RESEARCH

Comparison of modified-release hydrocortisone capsules versus prednisolone in the treatment of congenital adrenal hyperplasia

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Abstract

Background: Prednisolone and prednisone are recommended treatment options for adults with congenital adrenal hyperplasia (CAH); however, there is no randomised comparison of prednis(ol)one with hydrocortisone.

Design: Six-month open-label randomised phase 3 study and interim analysis of a single-arm extension study was the design of the study.

Methods: The method of the study was hydrocortisone dose equivalent and 09:00-h 17-hydroxyprogesterone (17OHP) from 48 patients taking prednis(ol)one at baseline.

Results: At baseline, the median hydrocortisone dose equivalent was 30 mg/day and 17OHP was < 36 nmol/L (3× upper limit of normal) in 56% of patients. Patients were randomised to continue prednis(ol)one or switch to modified-release hydrocortisone capsule (MRHC) at the same hydrocortisone-equivalent dose. At 4 weeks, 94% on MRHC and 71% on prednis(ol)one had 17OHP < 36 nmol/L. At 18 months in the extension study of MRHC, the median MRHC dose was 20 mg/day and 82% had 17OHP < 36 nmol/L. The per cent of patients with 17OHP < 36 nmol/L on a hydrocortisone dose equivalent ≤ 25 mg/day was greater at 18 months in the extension study on MRHC than while on prednis(ol)one at baseline: 57% vs 27%, *P* = 0.04. In the randomised study, no patients had an adrenal crisis on MRHC

and one on prednisolone. In the extension study (221 patient years), there were 12 adrenal crises in 5 patients (5.4/100 patient years).

Conclusion: MRHC reduces 17OHP at 09:00 h compared to prednis(ol)one and the dose of MRHC can be down-titrated over time in the majority of patients.

Keywords: adrenal insufficiency; CAH; congenital adrenal hyperplasia; cortisol; hydrocortisone; prednisolone; prednisone

Introduction

The control of congenital adrenal hyperplasia (CAH) is suboptimal on standard hydrocortisone replacement therapy because it does not control the overnight rise in adrenocorticotropic hormone (ACTH) that drives the production of adrenal androgens (1). To address this, clinicians have used a variety of treatment regimens, including the use of a higher dose of glucocorticoid at night in a reverse circadian treatment pattern. A recent comparison, using a higher dose of hydrocortisone in the morning vs a higher dose at night in children, showed no difference in overall 24-h control of markers of adrenal androgen excess (2). Anecdotally, some patients complain of poor sleep when taking glucocorticoids at night and taking hydrocortisone in the evening is associated with a worse metabolic profile (3). International guidelines suggest treating patients with the lowest dose of glucocorticoid required, with the recommendation being 15–25 mg of hydrocortisone a day in fully grown patients (4). In most reported studies of CAH treatment, the glucocorticoid dose exceeds that recommended for adrenal replacement, and it is believed this is in part responsible for the long-term poor health outcomes in adult patients with CAH (5). Prednisolone, prednisone, and dexamethasone are also given in the evening with the rationale that, being more potent and with a longer half-life, they could control the overnight rise in ACTH (6). Prednisolone and prednisone have a longer plasma elimination half-life after oral administration than hydrocortisone: 2.1 to 3.5 h vs ~1.5 h (7, 8); however, detailed studies of pharmacokinetics and disease control in CAH show that prednisolone levels fall by the morning and ACTH and 17-hydroxyprogesterone (17OHP) levels rise (9). There has been no formal comparison of prednisolone vs hydrocortisone treatment in adult patients with CAH although, in cohort studies, approximately a third of adult CAH patients are taking either prednisone or prednisolone, and biochemical control remains poor in the majority of patients (10, 11). Recently, increased mortality has been reported in patients receiving prednisolone for primary adrenal insufficiency, and therefore, there is a need to further examine the use of prednisolone in the treatment of CAH (12).

