Dexamethasone Treatment of Virilizing Congenital Adrenal Hyperplasia: The Ability to Achieve Normal Growth

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ABSTRACT. *Objective.* **To assess whether treatment of virilizing congenital adrenal hyperplasia (CAH) with long-acting glucocorticoids is associated with favorable growth outcomes.**

Method. **We examined the long-term growth of 17 boys and 9 girls with CAH treated with dexamethasone (.27 ± .01 mg/m²/day).**

Results. **For individuals with comparable bone age (BA) and chronological age (CA) at the onset of dexamethasone therapy, males were 2.8 ± .8 years (mean ± standard error of the mean; $n = 13$) and females were 2.4 ± 1.0 years ($n = 6$). Males were treated for 7.3 ± 1.1 years (ΔCA) over which time the change in BA (ΔBA) was 7.0 ± 1.3 years, and the change in height age (ΔHA) was 6.9 ± 1.1 years. Females were treated for 6.8 ± 1.3 years, over which time the ΔBA was 6.5 ± 1.0 years, and the ΔHA was 6.3 ± .8 years. During treatment 17 ketosteroid excretion rates were normal for age and 17-hydroxyprogesterone values were 69.6 ± 18 ng/dL. Testicular enlargement was first detected at 10.7 ± .8 years and breast tissue at 9.9 ± 1.2 years. Three boys and 1 girl had final heights of 171.8 ± 6 cm and 161 cm, respectively, compared with midparental heights of 176.1 ± 4.1 cm and 160 cm. Predicted adult heights for 6 other boys and 5 girls were 176.8 ± 2.0 cm and 161.4 ± 2.8 cm, respectively, compared with midparental heights of 174.6 ± 1.4 cm and 158.2 ± 2.0 cm. Statural outcomes were less favorable for 7 children started on dexamethasone when BAs were considerably advanced, although height predictions increased during therapy.**

Conclusions. **These observations show that children treated with dexamethasone for CAH can achieve normal growth with the convenience of once-a-day dosing in most cases.** *Pediatrics* **2000;106:767–773;** ***congenital adrenal hyperplasia, dexamethasone, growth.***

ABBREVIATIONS. CAH, congenital adrenal hyperplasia; SD, standard deviation; ACTH, adrenocorticotropin hormone; SDS, standard deviation score; HA, height age; BA, bone age; CA, chronological age.

Virilizing congenital adrenal hyperplasia (CAH) is caused by impaired adrenal steroidogenesis resulting in inadequate cortisol synthesis and the accumulation of adrenal androgens.[1–4] In infants and children, excessive adrenal androgen production induces virilization and accelerated skeletal maturation that compromises adult stature.[1–4] Untreated, children with CAH become extraordinarily short adults with mature heights as much as 6 standard deviations (SDs) below average.[2] Fortunately, with glucocorticoid therapy, adrenal androgen secretion can be reduced, excessive skeletal maturation attenuated, and final heights improved.[2–4] However, complicating the therapy of CAH, glucocorticoids inhibit growth in a dose-dependent manner.[2–4]

Since introduced as a therapy for CAH nearly 5 decades ago,[5,6] cortisone and its metabolite cortisol (hydrocortisone) have been the most widely used glucocorticoids in the treatment of CAH. However, because of their rapid elimination from the circulation, therapy with cortisone and hydrocortisone requires administration 3 or more times a day and is associated with breakthrough adrenal androgen secretion.[7–9] Reports of the long-term growth of children with CAH treated with cortisone or hydrocortisone show that adult stature is generally 1.5 SD (9 cm) below average adult and midparental heights, which may reflect the adverse effects of glucocorticoids on growth or inadequate adrenal androgen suppression.[10–13]

Because of its long half-life, it had been suggested that dexamethasone provides more continuous suppression of adrenal androgen secretion in CAH than can be achieved with cortisone or hydrocortisone. Thus, based on the observations showing that dexamethasone could effectively control adrenal androgen secretion in adolescents with CAH, we began routinely treating our patients with dexamethasone nearly 20 years ago. We now report our experience and show that boys and girls with CAH treated with dexamethasone for many years have normal patterns of linear growth.

