

Comparison of different glucocorticoid regimens in the management of classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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ABSTRACT

Background: There are recommendations regarding the total dose of hydrocortisone to be administered in the treatment of classical congenital adrenal hyperplasia (CAH) to achieve the twin objectives of glucocorticoid replacement and control of hyperandrogenism. However, there is evidence gap regarding the breakup, timing and type of the steroid regimen. **Objectives:** Efficacy of three different glucocorticoid regimens having the same total dose of steroid, differing in either the timing or type of evening steroid administered, in achieving biochemical control of the disease was assessed. **Materials and Methods:** The study was done in 13 prepubertal children with classical CAH over a 6-month period with 2 months devoted to each regimen. We used a prospective cross-over design using 10-15 mg/m² total dose of hydrocortisone. Two-fifths of the total dose of hydrocortisone was administered in the morning and one-fifth of the total dose was administered at noon in all the regimens. The regimens differed in the timing of the evening dose of hydrocortisone, 06.00-07.00 pm in regimen 1 and 09.00-10.00 pm in regimen 2. The third regimen had the evening dose of hydrocortisone replaced by an equivalent dose of prednisolone suspension which was administered at 10.00 pm. Serum 17-hydroxyprogesterone and testosterone levels were compared to assess the efficacy of treatment regimens. **Results:** The three different regimens were found to be similar in their ability to control 17-hydroxyprogesterone and testosterone levels. The percentage of patients with predefined criteria for biochemically controlled disease was similar in all the three regimens. However, there was a trend toward better control of 17-hydroxyprogesterone levels in patients receiving evening dose of prednisolone. **Conclusions:** There is no significant advantage in administering the hydrocortisone dose late at night in patients with classical CAH.

Key words: Congenital adrenal hyperplasia, glucocorticoid, hydrocortisone, prednisolone, regimen

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a disease in which there is considerable heterogeneity in management. While there are published guidelines regarding the exact dose of hydrocortisone to be given, there is not enough data on the breakup and timing of these doses.^[1,2] Physicians caring for these patients are often plagued by problems of androgen

excess due to under treatment or by problems of growth retardation and iatrogenic Cushing's syndrome due to over treatment by glucocorticoids. By far, the commonest problem among these patients is androgen excess and its related consequences like accelerated skeletal maturation and androgenization. There are few studies which have tried to look at the dosing of steroids in CAH in growing children with special emphasis on timing and the exact dose to be administered each time.^[3,4]

The management of patients with CAH involves replacement of glucocorticoids and suppression of ACTH secretion and thereby controlling the excess androgen secretion from adrenals. A variety of glucocorticoids (hydrocortisone, prednisolone, and dexamethasone) and dosage schedules are used for this purpose in adults.^[5,6] In children the

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typical dosing of hydrocortisone is 10-15 mg/m²/day administered orally in three divided doses.^[1,2] Infants may temporarily require doses up to 25 mg/m²/day to reduce the markedly elevated sex steroids. Similarly higher doses (up to 17 mg/m²) are required during children in puberty. Stress dosing of steroids is an often neglected, important aspect in the management of patients with severe forms of CAH. The steroid dose has to be 2-3 times the usual dose and has to be tapered down to maintenance dose once the child recovers. If the child cannot take orally or is subjected to major physical stress parenteral steroids should be given. The morning dose of steroid should be given as early as possible to blunt the early morning corticotrophin increase that begins during the pre-dawn hours.

Doses must be individualized by monitoring growth, bone age, and hormonal levels. Patients with disturbances of electrolyte regulation (salt losers) and elevated plasma renin activity require a mineralocorticoid in addition to the glucocorticoid. Additional salt supplementation is required to maintain normal electrolytes. Maintenance therapy with fludrocortisone acetate (0.05-0.3 mg daily) and sodium chloride (1-3 g) are usually sufficient to normalize plasma renin activity.^[1,2] Fludrocortisone is having 12-fold greater glucocorticoid potency comparing to cortisol. Hydrocortisone equivalent of fludrocortisone (1.2 mg for every 100 µg of fludrocortisone) should be considered while calculating the total glucocorticoid dose especially in children.