Two modified-release hydrocortisone formulations are available in Europe: modified-release tablets (Plenadren®, Takeda, Japan) and modified-release hard hydrocortisone capsules (MRHC; Efmody®, Diurnal Ltd,

UK). Plenadren is a tablet with an immediate-release outer layer and a sustained-release core, which provides once-daily hydrocortisone replacement but does not replace the physiological overnight rise in cortisol, as cortisol only rises after taking the dose on waking in the morning. MRHC has delayed release and sustained absorption was called Chronocort during development and has been shown to mimic the normal circadian rhythm of cortisol (13, 14). MRHC is taken twice daily, at bedtime and on waking, and has been shown to improve the morning control of markers of adrenal androgens in adults with CAH (14, 15). The phase 3 study for MRHC was the first large controlled randomised study of glucocorticoid therapy in patients with CAH. We have now undertaken an analysis of this phase 3 study and its single-arm extension study comparing 17OHP levels and glucocorticoid dose in patients on either prednisone or prednisolone (prednis(ol)one) at baseline.

Methods

Patients

Patients on prednis(ol)one at baseline of the phase 3 study were selected for the analysis (15). Patients had classic CAH due to 21-hydroxylase deficiency diagnosed in childhood, adequate mineralocorticoid replacement with renin less than two times the upper limit of normal (ULN), and were on stable glucocorticoid therapy over the preceding 6 months. In total, 84% of patients were salt-wasting on fludrocortisone, and this was balanced between the two groups. Patients completing the phase 3 study were invited to participate in a single-arm, open-label extension study. The study protocols were approved by The East Midlands – Leicester Central Research Ethics Committee (ref: 16/EM/0278) and the Medicines and Healthcare Products Regulatory Agency (NCT02716818 and NCT03062280; Eudract 2015-000711-40 and 2015-005448-32). The trials were performed in accordance with the principles of the Declaration of Helsinki and all patients gave informed written consent.

Trial design

Patients in the phase 3 study were randomised, based on prior therapy, to receive MRHC (Efmody, Diurnal Ltd)

or to continue on their existing therapy. This analysis looks only at those patients who received prednis(ol)one with or without hydrocortisone as prior therapy. MRHC was prescribed as 5, 10, or 20 mg capsules, and the initial dose was the hydrocortisone dose equivalent to their baseline therapy (hydrocortisone dose equivalent (HDE) = prednis(ol)one dose × 5, and if also on hydrocortisone, then the dose of hydrocortisone added). For MRHC, approximately one-third of the daily dose was taken at 07:00 h and two-thirds of the daily dose taken at 23:00 h. After 6 months, patients who had completed the phase 3 study were invited to enrol in the extension study where all participants received MRHC. Patient progress through the studies is summarised in Fig. 1. In the phase 3 study, dose titration for both treatment groups was conducted at 4 and 12 weeks, following instruction from independent titration physicians blinded to treatment, based on 24-h profiles of 17OHP and androstenedione (A4) and an investigator-completed adrenal insufficiency checklist compiling signs and symptoms of glucocorticoid over- or under-replacement. For the unblinded extension study, dose titration decisions were made by site investigators

at 4, 12, and 24 weeks and 6-monthly thereafter, based on measurements of 17OHP and A4 made at 09:00 and 13:00 and the adrenal insufficiency checklist. Dose titration rules for the phase 3 and extension study were otherwise identical, with dose adjustment performed to bring 17OHP to < 36 nmol/L and A4 into the reference range. The 36 nmol/L for 17OHP is approximately 3× the upper limit of the normal 'reference' range (3×ULN), and this level has previously been used to define an 'optimal range' because of the challenges in normalising 17OHP levels with physiological doses of glucocorticoid (10). Where 17OHP and A4 were inconsistent, precedence was given to A4 results. Hydrocortisone stress dosing and fludrocortisone dose adjustment occurred as medically indicated.

