood draw at 15:00. Thirteen blood samples were drawn over a 23-hour period for the measurement of ACTH, 17-hydroxyprogesterone and, androstenedione. A fasting 08:00 blood draw was performed for serum glucose and insulin levels. Additionally, 24-hour urine collections were performed for the measurement of creatinine, pregnanetriol, and 17-ketosteroids in those subjects who were toilet trained.

All samples except for ACTH were handled as per standard operating protocols of the Children's Hospital Boston clinical laboratory. ACTH samples were collected in EDTA tubes on ice. They were immediately spun down in a refrigerated centrifuge for 10 minutes and then aliquoted into 1 mL aliquots. They were then frozen at $-20^{\circ}C$ until the completion of each admission, at which point they were transferred to the clinical laboratories for further processing. 17-hydroxyprogesterone and androstenedione were quantified by liquid chromatography tandem mass spectrometry (LC-MS/MS) with a C18 LC column. Prior to injection, the analyte was isolated from the serum/plasma by liquid-liquid extraction. An internal standard was included in each sample to account for sample loss throughout the sample preparation procedure. The assay was linear between 10 and 1000 $ng \cdot dL^{-1}$. The intra-assay CV, for three levels of QC, determined over three months of instrument operation were 15.9% and 14.3% for 17OHP and androstenedione respectively. An IMMULITE 2000 analyzer (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA) was employed for ACTH quantification. The solid-phase, two-site sequential chemiluminescent immunometric assay has an analytical sensitivity of 5 $pg \cdot mL^{-1}$ and provides a linear response between 5 and 1250 $pg \cdot mL^{-1}$. The intra-assay CVs, for three QC levels, determined over three months of instrument operation averaged out at 4.1%. Cortisol was measured via an electrochemiluminescence immunoassay on the cobas e601 automated analyzer (Roche Diagnostics, Indianapolis, IN, USA). The lower limit of detection and that of quantification for cortisol are ≤ 0.036 and 0.31 $\mu g \cdot dL^{-1}$, respectively. The assay is linear over a concentration range of 0.036–63.4 $\mu g \cdot dL^{-1}$. The intra-assay CVs, for three QC levels, determined over three months of instrument operation averaged out at 2.3%. 17-Ketosteroids were quantified in urine using a Beckman DU-800 spectrophotometer. The assay has a linear range from 1 to 40 $mg \cdot L^{-1}$. The interassay CV for analyte levels of 5 and 23 $mg \cdot L^{-1}$ were 14 and 8%, respectively. Aliquots of urine were mixed with an internal standard and incubated overnight with glucuronidase to free the pregnanetriol from glucuronide conjugates. The pregnanetriol was then extracted, reduced, and subjected to alumina open column chromatography. The silane derivative of the collected pregnanetriol peak was analyzed using GC with a flame ionization detector. A standard, a blank, and two control pools are included in each assay batch. The assay was linear between 0.05 and 20 $mg \cdot dL^{-1}$. The inter- and intraday assay CVs, respectively, averaged out at 8.1 and 15.5% for the two control levels tested.

Standard therapy was defined as the individual subject's baseline hydrocortisone and fludrocortisone regimen as determined by their primary endocrinologist. Hydrocortisone doses were given at 08:00, 15:00, and 22:00 for subjects on a three-dose regimen and at 08:00 and 22:00 for the subject on a two-dose regimen. Dexamethasone was given at a reduction dose of 1 : 50 of the total daily hydrocortisone dose of each patient. The dexamethasone dose was given at 22:00 for three days starting on the evening 2 days prior to the second admission. The subject was then admitted on the afternoon of the third day for the second 24-hour admission. The second admissions occurred between 2 and 8 weeks after the first admission. All lab samples were obtained prior to the administration of a medication dose at the same time point.

On each admission, parents were questioned regarding how well the patient slept over the prior three days. A five-point Likert scale was used ranging from 1 = Very Poorly to 5 = Very Well. As a measure of self-reported compliance, parents were also asked to report the number of doses of

hydrocortisone missed in the past 3 days and number of doses of hydrocortisone missed on average per week over the preceding 3 months. All subjects were reported to be in good compliance.