METHODS

The records of patients treated by the authors with dexamethasone for CAH provided data for analysis. We included patients if they had biochemical evidence of 21-hydroxylase or 11-hydroxylase deficiency, had no other major illnesses, and were treated with dexamethasone for 3 years or longer. These individuals represented the patients that were consecutively treated for CAH by the authors. Thus, there was no selection bias in treating individuals with dexamethasone.

Diagnoses of enzymatic defects were initially established by assessment of adrenal steroid profiles before glucocorticoid therapy or by assessment of adrenal steroid profiles after intravenous administration of adrenocorticotropin hormone (ACTH). To reexamine the diagnoses that were initially established, dexametha-

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sone doses were recently withheld for 24 hours, and ACTH, 17-hydroxyprogesterone, 11-desoxycortisol (compound "S"), and cortisol levels were obtained. Steroid determinations were performed at Endocrine Sciences (Calabasa Hills, CA).

Elevations in 17-hydroxyprogesterone and no elevations in compound "S" levels were indicative of 21-hydroxylase deficiency. Elevations in compound "S" levels were indicative of 11-hydroxylase deficiency.

Growth was analyzed by examining longitudinal changes in statural growth and skeletal maturation, and by comparing mature or predicted adult heights with midparental heights (the genetic growth potential). Growth data were plotted on North American growth charts from the National Center for Health Statistics.[14] Height standard deviation scores (SDS; the number of SDs from the mean height for age) were determined with the use of standards of the National Center for Health Statistics, with the distance from the 50th to the 15th percentile corresponding to 1.0 SD.[14] Height age (HA) was the age at which the patient's height would be at the 50th percentile. Heights at maturity were predicted from HA and bone ages (BAs) with the use of the Bayley-Pinneau tables.[15] BAs were determined with the use of the Gruelich-Pyle atlas.[16] Patients were considered at their mature heights when there were no changes in height for 2 years or when radiographs showed epiphyseal fusion. Midparental heights corrected for sex were determined using standard equations.[17]

Patients were treated with an elixir of dexamethasone to ensure accuracy of dosing (Decadron [Merck and Co, Rahnay, NJ] or generic; .1 mg/mL). Oral doses were administered in the morning by syringe. When treatment was started, a dose of .25 to .28 $mg/m^2/day$ of dexamethasone was generally used. Patients were treated with doses of dexamethasone to maintain normal rates of growth and adrenal androgen secretion.

Patients were seen every 3 or 4 months, and BAs were obtained every 6 to 12 months. Mean dosages ($mg/m^2/day$) over the duration of therapy were determined from dosages, and heights and weights at each office visit. To assess biochemical control, serial 24-hour urine collections were used to assess 17-ketosteroid excretion in 24 patients. Serial serum 17-hydroxyprogesterone levels obtained in the afternoon were also followed in 5 patients. In some patients, 17-hydroxyprogesterone and ACTH levels were obtained in the morning before the dose of dexamethasone was given. Urinary 17-ketosteroid and creatinine concentrations, and serum 17-hydroxyprogesterone and ACTH concentrations were measured in hospital or reference laboratories. Samples were not extracted to remove other adrenal androgens before serum 17-hydroxyprogesterone concentrations were measured.

Patients were considered undertreated when 17-ketosteroid secretion rates increased above the normal ranges for age (1–8 years, .5–2.0 mg/day; 8–12 years, 2.5–8 mg/day; 12–16 years, 8–22 mg/day, and/or when afternoon serum 17-hydroxyprogesterone levels increased above 200 ng/mL [samples obtained between 1 PM and 5 PM]. Patients were considered overtreated when the growth rate slowed, the face became round, there was an increase in body hair, or the body weight increased more than expected for changes in height. In addition, if the morning 17-hydroxyprogesterone values were within or lower than the normal range for age (<200 ng/dL) and the ACTH concentration was <120 pg/mL, overtreatment was suspected.

When dose adjustments were made, changes ranged between 5% and 10% of the previous dexamethasone dose. If the weight increased or the face became round several weeks after dosage increases, the dosage was reduced.

