

ORIGINAL ARTICLE

Long-term prednisone versus hydrocortisone treatment in children with classic congenital adrenal hyperplasia (CAH) and a brief review of the literature

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Summary. *Background:* Debate still exist about the safety of long-term use of prednisone (PD) versus hydrocortisone (HC) for treating children with congenital adrenal hyperplasia -21OH D (CAH). Despite recent developments in congenital adrenal hyperplasia -21OH D (CAH), several issues related to patient growth and final height remain unsolved. Debate still exist about the safety of long-term use of PD versus HC for treating children with CAH. The mechanism by which glucocorticoid therapy interferes with growth is complex and multifactorial. Relatively slight supra-physiologic levels may be enough to blunt growth velocity. An increased risk of developing obesity is another possible consequence of hyper-cortisolism in children with CAH. *Objectives of the study:* To evaluate the anthropometric and biochemical effects of long-term PD versus HC treatment in children with CAH-21OHD. A brief review of the literature is also reported. *Patients and Methods:* This retrospective study evaluated linear growth and biochemical data of thirty children with classic CAH (19 females and 11 males), who were on PD (n=22) or HC (n=8) treatment, since their first diagnosis. Clinical data included age, gender, duration of therapy, dose of HC and or equivalent dose of HC in the PD group, blood pressure, height (Ht) and weight. Ht-SDS and BMI were also calculated. Biochemical data included measurement of 17- OH progesterone, cholesterol, triglycerides (TG), HDL, LDL, fasting glucose, and insulin concentrations. HOMA-IR was calculated. Carotid intima-media thickness (CIMT) was measured using high-resolution B-mode ultrasonography. Thirty normal age matched children were used as controls for the anthropometric and CIMT data. *Results:* The age of children and duration of treatment did not differ among the two treatment groups. After a mean of 6 years of treatment, the Ht-SDS and BMI did not differ between the three groups of children. The equivalent hydrocortisone dose of children on prednisone was significantly higher than the dose for the hydrocortisone group. Both systolic and diastolic blood pressures (BP) of children on PD was slightly higher compared to those on hydrocortisone group. However, the BP of the 2 treatment groups was not different compared to control children. Fasting blood glucose, homeostatic model assessment insulin resistance (HOMA-IR), plasma TG, HDL, and cholesterol did not differ among the two treatment groups. LDL levels were significantly higher in the PD group versus the HC group. The mean CIMT did not differ among the two treatment groups but was significantly higher in the treated groups versus controls. There was a significant linear correlation between BMI-SDS and CIMT ($r=0.37$, $p=0.047$). *Conclusions:* Children with CAH-21OHD who were kept on PD therapy for 6.4 ± 2.7 years, since the begin-

ning of diagnosis, have maintained normal linear growth. No difference in BMI, HOMA-IR, or CIMT was detected among the two treated groups. The efficiency, safety and convenience of a single daily dose of PD could be a good and relatively safe alternative to HC for the continuing medical treatment of patients with CAH-21OHD. However, more prospective studies across childhood and adolescence are necessary to draw definitive conclusions. (www.actabiomedica.it)

Key words: congenital adrenal hyperplasia (CAH), long-term corticosteroids treatment, growth, blood pressure, glucose, insulin, carotid intimal thickness, lipid profile

Introduction

Congenital adrenal hyperplasia (CAH) is caused by the loss or severe decrease in activity in one of the five steroidogenic enzymes involved in cortisol biosynthesis. In 90-95% of all cases a 21-hydroxylase deficiency (21-OH) is found (1). It is caused by mutations in the 21-hydroxylase gene (CYP21A2), which encodes the steroid 21-hydroxylase (p450c21). This enzyme converts 17-hydroxyprogesterone (17-OHP) into 11-deoxycortisol, and progesterone into 11-deoxycorticosterone, which are then converted into cortisol and aldosterone, respectively. Disturbance of cortisol production causes accumulation of precursors of cortisol by stimulation of ACTH, and these precursors lead to a pathway for adrenal androgen. Overproduction of androgens causes virilization, accelerated growth, advanced skeletal maturation, and early epiphyseal fusion (1,2).

Patients with classic CAH, especially those with the salt-wasting form, also need mineralocorticoids, and infants usually need sodium chloride supplementation. Non-salt-wasting 21-OHD may be diagnosed on genital ambiguity in affected females, and/or later the occurrence of androgen excess in both sexes.

