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EFFECT OF THE DOSE OF ORAL HYDROCORTISONE ON GROWTH RATE DURING LONG-TERM TREATMENT OF CHILDREN WITH SALT LOSING CONGENITAL ADRENAL HYPERPLASIA

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Abstract The effect of the dose of oral hydrocortisone on stature growth rate of patients with the salt losing form of congenital adrenal hyperplasia and adequate electrolyte balance was here assessed. Thirty patients (21 girls and 9 boys) were followed longitudinally for 0.52 to 8.64 years, between chronological ages 0.35 and 8.64 years. Nine consecutive periods (Ps) of follow up were defined in order to compare two auxological parameters, height (H) at the end of a follow up P and DH standard deviation score (SDS). According to growth rate during a particular P, two types of Ps were defined: Ps with DH SDS > -0.5 (Group 1, satisfactory growth rate) and Ps with DH SDS = or < -0.5 (Group 2, poor growth rate). A cut off value of 18.5 mg/m^2/day of oral hydrocortisone (95% CI upper limit of group 1) was defined to separate acceptable from excessive doses. In P2, mean (± SD) H SDS (-1.81 ± 1.15) was significantly lower than in any of the other Ps ($p < 0.001$). In P1 and in P2, DH SDS was negative, but it was positive in P3 and in P4. Hydrocortisone dose in P1 and in P2 was significantly higher than in the rest of the Ps. All patients in P1 and most patients in P2 , but not in other Ps, received excessive doses. Predicted adult H, calculated in 9 patients was not statistically different from their respective target H. It is concluded that, during the first year of life, our patients received an excess of oral hydrocortisone (> 18 mg/m^2/day) and grew poorly, but they were able to recover, at least temporarily, when the dose was adjusted during the following years.

Key words: hydrocortisone dose, congenital adrenal hyperplasia, growth rate under corticoids

Resumen ***Efecto de la dosis oral de hidrocortisona sobre la velocidad de crecimiento en niños con la forma perdedora de sodio de la hiperplasia suprarrenal congénita.*** El propósito del estudio fue evaluar el efecto de la dosis de hidrocortisona sobre la velocidad de crecimiento en pacientes con la forma perdedora de sodio de la hiperplasia suprarrenal congénita, en adecuado balance hidroelectrolítico. Se siguieron en forma longitudinal 30 pacientes (21 niñas y 9 niños) durante 0.52 a 8.64 años, con edades cronológicas entre 0.35 y 8.64 años. Se definieron 9 períodos (P) consecutivos de seguimiento para comparar: el *score* de desviación estándar (SDS) para talla (T) al final del P y el DSDS T (diferencia en el SDS de talla). Se definieron dos tipos de Ps: P con DSDS T > -0.5 (Grupo 1, velocidad de crecimiento satisfactoria) y P con DSDS = o < -0.5 (Grupo 2, velocidad de crecimiento baja). Se definió un límite de dosis de 18.5 mg/m^2/dia (límite superior del IC de 95% para el Grupo 1) para separar dosis excesivas de aceptables. En P2, la media (± DS) del SDS de T (-1.81 ± 1.15) fue más baja que en los otros Ps ($p < 0.001$). En P1 y en P2 el DSDS de T fue negativo, pero fue positivo en P3 y en P4. La dosis de hidrocortisona en P1 y en P2 fue más alta que en el resto de los Ps. Todos los pacientes del P1 y la mayoría del P2 recibieron dosis excesivas, pero los de los otros Ps recibieron dosis adecuadas. La media de la talla adulta prevista de 9 pacientes no fue diferente de las T blanco. Se concluye que, durante el primer año de vida, los pacientes recibieron una dosis excesiva de hidrocortisona (>18 mg/m^2/día) y crecieron poco. Sin embargo, la talla se recuperó cuando la dosis fue ajustada en años posteriores.