Arithmetic means are expressed as means ± standard error of the mean in the text, tables, and figures.

RESULTS

Clinical Characteristics at Onset of Dexamethasone Therapy

Seventeen boys and 9 girls were treated long-term with dexamethasone. Thirteen boys and 8 girls were diagnosed with 21-hydroxylase deficiency; 4 boys and 1 girl were diagnosed with 11-hydroxylase deficiency. The children with 21-hydroxylase deficiency had basal 17-hydroxyprogesterone levels of 34 227 ± 18 951 ng/dL when initially diagnosed. All but 3 of the children with 21-hydroxylase deficiency manifested salt-wasting. No patients had late-onset of nonclassical 21-hydroxylase deficiency. The children with 11-hydroxylase deficiency had basal compound "S" levels of 10 400 ± 540 ng/dL when diagnosed.

Sixteen patients had been treated with hydrocortisone before dexamethasone therapy (hydrocortisone doses: 18.9 ± 1.54 $mg/m^2/day$, administered 3 times daily). All salt-loosers were also treated with recommended doses of fludrocortisone (.05–.2 mg/day). When patients were changed from hydrocortisone to dexamethasone, the dose of fludrocortisone was not changed. None of the patients with 11-hydroxylase deficiency were treated with fludrocortisone.

Based on the BAs at the onset of dexamethasone therapy, patients were arbitrarily divided into 2 groups; those children in whom the BA was within 2 years of the chronological age (CA) at therapy onset (BA = CA; 13 males and 6 females), and those children in whom the BA was 2 years greater than the CA at therapy onset (BA≫CA; 4 males and 3 females). This distinction was made because we observed that children with skeletal advancement at the onset of therapy for CAH had worse statural outcomes than did children without advanced skeletal maturation at therapy onset. The clinical characteristics of these patients are shown in Table 1. In all cases of children with advanced BAs, the diagnosis of CAH was made at a late age. In contrast, CAH was

TABLE 1. Clinical Characteristics at Onset of Dexamethasone Therapy and at End of Observation Period

	Males		Females	
	Onset	End	Onset	End
BA = CA*	$n = 13$		$n = 6$	
CA (y)	2.8 ± .8	10.4 ± 5.1	2.4 ± 1.0	9.3 ± 1.4
BA (y)	2.8 ± .9	10.7 ± 5.5	2.5 ± 1.4	9.0 ± 1.6
HA (y)	2.7 ± .7	10.2 ± 5.3	2.6 ± 1.1	8.9 ± 1.4
Height (cm)	92.3 ± 23.6	138.3 ± 69.7	91.7 ± 38.3	133.2 ± 20.2
BA≫CA†	$n = 4$		$n = 3$	
CA (y)	4.7 ± 1.0	11.2 ± 4.4	5.0 ± 1.9	13.7 ± 1.3
BA (y)	10.1 ± .2	14.7 ± 2.6	8.2 ± 1.8	15.0 ± .5
HA (y)	5.6 ± 1.5	11.0 ± 2.6	5.9 ± 1.3	11.9 ± .2
Height (cm)	112.3 ± 30.3	144.1 ± 34.6	114.6 ± 24.8	152.3 ± 2.7

* BA within 2 years of CA at onset of dexamethasone therapy.
† BA 2 years or more than CA at onset of dexamethasone therapy.

generally diagnosed in infancy in the group without BA advancement.

Growth During Dexamethasone Therapy

During treatment with dexamethasone, growth was observed for an average of 7.3 years for males (range: 3–12.1 years) and for 6.8 years for females (range: 3.7–11.4 years; Table 2). In the patients with comparable skeletal ages and CAs at the onset of therapy, the CAs, BAs, and HAs increased proportionately during dexamethasone treatment (Figs 1 and 2; Table 2).