Traditional treatment consists of substitution of cortisol to reduce excessive androgen production and its consequences. Physiological cortisol production is estimated to be 5-6 mg/m²/d. The biological criteria to optimize treatment are controversial. Some authors use mainly clinical development (growth velocity and bone age). Others measure hormone levels: serum 17-OHP and/or serum Δ 4 androstenedione and/or testosterone which are believed to be the most sensi-

tive index of biochemical control. Renin, aldosterone and potassium are useful to monitor mineralocorticoid treatment (1). Undertreatment with steroids leads to androgen excess with advancement of bone age and reduced final height (FH). Overtreatment may impair growth through the growth-inhibiting effects of steroid and may predispose to obesity, hypertension and osteoporosis (1-5).

Hydrocortisone (HC) is the preferred glucocorticoid (GC) in children with CAH due to potential concerns of linear growth suppression associated with longer-acting and more potent GC formulations (1, 6, 7). However, individual differences in treatment needs make this difficult to evaluate the effect on linear growth.

A randomized controlled trial (RCT) showed that 25 mg/m² depressed growth in children with CAH compared to 15 mg/m² of HC and suggested that full suppression, or even normalization, of plasma concentrations of 17-hydroxyprogesterone and androgens should not be considered a treatment goal, but instead an indication of corticosteroid treatment excess (7). Reliable results using relatively smaller HC doses and mineralocorticoid replacement with fludrocortisone have been reported, when combined with antiandrogens (flutamide) and aromatase inhibitors (testolactone). However, this complex and expensive multi-drug scheme is demanding for routine use, especially in third-world countries (8).

Up till now, debate still exists about the difference in the effect on growth and metabolism when different GC formulations are used for treatment of CAH (9-15).

Tendency for overtreatment increases when potent longer-acting GC formulations, such as prednisone or dexamethasone are used. The bioequivalence dose ratio is based upon anti-inflammatory potency, because other clinical equivalence tables are not yet clearly available and can lead wrong estimation of the proper doses. Even “physiologic doses” may impair growth velocity and restrict final height.

Several mechanisms may be involved in this consequence: GC formulations interfere with the normal interactions in the growth hormone (GH)/IGF-1 signaling cascade at the level of the hypothalamus, pituitary, and target organ.

In human studies, excess GC formulations (pharmacological dose) causes a decrease in GH response to growth hormone releasing hormone (GHRH) and a paradoxical increase in IGF-1 levels, inducing a state of GH resistance. In addition, GC formulations may prompt apoptosis of chondrocytes through activation of caspases and inhibit the phosphatidylinositol 3 -kinase (PI3K) signaling pathway (9-14).

On the other hand, the use of long acting synthetic GC analogues to treat CAH-21OHD, may suppress ACTH more efficiently. Prednisolone (PD) has a molecular structure that resembles that of cortisol, with the C1-C2 double bond determining a longer half-life and possibly permitting single daily dose administration. It is convenient commercially available formulation (homogeneous oral solution) that permits fine therapeutic adjustments (15, 16).

This study aimed to investigate retrospectively the long-term effects of two different glucocorticoid regimens (PD versus HC) in children with CAH-21OHD with special reference to growth, lipids, insulin resistance, blood pressure and carotid intimal-media thickness. A brief review of the literature is also reported.

Patients and methods

Thirty children with classic CAH-21OHD (19 females and 11 males), attending the Endocrinology Clinic of Alexandria University Children's Hospital (Egypt) were enrolled in our study. Thirty healthy age and sex matched children were used as controls. Anthropometric measurements were assessed, including:

weight, height (Ht), body mass index (BMI), and Ht-SDS. Patients with other diseases, or those receiving drugs that could affect linear growth were excluded.

All data were extracted retrospectively from the patients' charts. The diagnosis of CAH-21OHD was based on both clinical symptoms and signs, and later on hormonal analysis and comprehensive genotyping.

Twenty-two children with CAH-21OHD were on continue treatment with a single morning dose of oral PD and eight were on daily oral dose of HC, divided in two daily doses. The doses were adjusted every 4 months to keep average plasma 17-hydroxyprogesterone concentration around 21 nmol/L (695 ng/dL). In addition, oral fludrocortisol (100-150 µg) was given to all patients as replacement mineralocorticoid therapy.