Assays

In the phase 3 study, 24-h 17OHP was measured at baseline 4, 12, and 24 weeks, and in the extension study, 09:00-h and 13:00-h 17OHP was measured at 6, 12, and 18 months. Hormones were measured in blood by HPLC–tandem mass spectrometry (Q² Solutions).
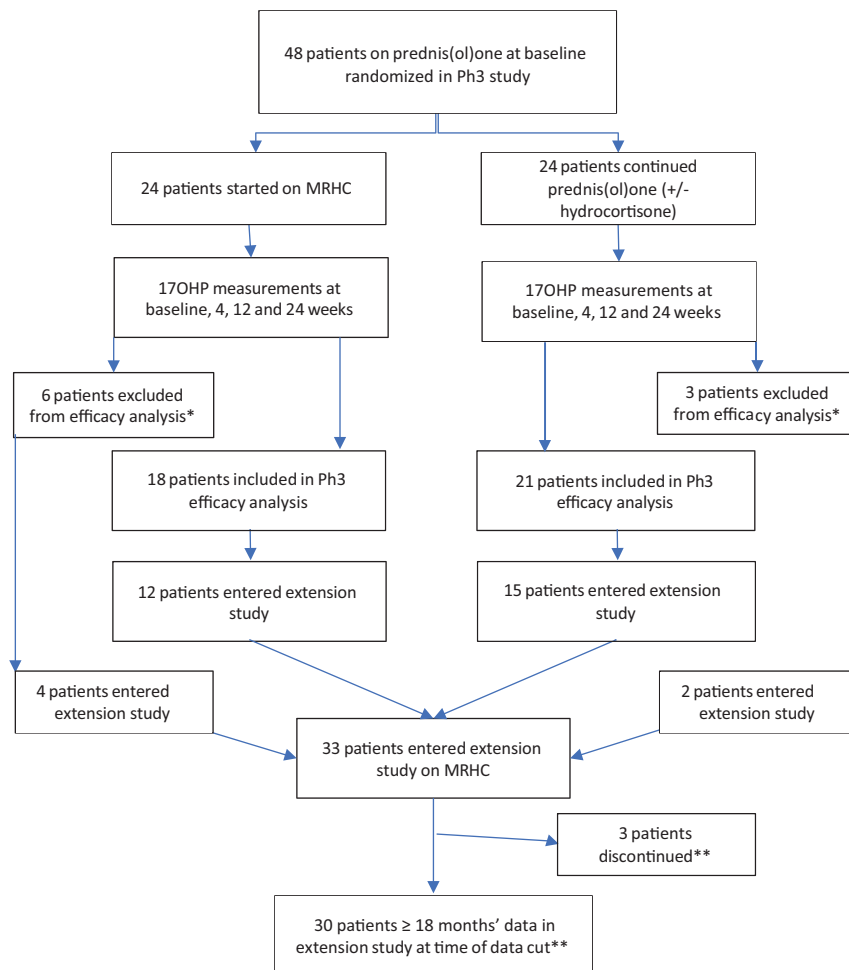
Figure 1

Consort diagram showing prednis(ol)one patients' path through the randomised phase 3 study and the single-arm extension study. *Patients were excluded from efficacy analysis from phase 3 study where data was lacking or as a result of protocol deviations. **Three patients discontinued from the extension study: one to pursue fertility treatment, one due to pregnancy, and one by physician/sponsor request. Each discontinued patient participated for > 2 years in the extension and is included in this analysis. Patients with < 18 months' treatment in the extension study are not included.

Statistical analysis

To compare 09:00-h 17OHP between arms in the phase 3 study, a two-tailed Mann–Whitney U test was applied. In the extension study, two quadrant analyses were conducted using individual patient 09:00-h 17OHP and HDE. Both analyses assessed whether patients' HDE exceeded the upper limit of current recommended treatment guideline doses (25 mg/day) (4). Two thresholds of 17OHP control were analysed, based on whether patients' 17OHP was above or below 36 nmol/L (3×ULN) and 12 nmol/L (ULN). Quadrant analysis was performed using the two-sided Fisher's exact test ($P < 0.05$ accepted significant). For comparison of daily dose from phase 3 baseline to 18 months in the extension study, a two-tailed Wilcoxon matched-pairs signed rank test was conducted.

Safety

Adverse events were recorded, including adverse events of special interest such as adrenal crisis, and have been reported for the whole cohort (15).

Results

Baseline characteristics

In total, 39/48 patients treated with prednis(ol)one, with or without hydrocortisone, were enroled in the phase 3 study and were included in the efficacy evaluable set. About 84% of patients were taking standard glucocorticoids after 18:00 h. Prednisolone was used in 34/39 patients in this group, and the remaining subjects (5/39) took prednisone. Their baseline characteristics are shown in Table 1, and the 17OHP 24-h profile in Fig. 2A. About 44% of these patients had an uncontrolled 09:00-h 17OHP > 36 nmol/L and 56% were on a HDE >25 mg at the time of study enrolment. These patients were randomised to either continue on prednis(ol)one or switch to MRHC.