In the patients with advanced BAs at the onset of dexamethasone therapy, skeletal maturation advanced at a slower rate than the CAs and the HAs (Figs 1 and 2; Table 2). For those individuals with advanced BAs at diagnosis, initial predicted adult heights were 149.2 ± 4.2 cm for 4 boys and 142.5 and 143.2 cm for 2 girls. The other female in this group had an initial BA of 5.8 years and was too young to be dealt with using the Bayley–Pinneau tables. At the end of the observation period, predicted adult heights were 156.0 ± 2.5 cm for boys ($P < .05$ vs initial values) and 145 and 150 cm for the 2 girls.

For individuals who underwent pubertal development during the observation period, the onset of puberty was also characterized by physical features. Measurements of gonadotropins and sex steroids and responses to gonadotropin-releasing hormone were not performed routinely. The onset of puberty in males was defined by an increase in testicular size to 4 mL or above. The presence of glandular breast tissue defined the onset of puberty in females. For individuals with comparable BAs and CAs at the onset of therapy, testicular enlargement was first detected at 10.7 ± .8 years, and breast tissue was first noted at 9.9 ± 1.2 years. These values are within the normal age range for the onset of puberty.[18,19]

One girl who was 2.0 years old at the initial diagnosis, with a BA of 5.8 years, had breast development at 4.8 years and was treated with leuprolide for precocious sexual development. One boy who was 2.5 years old at the initial diagnosis with a BA of 8 years was treated with leuprolide beginning at 10.6 years.

When we compared growth rates, rates of skeletal maturation, doses of dexamethasone, and final or predicted heights, differences between the children with 21-hydroxylase deficiency and 11-β-hydroxylase deficiency were not seen.

TABLE 2. Changes in CA, BA, and HA During Dexamethasone Treatment

	Boys		Girls	
	BA = CA* (n = 13)	BA≫CA† (n = 4)	BA = CA* (n = 6)	BA≫CA† (n = 3)
ΔCA (y)	7.3 ± 1.1	6.5 ± 3.8	6.8 ± 1.3	8.6 ± 1.5
ΔBA (y)	7.0 ± 1.3	4.3 ± 2.8	6.5 ± 1.0	6.5 ± 1.4
ΔHA (y)	6.9 ± 1.1	5.4 ± 2.8	6.3 ± .8	6.2 ± 1.5
ΔBA/ΔCA	.97 ± .08	.79 ± .14	.96 ± .11	.75 ± .07
ΔHA/ΔCA	.95 ± .11	.83 ± .21	.93 ± .11	1.49 ± .1
ΔBA/ΔHA	1.01 ± .08	.79 ± .25	1.01 ± .10	1.04 ± .3

ΔBA/ΔCA indicates the ratio of the change in BA to the change in CA; ΔHA/ΔCA, the ratio of the change in height age to the change in CA; ΔBA/ΔHA, the ratio of the change in BA to the change in height age.
* BA within 2 years of CA at therapy onset.
† BA 2 years or more than CA at therapy onset.

Mature and Predicted Stature After Therapy

Mature heights were available for 6 males (3 without advanced BAs at therapy onset) and 3 females (1 without advanced BAs at therapy onset). For growing individuals, adult height predictions were based on BAs and heights. Supporting the use of predicted adult height data to provide insights into long-term growth potential, final heights of the patients who completed growing were very similar to the patients' predicted adult heights at earlier ages (BA: 11 or greater; r = .94). Long-term growth data were examined relative to National Center for Health Statistics and parental heights.

Three boys without significant BA advancement at the onset of dexamethasone therapy, had final heights of 171.8 ± 6 cm (−.8 SDS; 20th percentile), compared with midparental heights of 176.1 ± 4.1 cm (−.16 SDS; 46th percentile; $P > .05$; Wilcoxon rank order test; Figs 3 and 4). For boys who were still growing (BA: 12.3 ± 1.0 years; n = 6), predicted adult heights were 176.8 ± 2.0 cm (−.03 SDS; 49th percentile), compared with midparental heights of 177.2 ± 1.4 cm (−.4 SDS; 33rd percentile; $P > .05$, Wilcoxon rank order test; Figs 3 and 4).

