Randomised controlled trial of growth effect of hydrocortisone in congenital adrenal hyperplasia

Ivani Novato Silva, Claudio Elias Kater, Cristiane de Freitas Cunha, Marcos Borato Viana

Abstract
The influence of 15 or 25 mg/m² of daily oral hydrocortisone with fludrocortisone 0.1 mg/day on growth and laboratory findings was evaluated in a prospective randomised crossover trial over 12 months in 26 children with 21-hydroxylase deficiency. Nine non-salt losers had fludrocortisone stopped for a further six month period. Height velocity was significantly decreased during treatment with 25 mg/m² as compared with 15 mg/m². This was the most sensitive indicator of corticosteroid treatment excess. A dose dependent effect upon plasma concentrations of 17-hydroxyprogesterone, testosterone, and androstenedione was found but increased values were still detected in more than half of the determinations made during the 25 mg/m² period. Height velocity and 17-hydroxyprogesterone concentrations were positively correlated. Growth hormone response to clonidine stimulation and insulin-like growth factor-1 concentrations were both within reference values and there was no difference between treatment periods. Withdrawal of fludrocortisone did not result in any difference for the non-salt losers. It was concluded that 25 mg/m² of hydrocortisone depressed growth in children with congenital adrenal hyperplasia, and that full suppression, or even normalisation, of plasma concentrations of 17-hydroxyprogesterone and androgens should not be considered a treatment goal, but instead an indication of corticosteroid treatment excess.

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Corticosteroids are successful as replacement treatment for children with congenital adrenal hyperplasia (CAH). In 21-hydroxylase deficient children, electrolytes become normal and progression of virilisation is halted soon after treatment starts. Maintaining normal growth velocity remains a challenge, however. Long term follow up studies show that patients with CAH fail to achieve their predicted final heights.1–3 Growth impairment has been attributed to the various corticosteroid schedules employed.4 However, individual differences in treatment needs make this difficult to evaluate.

Hydrocortisone and cortisone are regarded as the glucocorticoids of choice in treating children with CAH because of presumed lesser growth suppression.5 The ideal treatment regi-
appearance or increment of body hair and acne, deepening of the voice, abnormal weight gain, or changes in lean body mass as well as abnormal blood pressure and menstrual irregularities.

Morning fasting plasma concentrations of 17-OHP, testosterone, and androstenedione were determined at each visit, after the first hydrocortisone dose given at home. Patients were also submitted to a functional evaluation of growth hormone secretion, basal, and 75 minutes after oral clonidine (0.15 mg/kg). Plasma concentrations of insulin-like growth factor-1 (IGF-1) were determined at the end of each six month period.

Plasma samples were frozen at −20°C for subsequent analysis. All plasma steroids and IGF-1 concentrations were assayed by standardised radioimmunoassay methods, and growth hormone was determined by an immunoenzymometric assay.

After thorough explanation, all parents or legal guardians gave written informed consent to their children participating in the study.

### STATISTICAL METHODS

Means of the differences of height for age and weight for age z scores between the beginning and the end of each treatment period were compared using the two tail paired Student’s t test. The National Center for Health Statistics standards were used as reference population indices. The possibility of a carryover effect of the first over the second hydrocortisone treatment period was evaluated by F statistics. The steroid and the growth hormone values for each period were represented by the mean of approximately 52 hormonal determinations (two for each of the 26 children). The paired Student’s t test was used for comparisons. Growth and plasma steroid determinations from the four pubertal girls were analysed separately. Rejection of the null hypothesis was set at 5% (p<0.05).

### Results

The mean height and weight z scores of the two randomised groups at the beginning of the trial were not significantly different.

Figure 1 shows the statural growth of the 22 initially prepubertal children during the two study periods. There was a significantly (p=0.02) greater increase in height while using 15 mg/m² (mean (SE) z score = 0.28 (0.11)) as compared with 25 mg/m² (−0.06 (0.12)). Figure 1 also shows the statural growth of the whole group (n=26). There was a similar pattern of growth with significant increases in height (p=0.03) during the 15 mg/m² hydrocortisone period (z score = 0.18 (0.11)) when compared with the 25 mg/m² period (−0.10 (0.10)). Comparison of the statural growth during the two hydrocortisone dose schedules was possible due to a non-significant carryover effect (p=0.63). Because this effect was significant for weight gain, the comparison was made only for the first six months of the trial, with no apparent carryover effects.
Verences being detected (0.15 (0.54) \( \pm \) 0.02 (0.57), respectively for the 15 and the 25 mg/m\(^2\), \( p=0.55 \). Plasma steroid evaluations showed a variable pattern that was partially related to the hydrocortisone dosage (table 1). The most striking variations were observed for the four pubertal girls.