Area under the curves for the 23-hour profiles of 17-hydroxyprogesterone, androstenedione, and ACTH were calculated by the trapezoidal rule. Values less than the assay limit were estimated as half the difference between the lower assay limit and zero. AUCs were log transformed for analysis to reduce skew. Two-sided paired t-tests were used to compare mean log-transformed AUC, mean fasting blood glucose, and insulin values on the two therapeutic regimens.

3. Results

Figures 1–5 depict the 24-hour hormonal profiles for each of the subjects. Normal values in this age range for ACTH, 17-hydroxyprogesterone, and androstenedione are 6–55 pg/ml (1.3–12.2 pmol/L), less than 100 ng/dl (3025 pmol/L), and 10–47 ng/dl (349–1641 pmol/L), respectively. In all subjects on standard therapy, ACTH, 17-hydroxyprogesterone, and androstenedione values were suppressed throughout the night and rose sharply at approximately 04:00. These values peaked prior to the administration of the 08:00 hydrocortisone dose. They then dropped significantly by 10:00. These values tended to rise at 12:00 as the morning hydrocortisone dose effect waned until the administration of another dose of hydrocortisone at 15:00. In the subject on twice daily hydrocortisone therapy, these values continued to rise until 18:00. Subjects 2, 3, and 5 demonstrate a fall in hormonal values between 18:00 and 20:00 without additional hydrocortisone administration. This indicates the presence of an intact diurnal rhythm in these subjects despite lack of negative feedback from cortisol. All subjects' ACTH, 17OHP, and androstenedione levels were suppressed after the 20:00 dose of hydrocortisone and remained low throughout the night. There was exquisite concordance in the 24-hour curves for all 3 hormones.

In all subjects, nocturnal dexamethasone administration led to blunting of the early morning rise in ACTH, 17OHP, and androstenedione. This effect lasted throughout the day with a trend for higher hormonal levels in the afternoon as the dexamethasone effect waned. The degree of suppression of the hypothalamic-pituitary-adrenal axis depended on the level of suppression on standard therapy. Figure 6 summarizes the percent difference in the integrated area under the curves for the 23-hour hormonal profiles as well as the urine 17-ketosteroids. Mean log AUC was significantly lower for ACTH ($P = .031$) and marginally significantly lower for 17OHP ($P = .098$) on dexamethasone therapy. There was no statistical difference between mean log Androstenedione ($P = .475$) or 17-ketosteroids ($P = .175$) on the two regimens. Urine samples were only available for 3 subjects (Supplementaral Figures 1 and 2). Mean urine pregnanetriol levels were 2.4 and 0.1 mg/24 hours on standard and dexamethasone therapy, respectively. Mean urine 17-ketosteroids levels were 2.6 and 1.4 mg/24 hours on standard and dexamethasone therapy, respectively.

The mean fasting blood sugar was 83 mg/dl on both standard and dexamethasone therapy ($P = 1$). Mean fasting insulin levels were 6.95 and 9.63 mcIU/ml on standard and dexamethasone therapy, respectively ($P = .40$). Mean sleep scores were 4 and 4.5 on standard and dexamethasone therapy respectively, indicating that nocturnal dexamethasone did not lead to sleep disruption in this short time frame.

4. Discussion

Optimal monitoring and treatment of congenital adrenal hyperplasia remains quite difficult despite the availability of multiple glucocorticoid preparations and hormonal assays. Traditional dogma suggests that prepubertal children should be treated with a hydrocortisone dose divided twice or thrice daily and the degree of control should be assessed by monitoring 17-hydroxyprogsterone, androstenedione, and possibly testosterone levels [9, 10]. Invariably, the greatest apparent adrenal androgen suppression occurs 2–4 hours after each dose [11], and the duration of this suppressive effect is limited. Also, standard treatment with two or three daily doses of corticosteroids [12], treatment with different prednisone regimens [13], and even nocturnal administration of the total daily dose of hydrocortisone [11] do not prevent a pronounced rise in 17-hydroxyprogesterone level after midnight, reflecting lack of effective suppression of the nocturnal ACTH peak. However, when hydrocortisone is administered at 03:00 AM at 33% of the total daily dose, a marked reduction in the morning serum 17-hydroxyprogesterone levels is observed [14], indicating adequate suppression of the early morning rise in ACTH. Additionally, a recent study examining the efficacy of an extended-release hydrocortisone demonstrated good early morning control of ACTH and adrenal androgen production with waning effects in the afternoon [15].