One girl without significant BA advancement at the onset of dexamethasone therapy had a final height of 161 cm (−.46 SDS; 26th percentile), compared with a midparental height of 160 cm (−.63 SDS; 25th percentile; Figs 3 and 4). For 5 girls who were still growing (BA: 10.9 ± 1.0 years), predicted adult heights were 161.4 ± 2.8 cm (−.4 SDS; 27th percentile), compared with midparental heights of 158.2 ± 2.0 cm (−.93 SDS; 18th percentile; $P < .05$ Wilcoxon rank order test; Figs 3 and 4).

In contrast to the children without advanced BAs when dexamethasone was started, individuals with advanced BAs at therapy onset had mature and predicted adult heights that were well below the 5th percentile and midparental heights (Figs 3 and 4).

Treatment Regimens and Androgen Secretion and Excretion

Initially, the children were treated with hydrocortisone at younger ages and changed to dexamethasone after 1 to 2 years of age. However, over the past 10 years, we began treating children with dexamethasone at the time of the initial diagnosis including infancy. All patients treated with dexamethasone remained on long-term dexamethasone therapy while cared for by us, and no patients were changed to hydrocortisone therapy.

During treatment with dexamethasone, 17-ketosteroid excretion rates were 1.92 ± .21 mg/24 hours from 0 to 4 years, 1.92 ± .21 mg/24 hours from 4 to 8 years, 3.42 ± .5 mg/24 hours from 8 to 12 years, and 6.7 ± .76 mg/24 hours from 12 to 16 years of age. When morning samples were obtained before the dose of dexamethasone, 17-hydroxyprogesterone levels ranged between 200 and 2000 ng/dL; ACTH

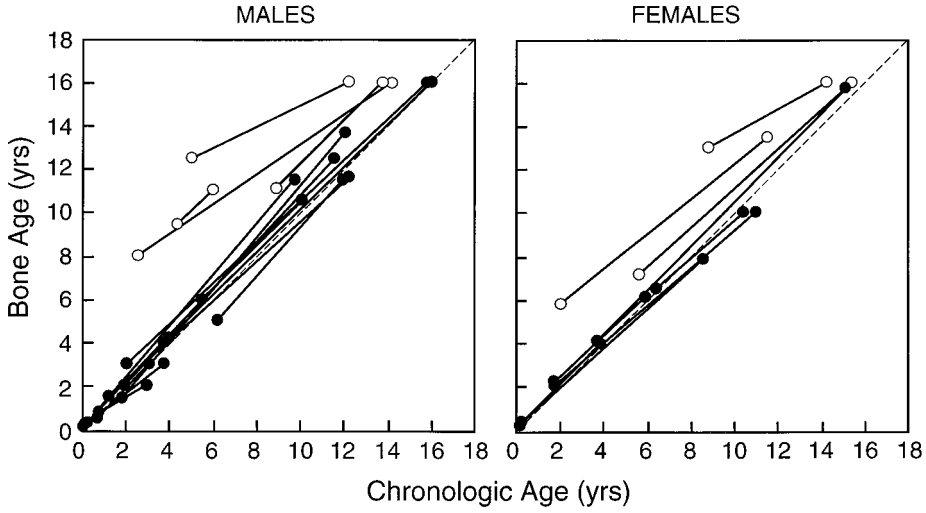

Fig 1. Changes in skeletal maturation during dexamethasone therapy. BAs are depicted at the onset of dexamethasone therapy and at the end of the observation period before epiphyseal fusion. The stippled diagonal line represents the line of identity between BA and CA. ● indicates BA within 2 years of CA at therapy onset; O, BA >2 years of CA at therapy onset.