Palabras clave: dosis de hidrocortisona, hiperplasia adrenal congénita, crecimiento bajo corticoides

Patients with early onset (classical) congenital adrenal hyperplasia are treated with glucocorticoids. If they have the salt losing form, they require, in addition, mineralocorticoids and sodium chloride supplement. In these patients, adequate water and mineral balance is necessary for normal growth. According to some reports[1, 2], the previously recommended dose of hydrocortisone (25 mg/m^2/day) is excessive for normal growth. Doses less than 20 mg/m^2/day[3], but high enough to avoid excessive adrenal androgen secretion need to be found and, ideally maintained, in these patients.

The dose of hydrocortisone recommended in the past was based on determination of cortisol secretion rates suggesting a mean value of 12 mg/m^2/day[4], and the assumption of 50% inactivation of oral hydrocortisone after intestinal absorption and hepatic clearance. Subsequent studies of cortisol secretion rate established

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that secretion was approximately 6-8 mg/m^2/day, suggesting that the accepted dose of oral hydrocortisone could be excessive[5, 6]. Therefore the question of possible side effects arose. The consequence of hydrocortisone induced growth suppression during infancy and early childhood, critical periods of rapid growth, could be an irreversible loss of adult height[7].

This study was undertaken with two purposes. 1) to study if our data confirm previous reports that the dose of oral hydrocortisone should stay below 20 mg/m^2/day for normal growth, and 2) to study if an excessive dose, administered for a prolonged period of time during infancy, can irreversibly affect final height prediction, even if it is adjusted during subsequent follow-up.

Patients and Methods

Thirty patients (21 girls and 9 boys aged between 0.35 and 8.64 years) with the classical salt losing form of congenital adrenal hyperplasia (21-hydroxylase deficiency) were longitudinally studied in our clinic. Follow up time ranged from 0.52 to 8.64 years. Patients had been treated with oral hydrocortisone, in divided doses, and 0.05-0.1 mg/day 9a-fluorhydrocortisone. Initial hydrocortisone dose in infants had been 24 mg/m^2/day. It was adjusted during follow up according to measurements of plasma 17-hydroxyprogesterone, androgens and renin activity concentrations that were determined at periodic clinical visits (between 3 and 6 months) and to regular assessments of growth velocity and bone age. Standard deviation (SD) scores (S) for height were calculated for chronological age, and bone age was re-evaluated by a single observer according to Greulich and Pyle[8]. Predicted adult height was estimated by the method of Bayley-Pinneau[9]. Target height was estimated by adjusting opposite sex parent height (±12.5 cm), and calculating the average value of the two parents.

In order to compare hydrocortisone dose with two auxological parameters, height (H) SDS at the end of a follow up period (P) and DH SDS, patients were divided in 9 Ps between 3 months and 8 years of age. The first year of life was divided in two Ps (P1 and P2) of shorter duration than the other Ps (0.29 ± 0.07 and 0.61 ± 0.22 years, mean ± SD, respectively) because of the rapid growth rate present during these Ps. Duration of P3 to P9 was close to 1 year for each P. Mean ± SD chronological age at the end of each P (n in parenthesis) was 0.49 ± 0.08 (n = 18), 1.03 ± 0.16 (n = 23), 1.92 ± 0.22 (n=16), 3.07 ± 0.18 (n = 15), 4.16 ± 0.23 (n = 15), 5.06 ± 0.30 (n=11), 6.11 ± 0.28 (n = 7), 7.01 ± 0.14 (n = 7) and 8.02 ± 0.25 (n = 7) yr., for P1-P9, respectively. In every patient, periods with serum 17-hydroxyprogesterone higher than 20 ng/ml or high plasma renin activity were excluded. In order to compare the dose of hydrocortisone with growth rate during a particular P, two types of Ps were defined: Ps with DH SDS > -0.5 (Group 1, satisfactory growth rate) and Ps with DH SDS = or < -0.5 (Group 2, poor growth rate). P1 was excluded from this analysis. Furthermore, a cut off value of 18.5 mg/m^2/day oral hydrocortisone was defined to separate acceptable from excessive doses. This value was the upper limit of the 95% confidence interval of oral hydrocortisone dose in Group 1. In 9 patients of P8 and P9, all of them older than 7 years of age, predicted adult H was compared to target H.