We hypothesized that a single nocturnal daily dose of dexamethasone, a longer-acting glucocorticoid [16], would lead to an improved suppression of the HPA axis. Several studies on dexamethasone treatment for congenital adrenal hyperplasia have been performed; however, most were done in adult patients at supraphysiologic hydrocortisone equivalent doses, often resulting in cushingoid side effects [16–20]. Hayek et al. [21] administered a single nocturnal dose of dexamethasone to four postpubertal patients with CAH, two of whom had the classic salt-wasting type. They demonstrated adequate suppression of adrenal androgens by measuring urinary 17-ketosteroid and pregnanetriol. No blood hormones were measured during this study nor was there any measure of the diurnal variation in hormone release. Rivkees and Crawford [7] reported their clinical experience with treating prepubertal children with CAH with single daily dose dexamethasone in the morning. Their patients had predicted adult heights that were comparable to target mid-parental heights with normal levels of adrenal hormones. Recently, Rivkees and Stephenson [22] reported on their experience in treating young children with dexamethasone starting in infancy. These children had normal growth patterns. These two studies demonstrate that it is

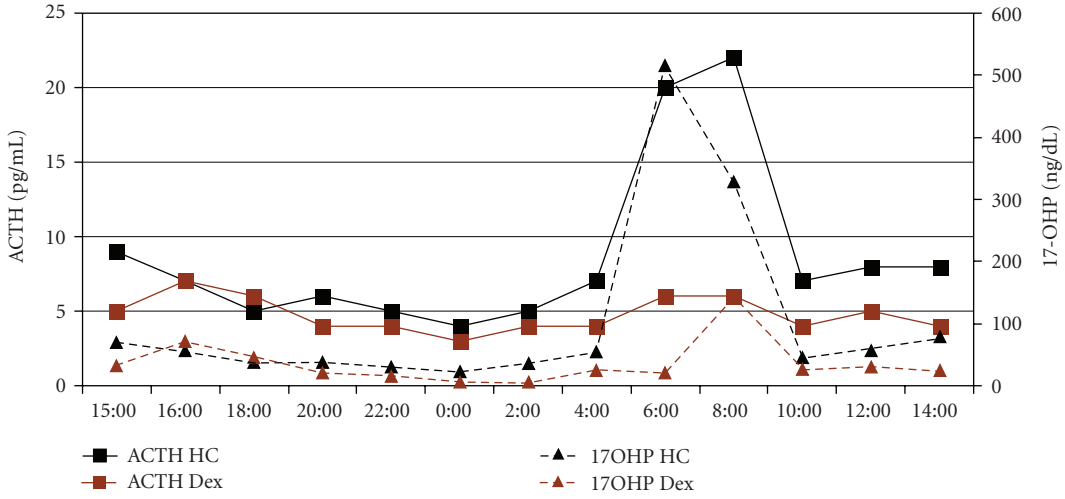

Figure 1: Subject 1 blood ACTH (squares) and 17 hydroxyprogesterone (17OHP, triangles) over 23-hour period while on hydrocortisone (HC, black) or dexamethasone (Dex, brown). Androstenedione levels were less than assay at all time points on both regimens in this patient. To convert to SI units, multiply ACTH by 0.2222 (pmol/L), 17OHP by 30.2572 (pmol/L), and Androstenedione by 34.9162 (pmol/L).