Laboratory investigations done during the last visit included: assessment of electrolytes, 17OHP, fasting glucose and insulin concentrations, lipid profile and homeostatic model assessment insulin resistance (HOMA-IR). High-resolution B-mode ultrasonography was performed to measure the carotid intimal-media thickness (CIMT) and to evaluate the color Doppler flow characteristics of the carotid arteries. A CIMT value more than 0.9 mm or over the 75th percentile were considered abnormal (17).

The Ethical Committee of Alexandria College of Medicine approved the study. Informed consent was obtained from all patients and controls before the study.

Statistical analyses were performed with the parametric t test when the data were normally distributed and nonparametric Mann-Whitney U test when the data were not normally distributed. Spearman's correlation coefficient was calculated to evaluate correlation of different variables with the Ht-SDS. Statistical analyses were done with the SPSS 10.0 software (SPSS Inc., Chicago, IL). A P value <0.05 was considered statistically significant.

Results

Comparison between the two groups of children with CAH-21OHD (PD versus HC) and controls is shown in table 1. The age of children and duration of treatment did not differ among the two treatment

Table 1. Comparison of different variables between CAH patients and controls

Variables	Type of steroid treatment		P1* Controls n =30	P2*	
	Hydrocortisone (n=8)	Prednisone (n=22)			
Age (years)	7.4±3.3	6.4±2.7	6.28±2.75	0.37	0.511
Systolic BP mmHg	96.5±13.4	98.5±6.9	97.47±7.65	0.01	0.828
Diastolic BP mmHg	61.3±8.3	63.9±4.2	63±4.34	0.01	0.677
Height (± SD)	-0.3±1.3	-0.7±1.6	-0.25± 0.80	0.25	0.249
BMI (kg/m ²)	19.0±3.6	18.7±5.1	19.8±5.42	0.57	0.399
Total daily dose (mg/m ² /day)	15.2±3.7	5.5±1.1	ND	<0.001 [#]	ND
17- OH progesterone nmol/L	26.8±70.0	3.0±3.3	ND	0.00	ND
Cholesterol mg/dL	144.5±20.4	162.0±30.9	ND	0.06	ND
TG mg/dL	69.1±27.6	74.1±25.5	ND	0.65	ND
HDL mg/dL	53.5±5.3	55.1±11.0	ND	0.69	ND
LDL mg/dL	72.9±20.5	91.3±27.0	ND	0.04	ND
Fasting glucose mg/dL	73.8±7.2	73.9±11.4	ND	0.97	ND
HOMA-IR	1.1±0.5	1.2±0.8	ND	0.73	ND
CIMT Mean (mm)	0.54±0.07	0.51±0.06	0.044±0.004	0.21	<0.001 [#]

Legend=CAH: congenital adrenal hyperplasia; * P1: hydrocortisone vs prednisone; ** P2: Patients versus controls; CIMT: carotid intimal thickness; TG: triglycerides; HOMA- IR: homeostatic model assessment insulin resistance; # p ≤ 0.05

groups. Ht-SDS and BMI did not differ between the three groups of children. The equivalent HC dose of children on PD was significantly higher compared to the dose given to the patients on HC treatment. The systolic (SBP) and diastolic (DBP) blood pressure of children on PD was slightly higher compared to HC group (p: 0.01). However the blood pressure of both groups of patients was not statistically different compared to controls.

Fasting blood glucose, HOMA-IR, plasma TG, HDL and cholesterol did not differ between the two groups of patients. LDL levels were significantly higher in the

PD group versus the HC group. The mean CIMT did not differ among the two treatment groups but was significantly higher in the treatment groups versus controls (<0.001).

Correlation studies showed a significant linear correlation between BMI-SDS and CIMT (r: 0.366, p: 0.047). However, CIMT did not correlate with other variables including: age, total daily dose (mg/m²/day), 17- OHP, LDL, fasting insulin, and TG concentrations or HOMA-IR (Table 2). Ht-SDS was not significantly correlated with the total daily dose (mg/m²/day) or 17-OH progesterone level (r=0.22 and -0.08, respectively; p>0.05)

Table 2. Correlation between mean carotid intimal thickness (CIMT, in mm) and different parameters in our patients with CAH