Statistical analyses. Mean H SDS, DH SDS and oral hydrocortisone dose in the different periods were compared using analysis of variance. Distribution of patients as a function of acceptable or excessive oral hydrocortisone doses was evaluated with the chi square test. A paired sample t test was used to compare predicted adult H with target H.

Results

Mean (± SD) H SDS in the 9 Ps is shown in Figure 1, upper panel. In P2, mean (-1.81 ± 1.15) was significantly lower than in any of the other Ps ($p < 0.001$): P1, -1.14 ± 1.44; P3 -1.15 ± 0.90; P4, -0.54 ± 1.02; P5, -0.62 ± 1.00; P6, -0.66 ± 1.08; P7, -0.41 ± 1.04; P8, -0.30 ± 1.07; and P9, -0.44 ± 0.89.

As shown in Fig. 1, lower panel, mean (± SD) DH SDS in P1 and in P2 was negative, -0.33 ± 1.29 and -0.70 ± 0.86, respectively, and significantly lower than in the rest of the periods ($p < 0.001$). In P3 and in P4, it was positive, 0.43 ± 0.67 and 0.76 ± 0.54, respectively, and significantly higher than in the following Ps ($p < 0.001$): P5, -0.07 ± 0.46; P6, -0.03 ± 0.32; P7, 0.07 ± 0.12; P8, 0.02 ± 0.38 and P9, 0.003 ± 0.27.

As shown in Fig. 2, mean (± SD) hydrocortisone dose during the first year of life, in P1 and in P2, was 25.4 ± 2.62 and 19.8 ± 2.37 mg/m^2/day, respectively. This was significantly higher than in the rest of the periods ($p <$

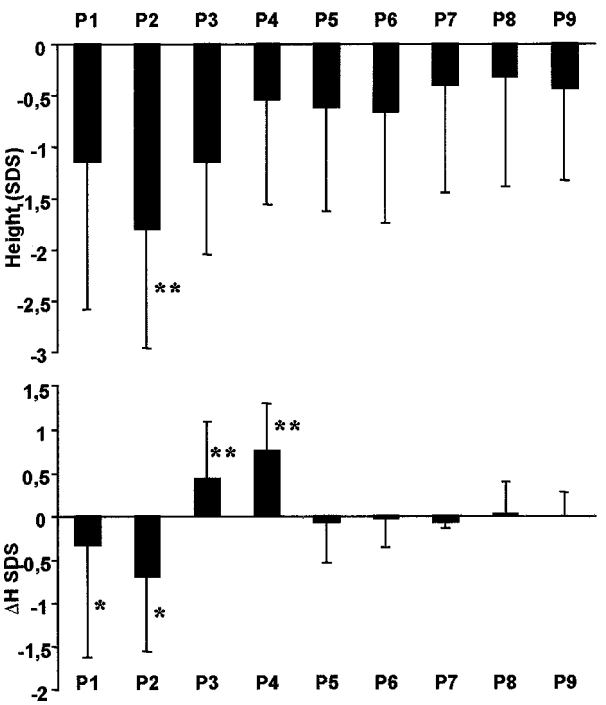

Fig. 1.– Mean ± SD H SDS (upper panel) and DH SDS (lower panel) at the end of P1 to P9. Statistical comparisons: * DH SDS in P1 and in P2 compared to P3 to P9, $p < 0.001$; ** DH SDS in P3 and in P4 compared to P5 to P9, $p < 0.001$; *** H SDS in P2 compared to P3 to P9, $p < 0.001$. SDS: deviation standard score. DH: Height difference. P1 a P9: Periods 1 to 9 follow-up.