The pharmacokinetics and pharmacodynamics of currently available glucocorticoids does not allow us to match the hormonal fluctuations in congenital adrenal hyperplasia completely. After oral intake both hydrocortisone and prednisolone are rapidly absorbed from intestine. The oral bioavailability of hydrocortisone is >90% and the time for maximum blood levels (T_{max}) is 1-2 hours.^[7] The elimination half-life is also short – 1.8-2 hours. Hydrocortisone is extensively protein bound (90-95%) and this makes its pharmacokinetics nonlinear. This leads to increased clearance rate with increasing dosage. The half-life of prednisolone, t_{1/2}, has been reported to be 3-4 hours. In children the t_{1/2} may be much shorter, 2.2 hours. Prednisolone also has pharmacokinetics similar to that of hydrocortisone due to high protein binding (70-90%) which gets saturated at higher doses.^[7]

After the morning dose of hydrocortisone, the maximum suppression of 17- hydroxyprogesterone and androstenedione occurs at 3-4 hours. Then the levels gradually increase and reach more than 50% of baseline after 6-7 hours after morning dose. After an evening dose, when the hypothalamic-pituitary-adrenal axis activity is

relatively low, the serum 17- hydroxyprogesterone and androstenedione remain suppressed till 6-8 hours after which there is a rapid rise in these variables. The variations in serum testosterone levels are less prominent. After an evening dose of prednisolone, 15-70% of subjects escaped from the 17-hydroxyprogesterone suppression in the morning in various studies.^[8,9] These studies are limited by small sample sizes.

The degree of 21-hydroxylase enzyme deficiency, age of the patient, pubertal status, coexisting illnesses and previous control of the disease will all influence the amount of glucocorticoid needed for control of the disease.^[1,2] Most of the studies in the pharmacotherapy of CAH are done in heterogeneous group of CAH, with different degree of enzyme deficiency and different age group. This makes interpretation of these clinical data difficult. The aim of the present study was to compare three different glucocorticoid regimens which differed in the timing and nature of evening steroid.

MATERIALS AND METHODS

This study was conducted in a sub group of prepubertal children with classical CAH, 21-hydroxylase deficiency treated in the department of Endocrinology, Amrita Institute of Medical Sciences, Kochi, India. Only prepubertal children with chronological age more than 1 year with classical CAH were included in the study. The diagnosis of classical CAH was made on the basis of documented salt wasting, electrolyte abnormalities and/or features of androgen excess in early infancy associated with elevated 17-hydroxy progesterone. Exclusion criteria included patients presenting with non classical CAH, recent poor clinical control of the disease (defined as either new onset hyper pigmentation, new onset pubic hair and/or recent acceleration in growth velocity above that is expected for the age), clinically apparent cushingoid features, treatment with glucocorticoids for illnesses other than for CAH, use of medications that interfere with the pharmacokinetic or pharmacodynamic profile of glucocorticoids, untreated hypothyroidism, known malabsorption syndromes and hypertension.

The primary objective of this study was to compare the efficacy of the same total dose of hydrocortisone on 17-hydroxyprogesterone and testosterone levels, when administered at two different times in the evening. The second objective was to compare the efficacy of two hydrocortisone regimens with a similar regimen characterized by the substitution of the evening dose of hydrocortisone with a pharmacologically equipotent dose of prednisolone on 17-hydroxyprogesterone and testosterone levels.

On careful scrutiny of existing literature no study could be located on the comparison of different evening hydrocortisone and prednisolone dose regimens in prepubertal patients with classical CAH due to 21-hydroxylase deficiency. Hence this was designed as a pilot study. The study was approved by the Institutional Ethics Committee and informed consent was taken from the parents or guardians of the patients included in the study.