Cases group	Mean CIMT	
	r	p
Age (years)	0.292	0.117
Total daily dose (mg/m ² /day)	0.349	0.059
BMI- SDS	0.366 [*]	0.047 [*]
17- OH progesterone	-0.214	0.257
HDL (mg/dL)	-0.021	0.910
LDL (mg/dL)	-0.214	0.257
Fasting Insulin (mIU/L)	0.053	0.780
HOMA-IR	-0.007	0.971
TG (mg/dL)	0.164	0.385

Legend=CIMT: carotid intimal thickness, in mm; HOMA- IR: homeostatic model assessment insulin resistance; *p ≤ 0.05

Discussion

HC acetate, is most similar to endogenous cortisol and therefore is considered as a potentially good therapeutic option for treating children with CAH-21OHD, in whom there is a risk of suppression of growth with the use of other longer acting synthetic GC preparations (6). Adherence to treatment is a cru-

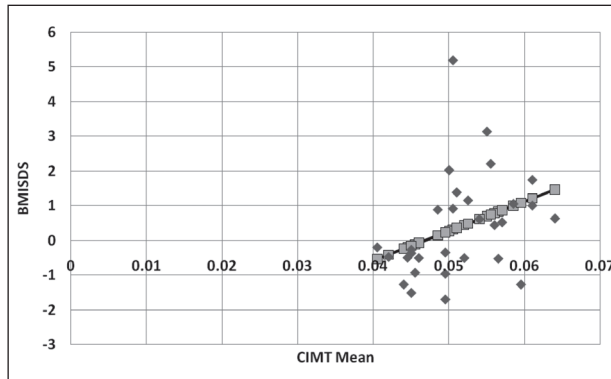


Figure 1. Correlation between CIMT and BMISDS in children with CAH ($r=0.336$, $p=0.0047$)

Legend=CIMT: carotid intimal thickness, in mm; BMI: body mass index, in SDS

cial issue to attain satisfactory results in children with CAH. Hence, it is of fundamental importance to seek a therapeutic scheme that adapts to the daily life of the patient and their parents. However, HC has a short biological half-life, requiring a maximum of 8-hour doses intervals. This hampers adherence to treatment and may lead to intermittent non-suppression of ACTH with the consequence of frequent androgen excess production (18). Additionally, the oral preparation of HC is not commercially available in many areas in Egypt. The liquid form is unstable (suspension) and precipitates in non-alcoholic diluent. These characteristics make it challenging to administer and leads to dosing mistakes in young children. The possibility of using single dose daily medication with GC with intermediate half-life has been proposed.

PD, an intermediate half-life GC, has been suggested as a therapeutic option in children and adolescents with 21OHase deficiency. It is a synthetic GC structurally like cortisol, whose only molecular difference is the existence of a double bond between carbons 1 and 2. This feature prolongs its plasma half-life and allows its use in a single daily dose. The pharmacokinetic profile of PD showed similarity to the published profile of dual-release HC. Therefore, once-daily PD has been suggested as a replacement to patients on treatment with HC. Some data suggest that PD profile is superior to the current standard of thrice-daily HC because mimicking the physiological cortisol profile and promoting a better compliance (19, 20).

In fact, Johannsson et al. (21) found an obvious patient preference for once-daily regimens vs thrice-daily regimens. Furthermore, the recommended initial dose of 3 mg /m², represents one fourth to one fifth of the HC dose. Its oral presentation is commercially available as a solution, which facilitates the acquisition and administration in children and the cost is lower when compared to formulated hydrocortisone (22-25).

Traditionally, PD bioequivalence to HC has been quoted at 1:4, although there are some evidences that the true value is closer to somewhere between 1:6 and 1:8, at physiological doses (25). The physiological dose of PD is uncertain. For anti-inflammatory effects PD is four-fold more potent than HC. Whether this relative potency is also true for the GC and mineralocorticoid effects is less clear. Using luciferase transactivation assay in CV-1 cells transfected with the human GC receptor, PD was 1.7-fold more potent than HC. When transfected with the human mineralocorticoid receptor, HC was 4.2-fold more potent than PD.

Bioequivalence of PD and HC derived from growth data in patients with CAH suggest that PD is from 6 to 8-fold more potent than HC (26, 27). However, the drawback of using PD is the potentially higher risk of negative impact on growth and metabolism (28-31).