## 17-hydroxyprogesterone levels and daily dose during phase 3 study

At baseline on prednis(ol)one, there was a rise in 17OHP overnight with some patients reaching very high levels in the morning, and a geomean 07:00-h 17OHP of approximately 36 nmol/L (Fig. 2A). Four weeks after randomisation, when patients were on the same HDE as baseline, the prednis(ol)one-treated patients had a similar 24-h profile to baseline, with an increase in the morning 17OHP. In contrast, the patients randomised to MRHC showed no overnight rise in 17OHP, and low levels throughout the 24 h (Fig. 2B). Table 2 and Fig. 2C show the 17OHP levels at 09:00 h and the HDE at baseline, 4, 12, and 24 weeks. 17OHP at 09:00 h was significantly lower in MRHC-treated patients compared to those continuing on prednis(ol)one at every time point after baseline. At 24 weeks, after dose titration in the phase 3 study, the median daily dose of MRHC was 28 mg/day and prednis(ol)one was 34 mg/day, with 94% and 71% of patients had 17OHP < 36 nmol/L on MRHC and prednis(ol)one, respectively.

17-hydroxyprogesterone levels and daily glucocorticoid dose during extension study

At the time of the interim analysis, 30 patients had a minimum of 18 months' data in the extension study during which the patients' glucocorticoid dose had been titrated by their clinician as per protocol. More patients had 09:00-h 17OHP < 36 nmol/L (3×ULN) on a HDE ≤ 25 mg on MRHC in the extension study than on their prednis(ol)one at baseline to the phase 3 study, 57% vs 27% ($P = 0.04$) (Fig. 3 and Table 3). At the interim analysis, 84% of patients had 17OHP < 36 nmol/L at 09:00 h, and the median HDE dose was 20 mg/day vs 25 mg/day at baseline ($P < 0.001$). Similarly, using the more stringent 17OHP threshold of < 12 nmol/L (ULN), more patients had 09:00-h 17OHP controlled on a HDE ≤ 25 mg on MRHC in the extension study than on their prednis(ol)one at phase 3 baseline, 43% vs 13% ($P = 0.02$).

Table 1 Baseline demographics for all patients and baseline prednis(ol)one patients entering the phase 3 study included in efficacy analysis.

	All subjects	Prednis(ol)one only
n	105	39
Female, n (%)	69 (66%)	29 (74%)
Age (median)	35	36
BMI (median)	27.06	27.06
Phase 3 initial dose (hydrocortisone-equivalent dose (HDE)	25	30
Patients on daily dose above 25 mg HDE, n (%)	43 (41%)	22 (56%)
Baseline 09:00-h 17-OHP (nmol/L) geomean	29.45	24.17
Patients with 09:00-h 17-OHP > 36 nmol/L at baseline, n (%)	53 (50%)	17 (44%)
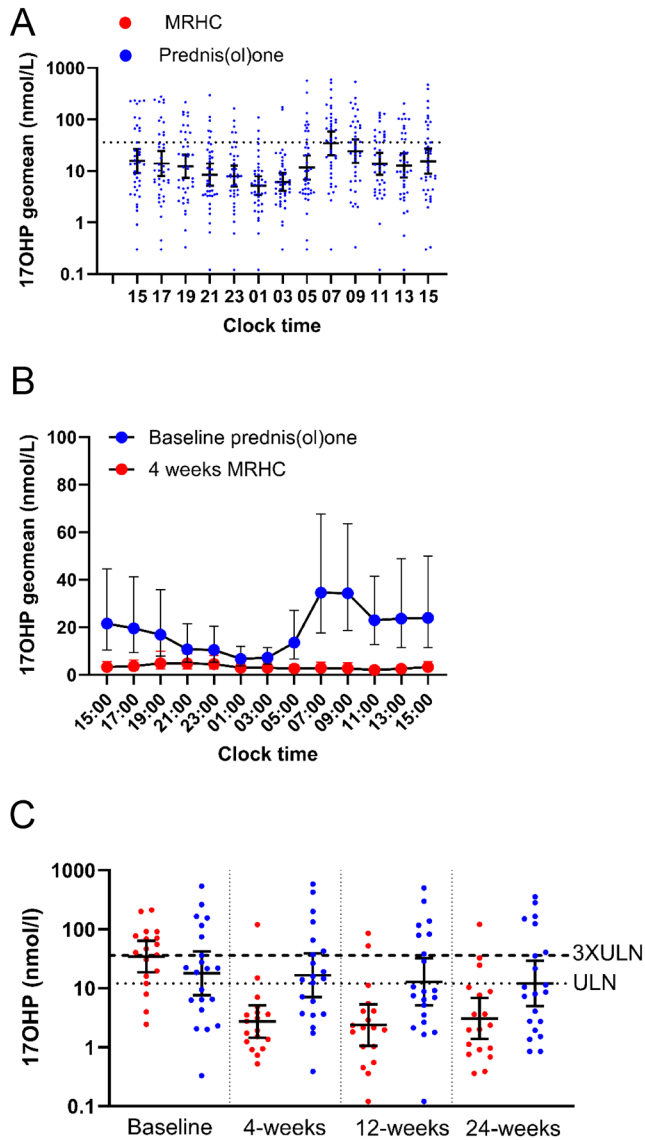
Figure 2