We observed dose dependent hydrocortisone suppression of plasma concentrations of 17-OHP and androstenedione for the 22 children. The lowest concentrations were associated with the 25 mg/m\(^2\) hydrocortisone dose (table 1). Testosterone concentrations did not change significantly.

Growth velocity and 17-OHP concentrations were positively correlated (fig 2). The regression line crosses the y axis (natural logarithms of 17-OHP) at 3.04, indicating that optimal growth velocity (z score difference = zero) occurred with average plasma concentrations of 17-OHP around 21 nmol/l. We observed no such association with androgens.

Discussion

Many reports have shown poor height prognosis for CAH treated patients. Mean final heights achieved by 282 adults ranged from z score = −0.67 to −2.2.1–3 5 21–25 Several investigators have advocated reducing the hydrocortisone replacement dose,91 0 mainly to increase final height by reducing any detrimental influence of pharmacological doses of corticosteroids on growth velocity.

Doses of corticosteroids which are even slightly supraphysiological during the first two years of life may compromise the accelerated growth velocity normal at this time. Absence of a later catch up would result in irreversible height impairment.11 26

Although mineralocorticoids are recommended for all salt losers, their role in improving growth of non-salt losers is controversial.10 27 Recent studies concerning adrenocortical production of cortisol showed that its physiological secretion rate is much lower6 than previously considered.28 Thus, children with CAH are possibly being given hydrocortisone in excess of their needs.

This limited term follow up of 26 children with CAH showed a significant decrease in growth velocity during the six month period of treatment with 25 mg of hydrocortisone/m\(^2\) as compared with the 15 mg/m\(^2\) dose period. These results indicate that doses of hydrocortisone in the upper limit of the frequently recommended range are not adequate.

Also remarkable was the fact that a decrease in growth velocity was the most sensitive clinical indicator of corticosteroid excess. Clinical signs of virilisation or hypercortisolism were rather scarce, if any, making recognition of drug excess difficult.

The present study was unable to show any relation between changes in growth hormone or IGF-1 and growth of children with CAH.
Growth hormone response to clonidine stimulation and plasma concentrations of IGF-1 were both within laboratory reference values and no differences were detected between the two periods of hydrocortisone intake.

Withdrawal of fludrocortisone did not result in any significant difference in growth velocity or laboratory data for the nine children without clinical evidence of salt loss.

The absence of a reliable laboratory value for treatment monitoring is one of the main problems in the management of CAH. It is common sense that clinical follow up is the most efficient way to evaluate the adequacy of hydrocortisone replacement, but since it cannot reflect day to day changes it is agreed that a laboratory marker is needed for fine tuning of the dose schedules.4 10 So far, plasma concentrations of androstenedione are believed to be relatively stable and reliable for this purpose.10 31

In our study, however, we observed that even high doses of hydrocortisone (25 mg/m²) were unable to fully suppress or even normalise the adrenal production of 17-OHP and androgens. There was a dose dependent effect upon the plasma concentrations of these steroids, but increased values were still present in more than 50% of the determinations during the 25 mg/m² dose period. The steroid concentrations in late puberty were specially unresponsive to increased doses.

We conclude that the current upper limit of hydrocortisone treatment in current recommendation doses.

Partial or incomplete adherence to the treatment regimen is often used to explain the variable steroid results in CAH treated patients.22 However, this seems unlikely in the present study because the effect of hydrocortisone intake on growth velocity was quite evident. In addition, the rhythmicity of adrenal steroid secretion22 makes a single morning plasma sample an unreliable marker of the metabolic status of these children throughout a 24 hour period.

A positive relation between the plasma concentrations of 17-OHP, but not of androgens, and growth velocity was shown. It suggests that smaller hydrocortisone doses may be beneficial to growth. In a regression analysis we detected optimal growth velocity (z score difference = zero) in the presence of 17-OHP concentrations about seven times the reference values for children. We consider this observation should be taken into consideration in the follow up of children with CAH.

Because of the trial design, generalisation for a better prognosis for final height cannot be inferred from our data.

It remains to be established whether and how the supranormal concentrations of androgens would affect bone age and ultimate growth. Though proposed,24 a specific adrenal androgen secretion controller has not yet been isolated.

Therefore, longer term follow up studies with lower doses of hydrocortisone are needed to evaluate the final height of patients with CAH.

We conclude that the current upper limit of hydrocortisone treatment doses for treating children with CAH is harmful to growth velocity at least on short term follow up. Because hydrocortisone doses high enough to compromise growth do not necessarily suppress steroid overproduction, full suppression, or even normalisation, of 17-OHP and androgen plasma concentrations should be avoided. Normal laboratory values should not be considered a treatment goal, but instead an indication of excessive corticosteroid treatment in these patients.

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References


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