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Original

Poor Response to Substitution Therapy with Cortisone Acetate in Patients with Congenital Adrenal Hyperplasia

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Abstract. Although cortisone acetate is approved worldwide as corticosteroid substitution therapy in congenital adrenal hyperplasia (21-hydroxylase deficiency), its effectiveness is uncertain since its biologic activity depends on activation by 11β-hydroxysteroid dehydrogenase (11β-HSD). We sought to compare the effect of cortisone acetate with that of hydrocortisone. In 10 patients with congenital adrenal hyperplasia, cortisone acetate was replaced with hydrocortisone in substitution therapy. During this change, blood concentrations of 17-hydroxy-progesterone, adrenocorticotropin (ACTH), and requirements for each drug were monitored. Concentrations of 17-hydroxyprogesterone decreased (mean 10.1 vs. 48.6 ng/ml), as did those of ACTH. Cortisone acetate dose requirements averaged 33.9 mg/m^2, while hydrocortisone dose requirements averaged only 20.3 mg/m^2. In one of the patients resistant to cortisone acetate therapy, DNA sequences in the coding regions and promoter of the 11β-HSD gene were analyzed, detecting no genetic abnormalities. Cortisone acetate is inferior to hydrocortisone as substitution therapy in patients with congenital adrenal hyperplasia.

Key words: cortisone acetate (CA), hydrocortisone (HC), congenital adrenal hyperplasia (CAH), 21-hydroxylase deficiency, 11β-hydroxysteroid dehydrogenase (HSD) type 1

Introduction

Congenital adrenal hyperplasia (CAH) is caused by deficiency of 21-hydroxylase in the adrenal glands. Cortisone acetate (CA) is used worldwide as an equivalent to hydrocortisone (HC), as the glucocorticoid component of substitution therapy for CAH. Fludrocortisone is often needed as a mineralcorticoid component. HC is identical to cortisol, while CA is nearly equivalent to cortisone apart from the presence of an acetate group at the C21 position. Cortisol represents active glucocorticoid, while cortisone is an inactive form. The hepatic enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1 catalyzes the conversion of cortisone to cortisol by reducing the keto group at the C11 position to a hydroxyl group. Accordingly, orally administered CA must be converted to cortisol by 11β-HSD in order to be bioactive.

The overall bioactivity of CA given orally has been reported to be 80% of that of HC (1). However, the biologic activity of CA has been reported to be unreliable. Furthermore, a patient with 21-hydroxylase deficiency has been reported as a poor

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responder to CA treatment (2). We converted 10 of our CAH patients from CA to HC substitution therapy, compared clinical and laboratory findings before and after the change.

Patients and Methods

Ten patients with CAH caused by 21-hydroxylase deficiency were studied (6 male, 4 female; ages, 4 to 35 yr). All patients had been treated with CA. Of the 10 patients, 8 were salt losers, who required fludrocortisone in addition to glucocorticoids. For all subjects, HC was administered instead of CA, initially at 80% of the previous CA dose. The dose of HC then was increased or decreased according to circulating concentrations of 17-hydroxyprogesterone (OHP) and/or adrenocorticotropin (ACTH). Target concentrations were below 10 ng/ml for 17-OHP and below 50 pg/ml for ACTH. Doses of fludrocortisone were not changed. To compare required doses of CA and HC, the CA requirement was calculated as the average of the several months preceding the change of drug, while the HC requirement was the dose found to provide stable control of CAH after several months. These doses were calculated as milligrams per square meter of body-surface area.

Before and after the drug change, we measured concentrations of 17-OHP and ACTH, as well as patients' height and weight. The mean observation period after the drug change was 10 mo (6 to 14 mo). A radioimmunoassay was used to measure 17-OHP, while ACTH was measured by immunoradiometric assay.

Genomic DNA of a patient who responded poorly to treatment with CA was obtained from peripheral leukocytes. All exons, exon-intron boundary regions and 2.4 kb of the promoter region of 11β-HSD were amplified by PCR. Then the DNA sequence was determined using an ABI PRISM 310 genetic analyzer. For bone age determination, the Tanner-Whitehouse 2 RUS method according to the Japanese standard was used.

Results

The mean 17-OHP concentration during treatment of our patients with CA was 48.6 ng/ml. This decreased to 10.1 ng/ml when the treatment was changed to HC (Table 1, Fig. 1). The mean concentration of ACTH was 198.0 pg/ml during treatment with CA, decreasing to 35.1 pg/ml during treatment with HC. We compared the dose of CA preceding the change of drug with that of HC after dose adjustment, when disease control was stable. The average drug requirement for CA was 33.9 mg/m^2, while it was 20.3 mg/m^2 for HC. The relationship can be expressed as an equation, HC = 0.58 × CA, and the coefficient is substantially lower than the conventionally reported dose ratio of 0.8 (1). In addition, older patients required more CA per square meter of body-surface than younger patients. The relationship between the CA dose shortly before the change of drug and the final HC dose is shown in Fig. 2. No significant change in the obesity index occurred in any subject in association with the change of drug. Among subjects who already had attained their adult height, all male patients (cases 5, 8, and 9) showed short stature attributable to precocious puberty. In case 5, the patient had been treated with HC at another hospital. Two patients, cases 8 and 9, had been treated with CA. Four patients (cases 1 to 4) who had been diagnosed by neonatal screening were at a prepubertal age. In cases 1 to 3, no change of height SD score was recognized before or after the drug change. Case 4 showed some auxological change related to medication, described below.