Our study compared different anthropometric and lab. variables in CAH-21OHD children on long-term treatment with PD (5.5 ± 1.1 mg /m² daily, equivalent to a HC daily dose of 22 mg/m²) versus HC treatment (15.2 ± 3.7 mg/m²), from the diagnosis of CAH. The Ht-SDS and BMI did not differ between children on PD, HC and controls (Ht-SDS=-0.7, -0.3, -0.25, respectively; BMI=19.1, 18.7, and 19.8 Kg/m², respectively). Serum 17 OHP was significantly lower in children on PD versus HC treatment.

In support to our data, Leite et al. (15) evaluated the growth parameters in 15 children with CAH. In the first year of treatment, HC (17.5 mg /m²/ day, divided in three doses) was used, followed in the second year by a morning daily dose of PD (3 mg / m² / day). The comparison between the two treatments during this relatively short period showed no significant difference in relation to Δ Ht- SDS, Δ bone age SDS and Δ BMI- SDS. No significant difference was observed in the serum levels of Δ 4 androstenedione (32).

Caldato et al. (22) evaluated 44 patients previously diagnosed as having the salt-losing or simple-virilizing forms of CAH-21OHD were randomly assigned to two groups, stratified according to sex, age, and pubertal status, in order to assess the clinical benefits of a one year treatment period with a single morning dose of PD, as compared to a three times a day (TID) HC replacement therapy. Growth velocity (expressed in SDS) was preserved in the PD group (from 1.2 to 1.2 in all; 0.79 to 1.13 in pre-pubertal children, whereas a slight increase occurred in the pre-pubertal HC-treated patients (from 1.1 to 1.9); Ht-SDS for bone age increased significantly in the PD group. Thus, patients with CAH-21OHD treated for one year with a single morning dose of PD appeared to achieve a better clinical control than those on TID HC. However, long-term follow-up is still necessary to demonstrate individual clinical benefits upon final stature and fertility.

In another prospective cross-over study done in 13 prepubertal children with classical CAH-21OHD, HC did not offer significant advantage in achieving biochemical control of disease. Replacing HC with PD, in the evening, resulted in similar hormonal control of the disease (33).

Khadilkar et al. (34) compared growth parameters of children with CAH treated with PD or HC. HC had a less negative growth effect than PD and patients treated with HC from the beginning showed near normal growth.

Linder et al. (35) hypothesized that alternate day prednisone therapy might be more efficacious in the treatment of CAH. To evaluate this hypothesis, they studied an 11-yr-old girl with salt-losing 21-OHD with alternate day PD therapy (20 mg every other day) for over 3 yr. This treatment regimen caused sustained adrenal androgen suppression and allowed normal growth and pubertal development, despite persistently elevated plasma ACTH and 17-OHP levels.

To evaluate the impact of HC dosage, age at diagnosis, compliance, genotype and phenotype on growth and height outcome in CAH patients, Grigorescu-Sido et al. (36) studied 37 patients (17 had completed growth and 20 were still growing). Doses >20 mg/m²/day during the first year and >15 mg/m²/day during age 1-5 and at puberty resulted in significantly lower

final height- SDS, predicted final height-SDS and in a greater height losses. The Authors concluded that HC substitution in CAH patients should be kept at the lowest efficient level, if possible <20 mg/m²/day during the first year and <15 mg/m²/day until age 5 and during puberty. Similar recommendations were reported by Bonfig et al. (14).

In summary, most of the studies in the pharmacotherapy of CAH-21OHD 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 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 (HC, PD, and dexamethasone) and dosage schedules are used for this purpose in children and adults (37). In children the typical dosing of hydrocortisone is 10-15 mg/m²/day administered orally in three divided doses. Infants may temporarily require doses up to 20 mg/m²/day to reduce the markedly elevated sex steroids.

Similarly higher doses (up to 15 mg/m²) are required during puberty. Doses must be individualized by monitoring growth, bone age, and hormonal levels.

Excess GCs intake can lead to increased weight gain, hypertension, osteoporosis / osteopenia and early onset diabetes. Furthermore, cardiovascular function and the elastic properties of major arteries are disturbed in children and adolescents with 21-hydroxylase-deficient CAH (38).

Our patients on PD therapy had slightly but significantly higher SBP and DBP, and higher plasma LDL compared to those on HC. These may impose an increased risk on developing further lipid abnormalities and atherosclerosis on the long-term treatment (39,40). In support of our blood pressure findings, other studies reported higher systolic blood pressure and abnormal blood pressure profile in children with CAH. (40,41).