Data from patients taking prednis(ol)one at baseline in the phase 3 trial: (A) 24-h 17OHP profile at baseline (*n* = 39); (B) 24-h 17OHP profile at baseline and 4 weeks for subjects randomised to prednis(ol)one (*n* = 21) or MRHC (*n* = 18); (C) Scatter plot showing 9 am 17OHP for subjects randomised to MRHC and prednis(ol)one. MRHC red symbols, prednis(ol)one blue symbols.

Safety

In the phase 3 study, there were no adrenal crises reported in the MRHC group, and seven crises in three patients in the standard treatment arm, with one in the prednis(ol)one group. In the ongoing extension study of all patients on MRHC (221 patient-years), there were 12 reported adrenal crises in five patients (5.4/100 patient-years).

Discussion

This was the first prospective randomised study of glucocorticoid therapy in patients with CAH. A third of patients in the study were using prednis(ol)one at baseline. Patients on prednis(ol)one at baseline had an early morning rise in 17OHP, and approximately 50% had a 17OHP at 07:00 h above that considered optimal treatment. Four weeks after switching to an equivalent dose of MRHC, 94% of patients in the MRHC arm showed 17OHP < 36 nmol/L compared to 39% at baseline on their prednis(ol)one. When patients were titrated by their own clinician in the extension study, the dose of MRHC was down-titrated to a median dose of 20 mg/day, which is within the recommended treatment guideline dose (4).

A meta-analysis of glucocorticoid treatment regimens in CAH found 12 retrospective studies that compared prednisolone with immediate-release hydrocortisone (16). In terms of 17OHP levels, most of these studies did not find any significant differences between treatment groups; however, one study found that mean 17OHP levels were lower in those individuals treated with hydrocortisone (17). Prednisolone use was associated with a higher glucocorticoid dose than hydrocortisone and a significantly lower final height. Metabolic outcomes were variably reported, with some studies reporting lower cardiovascular risk factors on prednisolone but a higher incidence of osteoporosis and fractures (16). Prednisolone is not recommended for use in growing children with CAH because of its negative impact on growth (4). One of the challenges of comparing glucocorticoid treatment regimens is the conversion factor used to calculate the hydrocortisone dose equivalent, which is based on historical studies and refers to the anti-inflammatory effects of glucocorticoids. In the meta-analysis, a 4× prednisolone dose was used, and in our study and previous studies, a 5× prednisolone dose was used to calculate hydrocortisone dose equivalents (11). The recommended prednisolone dose for adrenally insufficient adults is prednisolone 3–5 mg/day (17), which equates to 15–25 mg/day HDE. In our study, the median dose at baseline on prednisolone was 30 mg HDE, which equates 6 mg on a 5× conversion or 7.5 mg on a 4× conversion, which is greater than what is recommended for adrenal replacement. In the prednisolone group, the dose was increased to 34 mg HDE to achieve 09:00-h 17OHP < 36 nmol/L in 71% of patients, whereas the patients switched to MRHC were down-titrated to 27.5 mg, and 09:00-h 17OHP <36 nmol/L achieved in 94% of patients. In the open-label MRHC extension study, patients were further down-titrated to a median hydrocortisone dose of 20 mg, which is within the guideline range (15–25 mg/day) (17), whilst 09:00-h 17OHP < 36 nmol/L was maintained in over 80% of patients although 16.7% of patients on a hydrocortisone dose < 25 mg had a 17OHP > 3×ULN and 30% > ULN. Our data confirm that prednisolone doses in