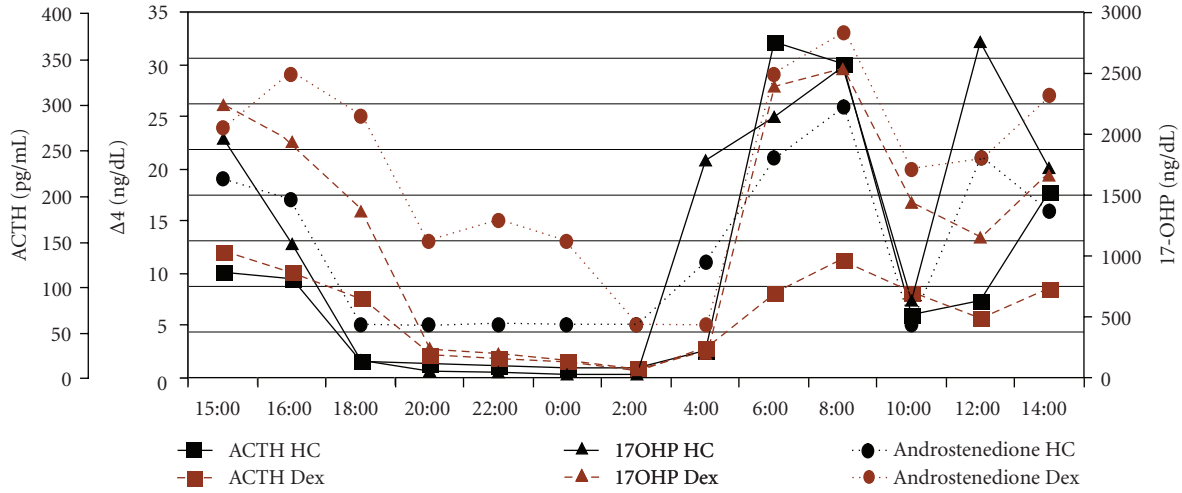

Figure 2: Subject 2 blood ACTH, 17 hydroxyprogesterone and androstenedione (circles) over 23-hour period while on hydrocortisone or dexamethasone. Abbreviations and symbols as in Figure 1.

feasible to treat prepubertal patients with single daily dose dexamethasone while maintaining adequate growth. These studies did not include any comparison groups nor did they examine our hypothesis regarding the timing of dosing affecting the efficacy of ACTH suppression.

Our pilot study is unique as it is a crossover study comparing the effectiveness of standard hydrocortisone therapy versus nocturnal dexamethasone therapy in a group of prepubertal patients with classic congenital adrenal hyperplasia. We demonstrated that nocturnal administration of the long-acting glucocorticoid dexamethasone given at 1/50th of the total daily hydrocortisone dose more effectively suppresses the morning rise in ACTH and adrenal androgens. While ACTH is not routinely used to monitor therapy in CAH, it has been shown to correlate with other clinical markers of control [23]. From a physiologic perspective, ACTH is the most proximal measurable indicator of the activation of the HPA axis and suppression by exogenous glucocorticoid treatment. It is the stimulus for adrenal hormone production and is responsible for its diurnal rhythm. Our study clearly demonstrates coordinated changes in ACTH and adrenal steroid blood levels throughout the day while on hydrocortisone therapy. This indicates that the steroid levels largely reflect regulation by ACTH. While we had a limited sample size, we believe that our results prove in principle that nocturnal dexamethasone administration could be more effective than thrice daily administration of hydrocortisone for the treatment of CAH.

Our study is limited in several respects. It was a short-term study that only used one dose of dexamethasone in a small number of subjects. As mentioned above, there is much debate as to the dose equivalency between hydrocortisone