There were 20 subjects who met the study inclusion criteria. Fifteen subjects consented for the study. We excluded two patients from the study analysis due to poor compliance with medications. The total dose of hydrocortisone equivalent for the individual patient was same in all treatment periods (10-15 mg/m²). All the patients had prepubertal Tanner staging during the study period. The study design was a prospective cross-over pilot design in which all the patients were given three drug regimens, each of 2-months duration. All the patients were administered the usual dose of hydrocortisone they were on before inclusion into the study. Two-fifths of the total dose of hydrocortisone was administered in the morning at or before 07.00 am as soon as the child woke up and one-fifth of the total dose was administered at 02.00 pm in all the three regimens. The regimens differed in the timing of evening dose of glucocorticoids, 06.00-07.00 pm in regimen 1 and 09.00-10.00 pm in regimen 2 as hydrocortisone while the third regimen had an equivalent dose of prednisolone suspension administered at 09.00-10.00 pm. Hydrocortisone regimen at 10.00 pm was initiated first followed by the 07.00 pm hydrocortisone regimen and then the 10.00 pm prednisolone regimen. The hydrocortisone tablets used were of 5-mg strength (tablet Hisone 5 mg, Samarth life sciences Pvt Ltd) and prednisolone was available as a suspension (syrup Predone, 5 mg/5 ml, Cipla Ltd). The bioequivalent dose of prednisolone to hydrocortisone was taken as 1:4. All the patients were on a dose of fludrocortisone which maintained serum potassium below 5 meq/l and serum sodium above 135 meq/l. This varied from 50 to 150 mcg in various subjects. The fludrocortisone tablets used were of 100 mcg strength – tablet Flurinef. Biochemical control of disease was defined as serum testosterone level less than 0.2 ng/ml which is the widely accepted cut off for prepubertal testosterone level.

The nature of the disease ruled out the possibility of a wash-out period. Clinical parameters monitored included cushingoid features, blood pressure, height and weight charting. Laboratory parameters included serum sodium, potassium, 17-hydroxyprogesterone and testosterone levels. Patients were assessed clinically and biochemically at end of each 2-month period. Sample collection for biochemical

estimation was done between 07:30 and 08:30 am just prior to the morning dose of hydrocortisone, which was slightly delayed on the day of the sampling. Serum 17-hydroxy progesterone levels were measured by ELISA. (Demetic diagnostics GmbH, Germany). The sensitivity was 0.034 ng/ml and the inter and intra-CV were less than 7%. Serum Testosterone was assayed with a one-step immunoassay using Chemiluminescent micro-particle Immunoassay (CMIA) technology. The sensitivity was 0.14 ng/ml. Compliance with medications was ensured by periodic phone calls to the caregiver and empty tablet foil count. If the patient developed any intercurrent illness on treatment they were advised to increase the steroid dose during illness as they were doing before. The blood samples of these patients were taken only after at least 2 weeks of symptom-free period.

Statistical analysis

The difference in the values of the hormonal parameters between the three drug regimens was compared using the Wilcoxon signed rank tests, taking two treatment periods at a time. The difference in the control of disease as assessed by suppression of 17-hydroxyprogesterone and testosterone levels among the three drug regimens was assessed by Mc Nemar's chi square tests, taking two treatment periods at a time.

RESULTS

Thirteen patients, 10 girls and 3 boys, with classical CAH were studied. Accelerated skeletal maturity was seen only in one boy, while all others were within 2 standard deviation of bone age for their age. All patients were on thrice daily hydrocortisone and once daily fludrocortisone before inclusion into study. Baseline characters are shown in Table 1. Since the sample size was small and the values of most of the variables were varying widely, median and range are given instead of mean and standard deviation.

The serum testosterone was suppressed to prepubertal levels (<0.2 ng/ml) in 69.2% of patients in 07.00 pm hydrocortisone, 10.00 pm hydrocortisone and 10.00 pm prednisolone treatment regimens. The serum

Table 1: Baseline characters

Parameters	Median	Range
Age (years)	6.5	1.9-12
Age at diagnosis (days)	2	1-40
Predicted adult height (cm)	152	144-172
Target height (cm)	155	147.5-167
BMI (kg/m ²)	14	12.6-20.5
Hydrocortisone (mg/m ² /day)	12.6	10-15
Mineralocorticoid (µg/d)	100	50-150