Table 2 09:00 h 17OHP and HDE in subjects at baseline, 4 weeks, and 24 weeks.

		MRHC, *n* = 18	Prednis(ol)one, *n* = 21	*P*
Baseline	17-OHP 09:00 h Geometric mean (nmol/L)	34	18	NS
	% Patients with 17-OHP < 36 nmol/L	39	71	
	Median daily dose (HDE (mg))	30	28	
4 weeks	17-OHP 09:00 h Geometric mean (nmol/L)	3	17	< 0.01
	% Patients with 17-OHP < 36 nmol/L	94	67	
	Median daily dose (HDE (mg))	30	28	
12 weeks	17-OHP 09:00 h Geometric mean (nmol/L)	2	13	< 0.01
	% Patients with 17-OHP < 36 nmol/L	88	67	
	Median daily dose (HDE (mg))	Not available	Not available	
24 weeks	17-OHP 09:00 h Geometric mean (nmol/L)	3	12	< 0.05
	% Patients with 17-OHP < 36 nmol/L	94	71	
	Median daily dose (HDE (mg))	28	34	
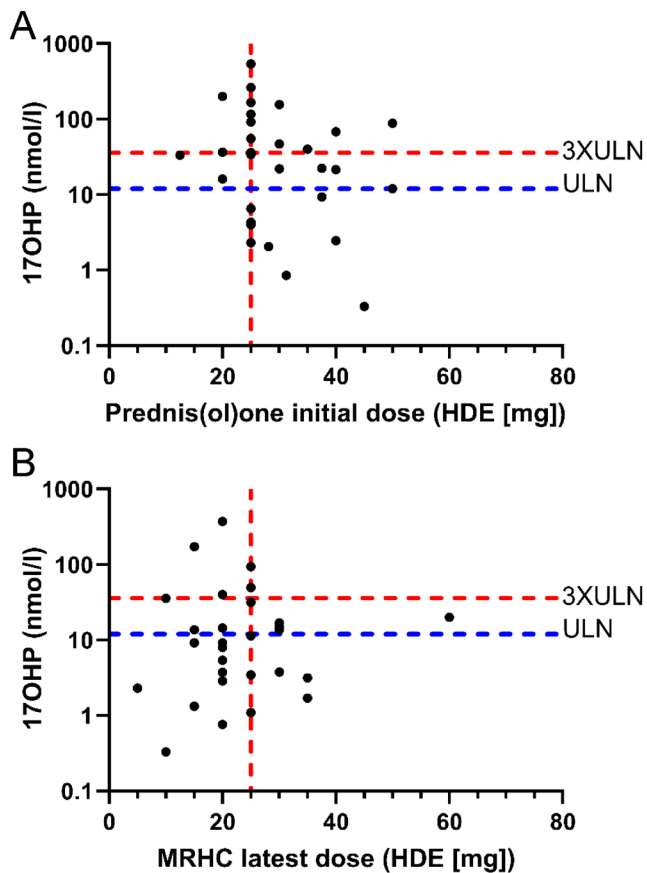
Figure 3

Quadrant analysis of daily glucocorticoid dose and 17OHP levels, comparing phase 3 study baseline on prednis(ol)one to 18 months on MRHC in the extension study (*n* = 30). The horizontal dotted red line represents 09:00-h 17OHP of 36 nmol/L and the vertical dotted red line represents HDE of 25 mg, the upper limit for the daily recommended hydrocortisone dose in adults. (A) Data at baseline and (B) data at 18 months on MRHC in the extension study. MRHC patients move to the bottom left quadrant, showing better control of 17OHP on a lower dose of glucocorticoid (*P* = 0.04).