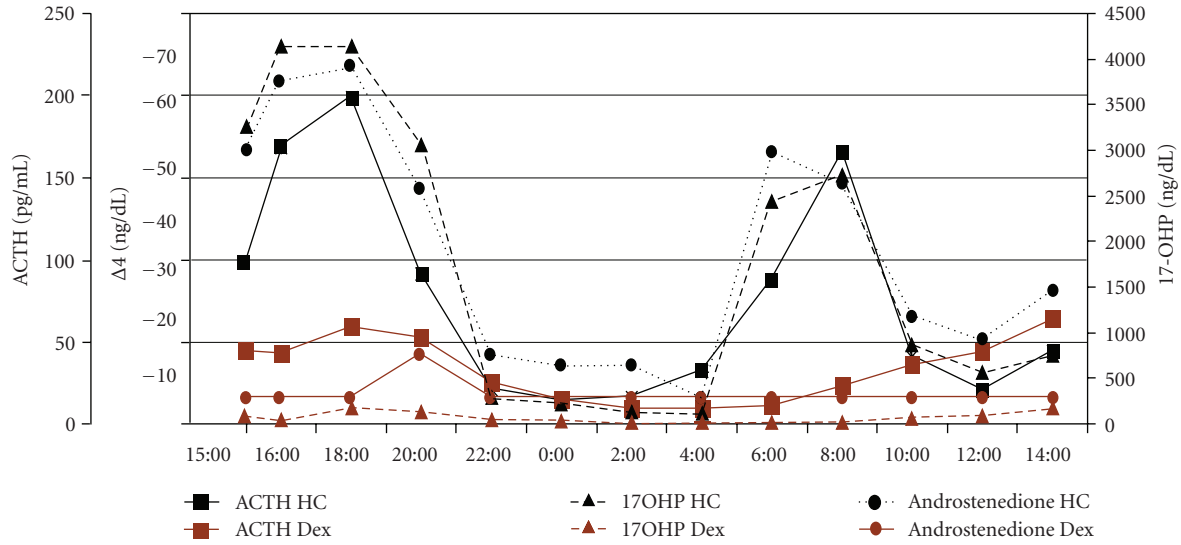

Figure 3: Subject 3 blood ACTH, 17 hydroxyprogesterone, and androstenedione (circles) over 23-hour period while on hydrocortisone or dexamethasone. Abbreviations and symbols as in Figures 1 and 2.

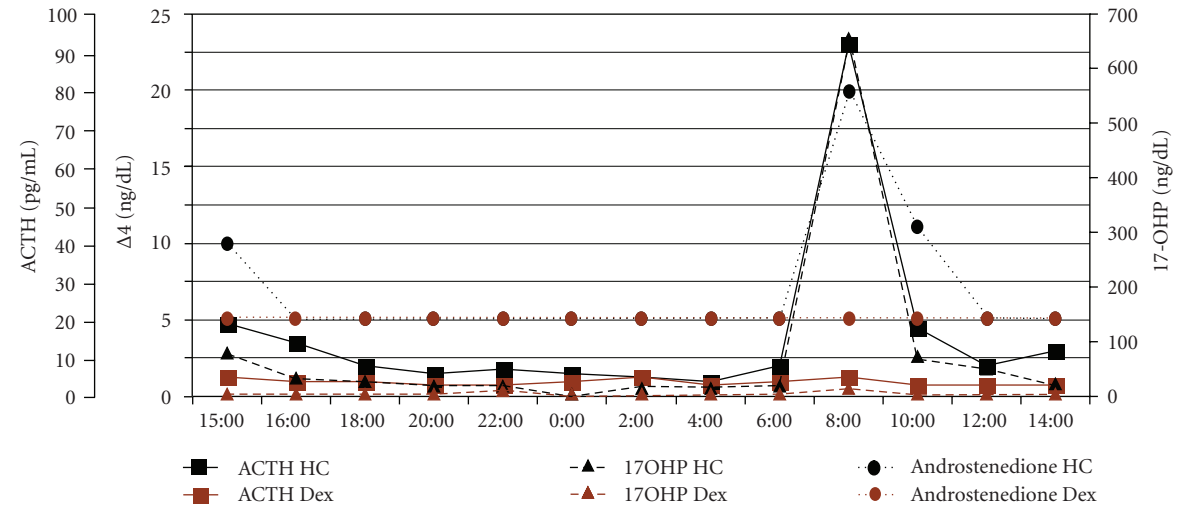

Figure 4: Subject 4 blood ACTH, 17 hydroxyprogesterone, and androstenedione (circles) over 23-hour period while on hydrocortisone or dexamethasone. Abbreviations and symbols as in Figures 1 and 2.

and dexamethasone with ratios ranging from 17 : 1 to 80 : 1 [5–7, 24]. Glucocorticoids have different potencies depending on the physiologic effect being investigated [5]. It is possible that the dexamethasone used in our study was more effective merely because it represented a higher effective dose of glucocorticoid. While this is a definite possibility, many of our patients had multiple ACTH, 17OHP, and androstenedione levels that were not completely suppressed while on the dexamethasone therapy, as well as normal 24-hour urine values of 17-ketosteroids. Subjects 1 and 2, who were given the lowest doses of dexamethasone as a function of body surface area, had clear diurnal rhythms in hormone release (Figures 1 and 2). These findings indicate that their adrenal glands were not completely suppressed by dexamethasone. Additionally, we did not find any rise in the fasting blood sugar or insulin levels which would be markers of overtreatment. However, all three subjects who completed the 24-hour urine collections did have very low values of pregnanetriol while on dexamethasone, and subjects 3 and 4 (who were given the highest doses of dexamethasone as a function of body surface area) had minimal variability in ACTH throughout the day. While it does not appear that the adrenal glands were completely suppressed, this does likely reflect a degree of oversuppression. Given the wide range of quoted potencies for dexamethasone in the literature, we chose a dose equivalency in the middle of the range. Ultimately, a longer-term dose-finding study must be done in which the dose of dexamethasone will be titrated