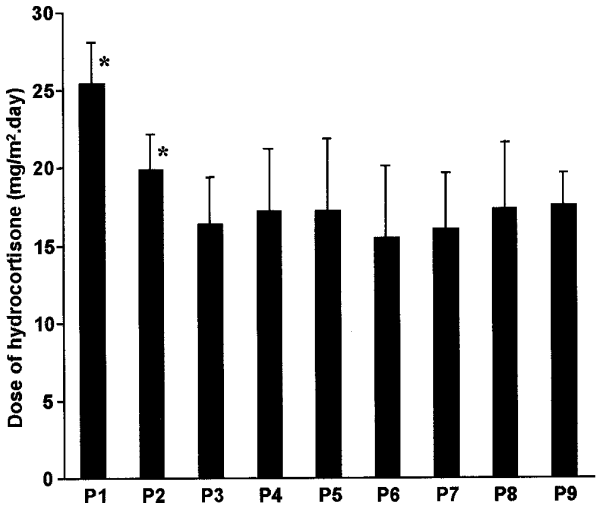

Fig. 2.– Mean ± SD hydrocortisone dose in P1 to P9. * P1 and P2 compared to P3 to P9, $p < 0.001$.

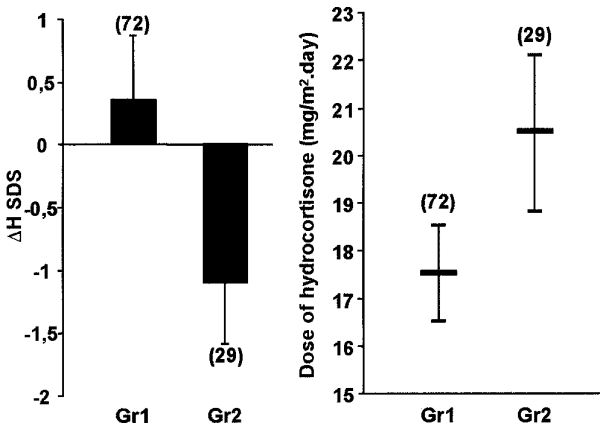

Fig. 3.– Left panel. Mean ± SD DH SDS in Group 1 (satisfactory growth rate) and in Group 2 (poor growth rate). Number of periods in parenthesis. Right panel. Mean and 95% confidence interval (vertical lines) of hydrocortisone dose in Group 1 and in Group 2.

0.001): P3, 16.3 ± 3.10; P4, 17.2 ± 4.06; P5, 17.2 ± 4.56; P6, 15.4 ± 4.57, P7, 16.0 ± 3.62, P8, 17.3 ± 2.98 and P9, 17.5 ± 2.14.

Hydrocortisone dose was analyzed as a function of DH SDS (Fig. 3). It was found that 72 Ps belonged to Group 1 (satisfactory growth rate), with mean (± SD) DH SDS of 0.36 ± 0.51, and a mean (± SD) hydrocortisone dose was of 17.5 ± 4.28 mg/m²/day, 95% confidence limits 18.5-16.5. Twenty nine Ps belonged to Group 2 (poor growth rate), with DH SDS of -1.11 ± 0.47, and a hydrocortisone dose of 20.5 ± 4.32, 95% confidence limit 22.1-18.8.