Case 4: A 10-yr-old boy was found to have an increased concentration of 17-OHP at 6 yr of age, and was treated with CA. The CA dose was increased from 20 mg/m^2 at 6 yr to 35 mg/m^2 at 8.2 yr. During this period, height velocity increased, as did height SD score (−0.1 to 0.8). The bone age (BA) / chronological age (CA) ratio also increased (0.9 to 1.2). After conversion to HC at 9.4 yr of age, control of disease improved as evidenced by a

Table 1 Demographic, pharmacologic, and endocrinologic data for individual subjects

Case no	Gender	Age	CA dose (mg/m^2)	HC dose (mg/m^2)	HC/CA ratio	17-OHP during treatment with CA	17-OHP during treatment with HC	ACTH during treatment with CA	ACTH during treatment with HC	height SD score during treatment with CA	height SD score during treatment with HC
1	M	4	17.0	10.8	0.64	0.1	0.4	8.1	31.3	−1.4	−1.3
2	F	6	17.8	13.0	0.73	15.0	14.8	73	43	−1.4	−1.4
3	M	7	15.3	11.0	0.72	2.6	0.1	565.3	48	0.5	0.5
4	M	10	36.1	20.9	0.58	36.2	0.5	192	34.6	0.9	0.6
5	M	13	35.5	21.4	0.60	204.0	10.4	706.9	10.9	−4.6 (final height)	
6	F	23	39.8	31.9	0.80	34.1	9.2	80.5	25.8	−1.3 (final height)	
7	F	24	39.3	27.5	0.70	11.1	1.2	15	8.5	−2.1 (final height)	
8	M	24	38.3	20.6	0.54	1.7	3.2	16.2	46.1	−4.3 (final height)	
9	M	32	47.7	25.2	0.53	179.4	59.2	314.6	94.4	−2.9 (final height)	
10	F	34	52.5	21.1	0.40	1.3	2.1	8.1	8.1	−1.0 (final height)	
Mean		17.7	33.9	20.3	0.62	48.6	10.1	198.0	35.1		

CA, cortisone acetate; HC, hydrocortisone; OHP, hydroxyprogesterone; ACTH, adrenocorticotropin; SD, standard deviation.

decrease in 17-OHP. At 10.1 yr of age, the height SD score had decreased to 0.6, and the BA/CA ratio had decreased to 1.1. The HC requirement was 20.9 mg/m^2.

In case 5, we performed DNA sequence analysis for 11β-HSD type 1 because treatment with CA had no effect at all. The details are described below.

Case 5: A 13 -yr-old boy was referred from another hospital where he had been treated with 28 mg/m^2 of HC. In our outpatient clinic, treatment was changed to 36 mg/m^2 of CA. Soon afterwards 17-OHP increased abruptly to 260 ng/ml from 5.3 ng/ml. The plasma level of ACTH increased to 1038 pg/ml from 8.3 pg/ml. Since this patient appeared to be a poor responder to CA, 28 mg/m^2 of HC was substituted for CA. Subsequently, both 17-OHP and ACTH decreased. The final HC dose requirement proved to be 21 mg/m^2. Inability to respond to CA initially was thought to result from impaired low conversion of cortisone to cortisol, because of low activity of 11β-HSD type 1. However, DNA sequence determination in the gene encoding this enzyme detected no changes from the reported normal sequence in any of the six exons, exon-intron boundary regions, or the promoter region (2.4 kb) (3).

Discussion

In 10 patients with 21-hydroxylase deficiency, we changed the glucocorticoid for the substitution therapy from CA to HC. Indices of control of CAH such as 17-OHP, and ACTH decreased, indicating improvement. On average, the final requirement for HC based on these indicators, was only 0.58 times the previous dose of CA, which was smaller than previously reported (1). Whorwood and Warne (4) determined urinary tetrahydrocortisone (THE) / tetrahydrocortisol (THF) ratios for 14 CAH patients treated with CA, and found that better control of the disease was associated with lower THE/THF ratios.