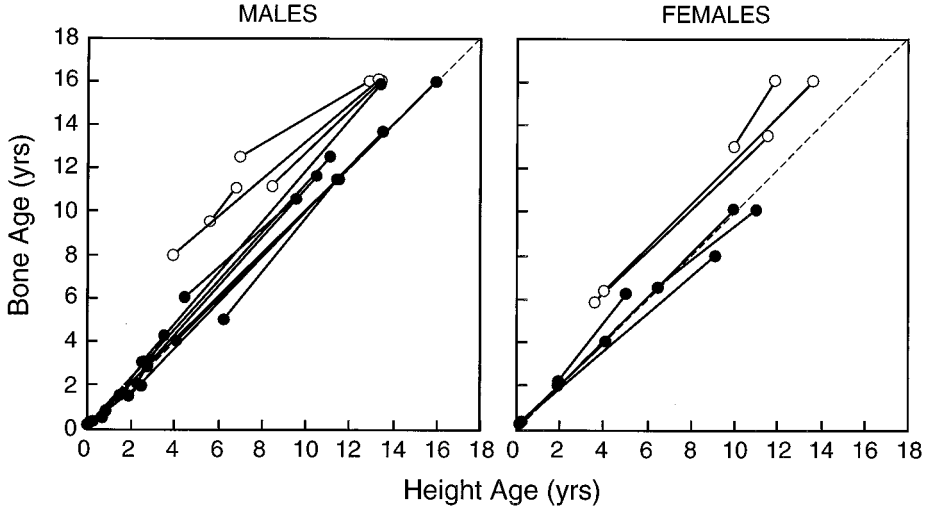

Fig 2. Changes in skeletal maturation relative to height during dexamethasone therapy. BAs and HAs are depicted at the onset of dexamethasone therapy and at the end of the observation period or just before epiphyseal fusion. The stippled diagonal line represents the line of identity between BAs and HAs. ● indicates BA within 2 years of CA at therapy onset; O, BA >2 years of CA at therapy onset.

levels ranged between 80 and 200 pg/mL. In 4 individuals with afternoon serial serum 17-hydroxyprogesterone determinations, mean values were 69.6 ± 18 ng/dL. One individual with documented poor compliance had afternoon serum 17-hydroxyprogesterone values of 742 ± 353 ng/dL (range: 187-2800).

No differences in dexamethasone doses were observed between males and females. Most patients were well-controlled on single-morning doses ranging between .24 and .33 mg/m^2/day (.27 ± .01 mg/m^2/day). Two patients required daily doses of .44 and .71 mg/m^2/day, divided among a morning (2/3) and an evening dose (1/3). The patient requiring the higher dose had documented poor compliance. In the other child requiring 2 doses a day, by measuring dexamethasone levels after an administered dose, we observed rapid metabolism.

Five patents required relatively lower doses of

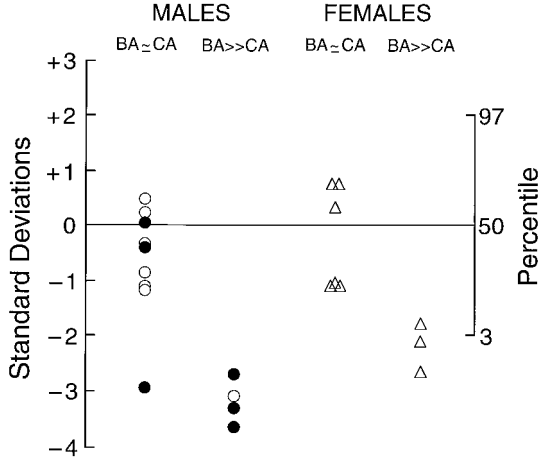

Fig 3. Mature heights (solid symbols) or predicted adult heights (open symbols) after treatment with dexamethasone. Heights are given as SDS or percentile. △ indicates females; ○, males.