BMI: Body mass index

17-hydroxyprogesterone was suppressed to <10 ng/ml in 76.9%, 78.9% and 84.6% of patients in 07.00 pm hydrocortisone, 10.00 pm hydrocortisone and 10.00 pm prednisolone treatment periods, respectively. The difference was not statistically significant in different periods for control of 17-hydroxyprogesterone and testosterone. The median testosterone was 0.13 ng/ml, 0.16 ng/ml and 0.13 ng/ml in the 07.00 pm hydrocortisone, 10.00 pm hydrocortisone and 10.00 pm prednisolone group, respectively. The median 17-hydroxyprogesterone was 3.9 ng/ml, 6.0 ng/ml and 3.3 ng/ml in the 07.00 pm hydrocortisone, 10.00 pm hydrocortisone and 10.00 pm prednisolone group, respectively. The difference in median was not statistically significant for serum 17-hydroxyprogesterone and testosterone levels [Tables 2 and 3].

Suppression of 17-hydroxyprogesterone to values less than 1 ng/ml which is undesirable was observed in three (23%) patients. Only one patient in the 06.00-pm group has a suppressed 17-hydroxyprogesterone. Serum 17-hydroxyprogesterone and testosterone values at the end of 3 different treatment regimens of the thirteen patients studied are shown in Table 4.

DISCUSSION

This study which compared the effects of three different glucocorticoid dose regimens which differed with respect to the timing and nature of evening dose of glucocorticoid in the treatment of classical CAH showed no significant advantage of one regimen over the other at least in the short term control of disease. Thrice daily oral hydrocortisone is the preferred treatment for CAH world over.^[1,2] In the absence of clear supporting evidence or guidelines most institutions follow their own treatment regimens. The chief inadequacy of currently available regimens is their inability to normalize early morning

increase in 17-hydroxyprogesterone levels^[10,11] in all patients. However, 17-hydroxyprogesterone by itself is not active; it needs to be converted to testosterone for its clinical effects to manifest. Monitoring of androstenedione level is recommended by many experts. However, our resource limited environment does not allow routine monitoring of androstenedione. There are regimens in which late bed time dose of hydrocortisone is advocated over more conventional evening dose of hydrocortisone with the hope the bedtime dose will have greater suppressive effects on early morning serum 17-hydroxyprogesterone and testosterone levels.^[12] However, currently there is no clear evidence to support this practice. This is the first question which we sought to answer by subjecting the same patient to both the regimens, i.e. evening dose of hydrocortisone at 07.00 pm and 10.00 pm in succession. The nature of the disease obviates the need for any washout period. This study, notwithstanding its limitations, gave a clear indication that the regimens are no different with regards to the hormonal parameters.

Prednisolone is not preferred in children because of the side effect profile including growth suppression.^[1,2] However, it is an intermediate acting steroid and theoretically has the potential of suppressing the 17-hydroxyprogesterone surge in early morning hours.^[13] Whether an equipotent replacement dose of prednisolone at bedtime is better than equivalent dose of hydrocortisone in the treatment of CAH is the second part of the study which we sought to answer. Again it was proved that evening replacement dose of prednisolone is no better than hydrocortisone. It has to be noted that the 17-hydroxyprogesterone levels were lower in the prednisolone group although it did not achieve statistical significance. Undesirable over suppression of 17

Table 2: Median 17-hydroxy progesterone and testosterone levels in different regimens

Treatment regimen (n=13)	Median 17 OHP (range)	Median testosterone (range)
7pm hydrocortisone	3.9 (0.99-27.9)	0.13 (0.08-0.65)
10pm hydrocortisone	6.0 (1.98-28)	0.16 (0.08-0.31)
10pm prednisolone	3.3 (0.12-18.8)	0.13 (0.08-0.34)

Table 3: Comparison of median 17-hydroxy progesterone and testosterone levels between different regimens

Treatment regimen (n=13)	17 OHP (P value)	Testosterone (P value)
Hydrocortisone 10 pm Vs 7pm	0.807	0.575
Hydrocortisone 10 pm Vs prednisolone	0.311	0.657
Hydrocortisone 7 pm Vs prednisolone	0.463	0.398