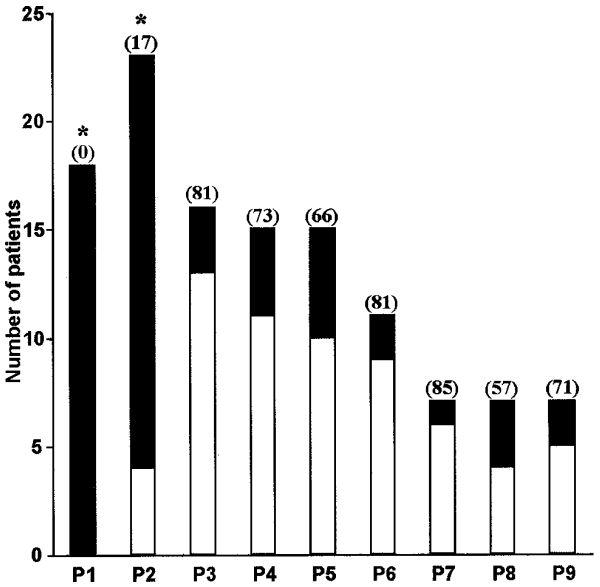

Fig. 4.– Distribution of patients as a function of hydrocortisone dose within each of the 9 periods of follow up. Black and white bars: dose > and = or < 18.5 mg/m².day, respectively. In parenthesis, % of patients with a dose = or < 18.5 mg/m²/day.

An analysis of the distribution of excessive doses among Ps (Fig. 4) showed that all patients in P1 and 13/17 patients of P2 received excessive doses, while most patients of the other Ps received adequate doses.

In order to study whether the excessive doses received by most patients during the first year of life, could affect their final height, predicted adult height (in SDS) estimated during the last visit was compared with target height. In 9 patients, predicted adult height was -0.59 ± 0.98 and target height 0.30±1.34. The difference was not statistically significant.

Discussion

In this retrospective study we have carried out a cross-sectional periodic evaluation of a longitudinal follow up, focusing on the effect of the dose of hydrocortisone on statural growth rate of children with the salt losing form of congenital adrenal hyperplasia. To normalize data height and growth rate was examined in terms of SDSs and dose was expressed as a function of square meter of body surface.

Data show that the lowest height was observed at the end of the first year of life. Furthermore, during the first year of life, DH SDS reached negative values. A catch up effect was observed during the second and third years of life. Later on, growth rate of patients under treatment was similar to that of the normal population. On the other

hand, data show that the dose of hydrocortisone during the first year of life, particularly during the first half of this year, was higher than during the following years. These findings suggest that stunted growth was secondary to an inhibitory effect of hydrocortisone on growth rate. To further stress the relationship between growth rate and hydrocortisone dose, we compared doses during periods of satisfactory and poor growth rates. P1 was excluded from this analysis because of the influence of the pre-treatment period on growth rate. We found a significant difference between mean doses of the two groups, as well as the 95% confidence limits of the distribution of these means, which were not superimposed.

It has been suggested that over treatment during infancy may not be followed by catch up growth after dose reduction and might affect final height[10,12]. To analyze if the catch up growth observed during the second and third years of life was sufficient to normalize height, we compared adult height prediction with target height in a group of patients with long follow up. Even though mean predicted adult height was lower than target height, the difference was not statistically significant, suggesting that adult height was not affected. It is true, however, that prediction methods have considerable errors and final height might be affected by difficulties in controlling the disease during puberty. Gussinye *et al.*[13] reported, in a group of 24 patients, lower growth rate than that of a control population during the two periods of higher growth potentiality: the first year of life and puberty, and this resulted in adult height impairment. In a recent report, Cabrera *et al.*[14] concluded that adult males with congenital adrenal hyperplasia do not achieve the height predicted from parental heights. In another publication, it was found that treatment with growth hormone alone or in combination with GnRHa results in an improvement of growth rate and height prediction, and a reduction in height deficit for bone age[15]. Therefore, since our patients have not yet reached the phase of pubertal growth, it is necessary to wait until final height is achieved to draw final conclusions.

In conclusion, our data confirm that a dose of hydrocortisone lower than 18.5 mg/m^2/day is recommended for treating these patients. However, the side effect on growth rate induced by a high hydrocortisone dose administered during the first year of life can be temporarily overcome by dose adjustment during the following years. The effect on final height remains to be elucidated.

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