A recent systematic review and meta-analysis suggested that, compared with controls without CAH-21OHD, individuals with CAH had increased SBP, DBP, insulin resistance, and carotid intima thickness (42). No statistically significant difference was noted in fasting blood glucose or lipids. The Authors

were unable to draw conclusions regarding the effects of several important variables such as sex, glucocorticoid type and dose, fludrocortisone dose, and genotype (42). Nevertheless, there are no evidence of actual morbidity or mortality due to cardiac events. Long-term prospective studies are warranted to assess strategies for reducing cardiovascular risk in individuals with CAH-21OHD.

However, in CAH-21OHD patients, intima media thickness of abdominal aorta (AIMT) and common carotid arteries (CIMT) are influenced by androgens and obesity. CIMT is an independent predictor of future cardiovascular risk and is positively correlated with body mass index (BMI) and systolic blood pressure (43-45). In our children with CAH-21OHD there was a positive significant correlation between CIMT with BMI. Furthermore, in our study, an increased of CIMT has been observed in our patients with CAH-21OHD, both on HC and PD, compared to control children. On the other hand, our study did not detect difference in CIMT between patients on HC compared to patients on PD.

It was observed that cardiovascular risk factors detected in childhood such as elevated LDL-c, SBP, and BMI were associated with increased CIMT and that progression to atherosclerosis may be predicted in childhood independent of risk factors identified later in adulthood (46). Our children on PD therapy had slightly higher LDL and blood pressure compared to those on HC therapy.

In a small group of prepubertal children with classic CAH, serum insulin concentrations were reported to be significantly higher than those of healthy counterparts (47). However, in our patients on PD and HC treatment, fasting glucose level and HOMA-IR were normal.

Varying data have been reported on triglyceride levels, with one study reporting higher levels in a group of prepubertal patients on GC treatment compared with age-matched controls and another showing a lipid profile in CAH children similar to that of controls (48, 49). Our patients on PD and HC had normal triglyceride levels with no difference among the two groups.

In brief, our children with CAH-21OH who were on single daily dose of PD for a 6.4 ± 2.7 year,

since the beginning of their diagnosis, maintained a normal linear growth with no or minimal effect on statural growth compared to TID therapy with HC. No difference in BMI, fasting glucose level, HOMA-IR, or CIMT was detected among the two groups of patients. Mild increase in BP, LDL levels was detected in the PD group versus the HC group. 17-OHP levels were significantly lower in the PD group versus HC group suggesting a better biochemical control. Consequently, when the convenience of a single daily dose, compliance and cost-effectiveness are considered, PD appears to be a good and relatively safe alternative choice to HC.

We did not include in the present study the impact of PD or HC on bone mineral density (BMD) of our patients. GC therapy using pharmacological doses has a detrimental effect on bone, which is known to be strongly dose dependent.

Longitudinal studies in patients with CAH are scarce: a study including 15 patients with CAH reported an increase in L1-L4 BMD but a decrease of femoral neck BMD after 8-10 years (50); another study also showed a mixed response (51). Although, Jääskeläinen and Voutilainen et al. (52) reported that adult patients substituted with HC were less often over-treated and had better BMD Z-score means than patients substituted with PD or dexamethasone, no longitudinal study has examined the effect of different GCs in detail. Because the potential risk for osteoporosis remains, we suggest to monitor and eventually to treat bone disease, even in young patients.

In conclusion, the aim of CAH treatment is the replacement of mineralocorticoids and glucocorticoids and the normalisation of elevated androgen concentrations. Long-term treatment with glucocorticoids will improve the androgen symptoms but may result in long-term complications, such as obesity, insulin resistance, hypertension, osteoporosis and fractures. However, optimising replacement therapy in patients with CAH-21OHD remains challenging. Furthermore, management of CAH requires parents to administer oral steroids, typically HC, up to three times daily within school and activity schedules, supplementing maintenance doses with oral "stress dosing" during times of illness and an emergency intramuscular (IM) injection of HC when a child is unable to tolerate oral

medications and/or if signs of adrenal crisis are present. Prednisone is a potentially good alternative when HC is not available or once daily dose is required for improving compliance. "These patients should therefore be carefully followed-up, from childhood through to adulthood, to avoid these complications and to ensure treatment compliance and tight control of the adrenal androgens, by multidisciplinary teams who have knowledge of CAH" (53).

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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