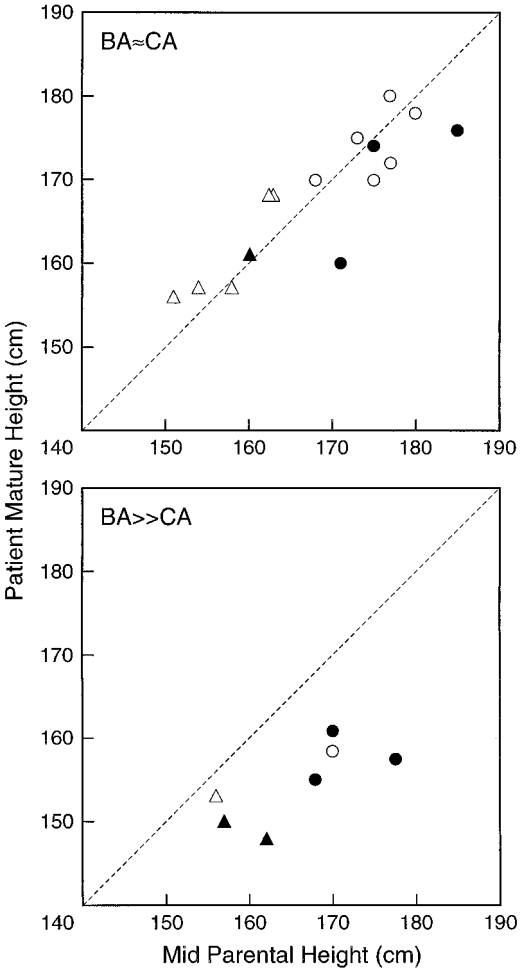

Fig 4. Mature heights (solid symbols) or predicted adult heights (open symbols) of children treated with dexamethasone, compared with midparental heights corrected for sex. The stippled diagonal line represents the line of identity between patients' and midparental heights. The top panel depicts patients with BA within 2 years of CA at therapy onset; the bottom panel depicts patients with BA >2 years of CA at therapy onset. △ indicates females; ○, males.

dexamethasone (.04, .14, .15, .16, and .17 mg/m^2/day) and developed excessive body hair and facial roundness on higher doses.

DISCUSSION

Glucocorticoid treatment of CAH involves the delicate balance of suppressing adrenal androgen secretion while maintaining normal statural growth. Our observations suggest that carefully titrated doses of dexamethasone can be used to suppress adrenal androgen secretion and achieve normal growth in children with CAH.

Dexamethasone treatment of CAH has been avoided in children because of the unsubstantiated assumption that this potent glucocorticoid suppresses growth to a greater extent than other glucocorticoids. Previous reports of dexamethasone treatment of CAH involving adolescents and adults have described suppression of adrenal steroidogenesis along with the development of cushingoid features in some patients.[2,20–22] However, the dexamethasone doses used in those reports were greater than the doses our patients received. The use of dexamethasone tablets in those reports, rather than dilute liquid preparations, also limits the precision of dosing of this potent glucocorticoid and may have contributed to overtreatment.

When the daily doses of hydrocortisone and dexamethasone our patients received were compared, dexamethasone was 70-fold more potent than hydrocortisone. This observation is consistent with previous observations that dexamethasone is 80-times more potent than hydrocortisone in suppressing adrenal androgen production.[2] These relative potency ratios contrast past and current pharmaceutical manufacturers' claims that dexamethasone is 30-fold more potent than hydrocortisone.[23] Thus, it is not surprising that dexamethasone doses based on manufacturers claims of hydrocortisone equivalency result in overtreatment and growth failure in children. When making dexamethasone:hydrocortisone dose conversions, calculations should be based on a potency ratio of 70 mg of hydrocortisone being equivalent to 1 mg of dexamethasone.

When examining patterns of growth during dexamethasone treatment, we found that the CAs, skeletal ages, and HAs advanced at similar paces in both the boys and the girls. ΔBA/ΔHA ratios approximated 1.0, showing that there was no excessive skeletal maturation during the treatment period. Changes in skeletal maturation closely matched changes in CA, showing that normal maturation occurred over the term of dexamethasone treatment. We also found that the predicted or final adult heights of most patients were between +.5 SD and −1.0 SD of normal adult heights. Comparison of mature or predicted heights with midparental heights revealed no or modest statural deficits that were within the normal variance of offspring versus parental mature height (± 1.3 SDS).[17]

One boy had a relatively low SD score after long-term dexamethasone treatment. However, this may reflect constitutional factors rather than inadequate control because the patient's BA and CA were always within 6 months of each other until adult height was reached.

Although our data reflect our long-term experience, we recognize that final heights are not available for most of the patients. However, when we compare the final heights of patients with their predicted adult heights when they were growing, we find excellent correlation. Thus, we anticipate that the final heights of the growing patients will be close to their current, excellent height predictions.