The pharmacologic effect of CA depends on conversion of cortisone to cortisol by 11β-HSD. However, when we performed gene sequencing in one of our poor CA responders, we found no

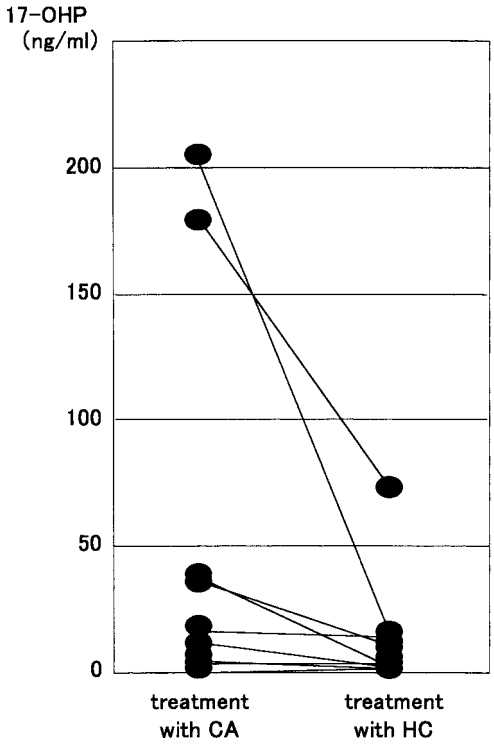

Fig. 1 Serum concentrations of 17-hydroxyprogesterone (OHP) during treatment were significantly lowered by changing from cortisone acetate (CA) to hydrocortisone (HC). Each data point represents the mean concentration of 17-OHP of an individual during treatment with CA or HC.

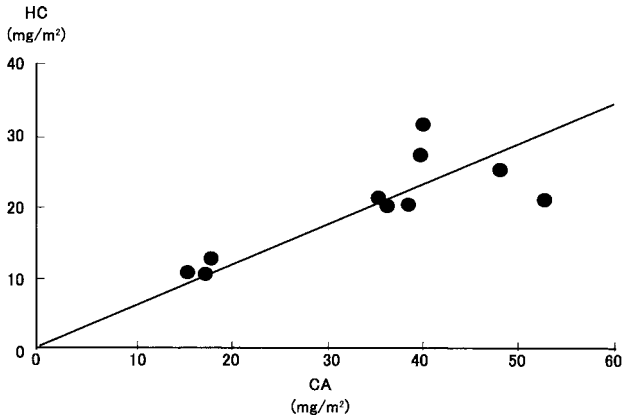

Fig. 2 Relationship between the dose requirements of cortisone acetate (CA) and hydrocortisone (HC). The solid regression line can be expressed as: HC = 0.58 × CA.

mutation in the 11β-HSD gene including the promoter region. Nordenstrom *et al.* (2) similarly reported failure to detect a mutation in the 11β-HSD gene. Up to the present, no 11β-HSD gene mutation has been detected in poor responders. Even single-nucleotide polymorphism has not been common, apart from the recently reported intronic gene polymorphism (5). As described for case 4, an individual patient's response to CA can vary with age or other factors. In addition, blood concentrations of cortisone have been reported to be higher than those of cortisol in the neonatal period and early infancy (6). Accordingly steroid metabolism in young children may differ from that in school-age or older children. In our study, poor CA responders often were adolescents or older patients. A poor response to CA, therefore, may involve variability of 11β-HSD activity rather than genetic changes. Changes in 11β-HSD activity have been linked to certain pathophysiologic variables. Jamieson *et al.* (7) reported a 36-yr-old woman who had clinical features of hypercortisolemia associated with a normal plasma cortisol concentration and an elevated urinary THE/THF ratio, possibly caused by a defect in hepatic 11β-HSD. In another case of 6 yr old boy with precocious pubarche had an elevated urinary THE/THF ratio (decreased THF/THE ratio) attributed to low activity of 11β-HSD (8).

This enzyme has attracted considerable attention in studies concerning obesity and other endocrinological disorders. An agonist at the peroxisome proliferator-activated receptor is suspected to regulate 11β-HSD, decreasing its activity (9). Among patients with CAH, good responders to CA possibly show high 11β-HSD activity. On theoretical grounds, therefore, good responders to CA might tend to be overweight. However, we found no relationship between

response to CA and obesity.

Among our subjects who attained adult height, male patients were shorter than previously reported adult patients with CAH (10). Two had been treated with CA. Another had been treated with HC. Our findings provided no definitive indication of whether or not HC is superior to CA in achieving a desirable height. However, in one growing child (case 4), changing the drug from CA to HC decreased the BA/CA ratio. Final height in patients treated with HC might prove to be greater than that in patients treated with CA.

As a therapeutic agent, CA shows considerably greater inter- and intra-individual variations in efficacy than HC. In addition, we found greater difference in pharmacological activity between CA and HC than has been previously reported. We have found management of CAH to be difficult and sometimes unsatisfactory. CA would seem inadequate for substitution therapy not only in patients with CAH, but also those with other forms of adrenal insufficiency such as adrenal hypoplasia or hypofunction caused by pituitary disorders. Treatment with HC is recommended for these patients as well. However, since HC has been reported to be too bioavailable to maintain cortisol concentrations within physiologic limits (11), careful evaluation of physiologic aspects of HC-based substitution regimens may be needed.

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