Table 4: Course of the 13 patients on different regimens- Biochemical control of 17-hydroxy progesterone and testosterone levels in the different regimens

Patient	Serum 17-hydroxyprogesterone (ng/ml)			Serum testosterone (ng/ml)		
	10pm HC		Prednisolone	10pm HC		Prednisolone
	10pm HC	6pm HC		10pm HC	6pm HC	
1	1.98	2.3	0.48	0.08	0.16	0.33
2	28	27.9	3.75	0.22	0.26	0.08
3	6	3.9	1.48	0.08	0.08	0.08
4	7	0.99	0.9	0.08	0.08	0.08
5	17.6	21.3	16.9	0.18	0.12	0.08
6	2.03	2.14	0.12	0.25	0.3	0.13
7	6.33	9.04	1.29	0.24	0.13	0.08
8	9	1.1	7.6	0.31	0.08	0.22
9	2.7	7.1	10	0.16	0.1	0.13
10	2.36	4.44	2.6	0.08	0.08	0.16
11	4.23	3.4	5.16	0.08	0.32	0.34
12	10.5	15.35	18.8	0.18	0.65	0.25
13	2.51	1.43	3.3	0.1	0.19	0.08

hydroxyprogesterone in 23% patients in the prednisolone group is probably indicative of the deleterious effects of prednisolone on long-term use. It is possible that larger sample size would have demonstrated a significant suppression of 17-hydroxyprogesterone levels with prednisolone treatment. Moreover most of the patients in this study belonged to the “clinically controlled” group even prior to entry into study. It would be interesting to look at prior uncontrolled patients separately to see if one time short-term prednisolone is useful for achieving better disease control without overt growth suppression.

It has been shown previously that the evening dose of hydrocortisone administered could not adequately suppress the early morning rise in adrenal androgens in many patients with CAH.^[3,4] In another study no significant difference was found between high morning and evening hydrocortisone in children with CAH.^[12] These pharmacodynamic studies included patients with varying severity of disease and wide age range.

There are limited studies on the management of children with CAH with prednisolone. Single dose of prednisolone was effective in control of disease in CAH comparable to hydrocortisone.^[9,14,15] Small sample size, wide age group and differing severity of CAH are important factors that limit meaningful interpretation of these studies.

The chief strength of this study lies in inclusion of only patient with classical CAH in the post-infancy prepubertal age group where large fluctuations and need for higher than usual doses of steroids are relatively uncommon. Most of the previous studies looked at levels of metabolites in different subjects with or without treatment with different regimens. This study used a cross-over design which probably is the only way the different regimens can be compared with any degree of confidence.

This study has several limitations. We relied on single morning sample of serum testosterone and 17-hydroxyprogesterone as a marker of control of disease. A single spot sample of serum testosterone and 17-hydroxyprogesterone do not reliably reflect the 24-hour control of the disease. The pharmacokinetics of different steroid formulations was not studied by serial blood estimation in our study. Another area of controversy is the bioequivalence dose of prednisolone. We used the 1:4 conversion of prednisolone to hydrocortisone dosing. Several studies showed different bioequivalent doses of hydrocortisone with respect to the androgen suppression properties.^[9,13-15]

Despite all these limitations, this study has addressed one key issue i.e. timing of replacement/suppressive steroids

in the management of CAH. We were able to dispel some assumptions regarding the timing of the evening dosage of steroids. This study could not demonstrate any significant difference in hormonal suppression with different evening timings of hydrocortisone. Lack of superiority of prednisolone in children with CAH, at least in those who are controlled with standard therapy with thrice daily hydrocortisone could also be demonstrated. However, we acknowledge that the study included only patients who were largely controlled prior to enrollment into the study.

CONCLUSIONS

This study showed that late administration of hydrocortisone does not offer significant advantage in achieving biochemical control of disease. Replacing hydrocortisone with prednisolone in the evening resulted in similar hormonal control of the disease. Studies with larger sample size and longer duration are needed to arrive at valid conclusions to settle the management issues in CAH. Until then we recommend the use of thrice daily oral hydrocortisone with flexible evening dose timings for the management of CAH.

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