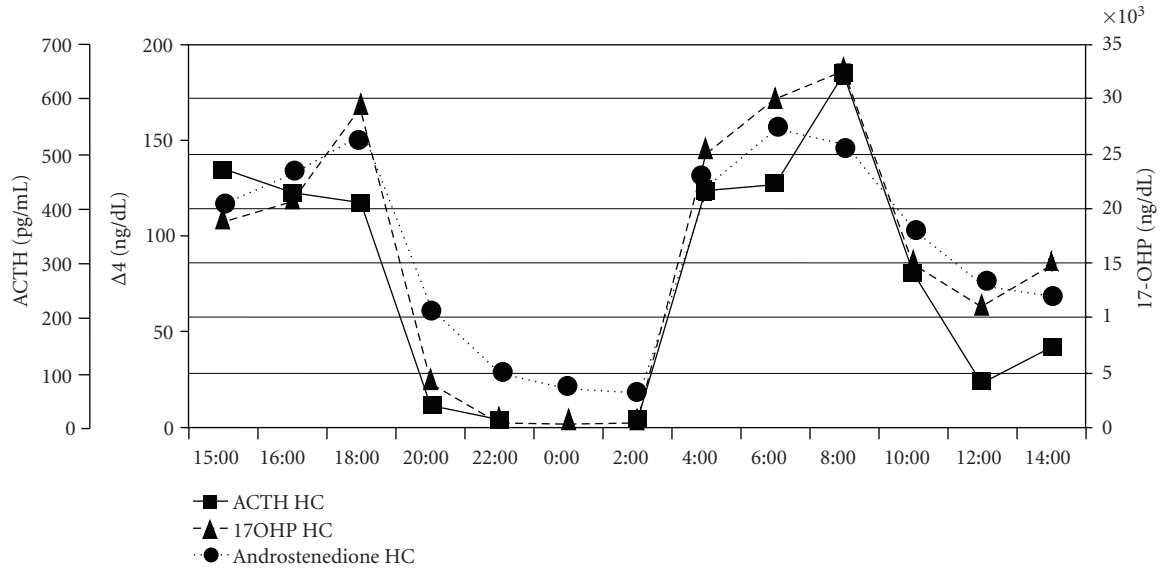

Figure 5: Subject 5 blood ACTH, 17 hydroxyprogesterone, and androstenedione (circles) over 23-hour period while on hydrocortisone. Subject 5 did not complete the dexamethasone admission due to technical difficulties. Abbreviations and symbols as in Figures 1 and 2.

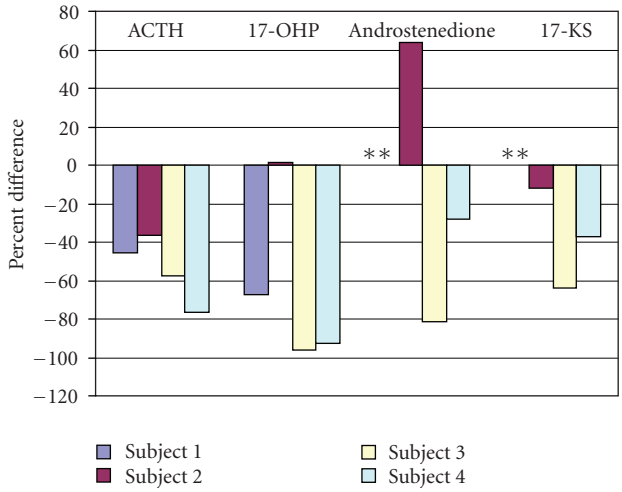

Figure 6: Percent difference in area under the curve on dexamethasone versus hydrocortisone for ACTH, 17 hydroxyprogesterone, androstenedione, and urinary 17-ketosteroids (17-KS) for subjects 1–4. Subject 1 had androstenedione levels less than assay at all time points on both regimens and did not perform a urine collection for 17-ketosteroids.

based on clinical parameters while monitoring for signs of oversuppression. Based on our study, we believe that dexamethasone has a potency at least 50 times greater than that of hydrocortisone. There are also concerns that long-term administration of nocturnal dexamethasone could lead to suppression of growth hormone secretion [25]. Given these concerns, we believe that further research is necessary for comparing the efficacy of various glucocorticoid regimens, including nocturnal dexamethasone, over a period of time that allows assessment of HPA axis suppression and potential sequelae of glucocorticoid overtreatment, prior to deciding whether this approach could be a part of routine care.