In contrast to the children without skeletal advancement at therapy onset, the predicted and actual final heights of children with advanced initial BAs were 2 to 4 SD below both normal adult and midparental heights. When we compared predicted heights at the onset of dexamethasone therapy with final or predicted adult heights, increases in adult height projections were seen. However, this increased growth potential was not sufficient to overcome the penalty of late diagnosis or inadequate therapy.

One limitation of our report is that there is not a group of children treated by us with hydrocortisone

alone for comparison, because it was our routine practice to use dexamethasone to treat children with CAH. However, when we compare the growth data of the children treated with dexamethasone by us with that of children treated with hydrocortisone by others, we find that the growth the dexamethasone-treated children is better, or at the very least comparable, to that reported by others.[10–13] Several reports show that the heights of children treated with hydrocortisone fall 1 to 2 SD (6–12 cm) below normal or midparental heights.[10–13]

The loss in adult stature associated with hydrocortisone therapy is believed to reflect cumulative adverse effects of glucocorticoids on growth and/or inadequate suppression of adrenal androgen secretion. Reflecting the short half-life of hydrocortisone, androgen levels rise within 4 to 6 hours after doses, which may contribute to accelerated skeletal maturation.[7,9,24] The inconvenience of dosing 3 or 4 times a day also makes compliance difficult and may contribute to breakthrough androgen secretion. In contrast, adrenal steroid production can be suppressed for up to 24 hours after a single daily dose of dexamethasone.[21,22,25,26]

Reflecting long-term dexamethasone action, we also noted that when the daily dose of dexamethasone was not administered, the children fared well and usually did not manifest symptoms of adrenal insufficiency. In contrast, we have observed that missed doses in hydrocortisone-treated children, more commonly result in anorexia, listlessness, and poor school performance.

Whereas most of the children with CAH were treated with a single morning dose of dexamethasone that averaged .27 mg/m^2/day, some children had lower or higher dose requirements. The parents of 2 of the 3 children who required higher doses of dexamethasone reported poor compliance with medication administration. In the other patients with either lower or higher dose requirements, variability in the doses may be related to the well-recognized patient-to-patient differences in the absorption and/or clearance of glucocorticoids (11,40). We also observed that 2 patients required dosing twice a day to achieve adequate control. In 1 child this was attributable to poor compliance. In the other child, we observed more rapid clearance of dexamethasone. We have also observed altered dose requirements in children placed on anticonvulsants. Thus, as with other glucocorticoids, dexamethasone doses need to be carefully adjusted, guided by the response to therapy.

Because of its high potency, we believe that it is essential that dilute preparations of dexamethasone elixir be used (.1 mg/mL). Care should also be taken to observe for signs of overtreatment, which include weight gain or the development of facial roundness even in the presence of normal linear growth. If dose changes are too generous, parents and children may observe these signs after several weeks on the higher dose. When illness occurs, we instruct families to administer the usual dose or a double-dose of dexamethasone both in the morning and evening. If repeated vomiting or lassitude develops, patients are told to contact us immediately and they are often referred for intravenous fluids and glucocorticoids.

Nearly 50 years have passed since cortisone was introduced as a therapy for CAH.[5,6] Despite inconvenient dosing regimens, breakthrough androgen secretion, and compromised adult stature, cortisone and hydrocortisone remain the mainstays of therapy for CAH. Our observations suggest that carefully adjusted doses of dexamethasone are at least as effective as cortisone and hydrocortisone in the treatment of CAH. Our biochemical evidence shows that children treated with dexamethasone have very well-controlled adrenal androgen secretion. We also show that dexamethasone-treated children grow normally, have normal rates of skeletal maturation, undergo puberty at a normal age, and can reach acceptable adult stature with the convenience of once-a-day dosing in most cases. Because of the high potency and the long duration of dexamethasone action, exquisite care in dose adjustment and consistent supervision are needed.

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For D. N. M.

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POPULATION EXPLOSION

Neither an expanding population nor ever-expanding aspirations are tolerable and the two in harness will be fatal.

Anonymous. Horse manure after Rio. *Lancet*. 1992;339:1515–1516. Editorial

Submitted by Student

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