Additionally, our results demonstrate some important points for monitoring of therapy in CAH regardless of treatment regimen. The data clearly show that there is exquisite synchronicity in the patterns of ACTH, 17-hydroxyprogesterone, and androstenedione production. It has been suggested that individual androstenedione values may be a better marker of adrenal suppression than 17-hydroxyprogesterone [26–28] as androstenedione purportedly has less diurnal variability [29]. Our data do not support this belief as poorly controlled patients had androstenedione values that varied up to 13 folds during a 24-hour period. The magnitude of change is smaller than that of 17-hydroxyprogesterone, but the degree of variation is still quite marked. It is possible that we were able to better delineate this variation due to our use of tandem mass spectrometry to measure androstenedione levels.

Our study also illustrates the high variability in adrenal hormone production depending on both the time of day and timing of sample acquisition relative to glucocorticoid administration. Three of our patients' hormonal values fell in the early evening without additional hydrocortisone administration suggesting that patients with congenital adrenal hyperplasia continue to have an inherent diurnal rhythm for ACTH secretion even in the absence of negative glucocorticoid feedback. In fact, it appears that the normal night-time diurnal suppression of ACTH release is hierarchically more important than negative feedback suppression of ACTH by cortisol as the former occurs in the absence of the latter. Therefore, we conclude that administration of short-acting glucocorticoids after 18:00 does not assist in suppression of the HPA axis as it is already inherently shut off. Verma et al. [15] drew a similar conclusion in their study which is also supported by a recent study by German

et al. [30] that showed no difference in disease control as assessed by 08:00 hormonal levels in subjects receiving a higher dose of hydrocortisone in the evening versus the morning. Furthermore, these authors showed that there was no difference in sleep quality as measured by actigraphy on the two regimens. Our study supports this finding by showing that nocturnal administration of dexamethasone, a steroid significantly more potent that hydrocortisone, did not lead to sleep disturbance in any of our patients.

Additionally, our study clearly demonstrates how a single measurement of 17OHP or androstenedione can be misleading in assessing a patient's overall level of adrenal suppression. Within-subject variation of 17OHP was as great as 40 folds over a 24-hour period. This variability can lead to both over- and underestimates of the degree of adrenal suppression. For example, subject 3 had a 17OHP value of 560 ng/dl and androstenedione of 16 ng/dl at noon. His peak values were 4140 ng/dl and 67 ng/dl, respectively (Figure 3). Thus, the noon value, which represented the effect of the 08:00 hydrocortisone administration, could falsely reassure the clinician that this patient is well controlled when he is actually undertreated. As a result of this phenomenon, some have advocated measuring hormonal levels at 08:00 prior to the administration of the morning glucocorticoid dose [10, 31]. However, this too can be misleading as is demonstrated by subject 4 (Figure 4). This patient had an 08:00 17OHP value of 655 ng/dl and androstenedione of 20 ng/dl, both values within the target range for good control of CAH. However, the remainder of the 17OHP values were all less than 100 ng/dl, and the majority of the androstenedione values were less than 10 ng/dl. This patient's 24-hour profile suggests that she was being over treated while the 08:00 value provided false reassurance of good control. Thus, we urge great caution in the interpretation of any single 17OHP or androstenedione value at any time of day. It is possible that 24 hour urine collections of adrenal metabolites such as pregnanetriol and 17-ketosteroids, although cumbersome, more accurately reflect the overall degree of HPA activity as they integrate hormonal secretion over an entire diurnal cycle.

5. Conclusions

We have performed a crossover pilot study comparing the efficacy of standard hydrocortisone therapy versus nocturnal dexamethasone therapy in children with congenital adrenal hyperplasia. Nocturnal dexamethasone administration led to a decrease in the morning rise in ACTH and adrenal hormones, which we believe may translate into improved long term outcomes. Finally, our study clearly demonstrates the variability in ACTH, 17-hydroxyprogesterone, and androstenedione levels in relation to time of day and timing of glucocorticoid administration. Further research comparing the long-term safety and efficacy of various glucocorticoid regimens for the treatment of children with congenital adrenal hyperplasia is needed, in the hope of designing a better treatment of CAH that includes more robust suppression of the adrenal axis combined with less glucocorticoid toxicity.

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