excess of the guideline range are used in patients with CAH, and despite this, 24-h 17OHP profiles demonstrate that androgens remained poorly controlled during the important early morning period. In contrast, 17OHP can be better controlled in some patients throughout the 24-h period on MRHC, similar to that seen in healthy subjects who have minimal variation in 17OHP over 24 h (18). We focused on 17OHP in this study because one of the learnings from our studies is that when biochemical control is improved, A4 levels become low (15). We believe this is because in health, A4 is generated from DHEA through the classic androgen pathway, whereas in CAH, the classic pathway is down-regulated and A4 is generated from 17OHP. So, as 17OHP comes down, the A4 levels may be very low (19). Thus, 17OHP is the more sensitive marker of CAH biochemical control.

Health outcomes in patients with CAH are poor, and this is considered related to excessive glucocorticoid treatment (20). This is exemplified in the recent publication of the NIH natural history study, where 56% of children and 49% of adults with CAH were obese with increased cardiovascular risk (5), and fracture risk increased with glucocorticoid dose (21). The major challenge in glucocorticoid therapy in CAH is controlling the early morning rise in adrenal androgens, and for this reason, clinicians have used reverse circadian dosing with a dose of glucocorticoid at night. This was true of the patients in this prospective randomised study. This is unphysiological, providing a dose of glucocorticoid at the time of sleep onset when cortisol levels are low. Anecdotally, some patients complain it stops them from sleeping, and there is some evidence that dosing glucocorticoid in the evening results in an adverse metabolic profile in patients with adrenal insufficiency (3), and increased 24-h cortisol exposure, as seen in stress, is associated with increased risk of metabolic syndrome (22). Prednisolone has a longer half-life than hydrocortisone, but despite this, levels peak shortly after going to sleep and have waned by the time of waking and do not control ACTH in the majority of patients (9). Consistent with this, in the present study,

Table 3 Proportion of patients in each quadrant.

	Baseline on prednis(ol)one		18 months on MRHC	
	≤ 25 mg dose	> 25 mg dose	≤ 25 mg dose	> 25 mg dose
Treatment outcome quadrant analysis based on 3×ULN				
> 3×ULN	8/30 (26.7%)	5/30 (16.7%)	5/30 (16.7%)	0/30 (0%)
≤ 3×ULN	8/30 (26.7%)	9/30 (30%)	17/30 (56.7%)[a]	8/30 (26.7%)
Treatment outcome analysis based on ULN				
> ULN	12/30 (40%)	8/30 (26.7%)	9/30 (30%)	3/30 (10%)
≤ ULN	4/30 (13.3%)	6/30 (20%)	13/30 (43%)[b]	5/30 (16.7%)

[a]Change from baseline in number of patients on dose ≤ 25 mg and 17OHP ≤ 3×ULN $P = 0.04$; [b]Change from baseline in number of patients on dose ≤ 25 mg and 17OHP ≤ ULN $P = 0.02$.

24-h profiles taken in patients at baseline indicate that despite supraphysiological doses of a glucocorticoid with a longer half-life, 17OHP levels are raised in the early morning. In contrast, MRHC has delayed release such that there is no exposure to cortisol last thing at night before going to sleep, and levels build to peak in the early morning (13). In cohort studies of CAH patients on standard treatment, approximately a third of patients have biochemical control on physiological doses of glucocorticoid. MRHC improves the biochemical control of CAH over standard treatment, but it is clear there are still patients that require a high dose of glucocorticoid. The dose required reduced over time in patients on MRHC, and it is possible that with improved control, the hyperplastic adrenal becomes less sensitive to ACTH or the HPA less active, but other variables such as genotype, pharmacokinetics, and sensitivity to cortisol may be important in determining biochemical control.

Patients with CAH have increased mortality up to five times that of the healthy population (23, 24), with adrenal crisis as the leading cause of death (24). There has been no comparison of prednisolone vs hydrocortisone on mortality in CAH; however, in primary adrenal insufficiency, there is evidence that prednisolone treatment is associated with increased mortality compared to hydrocortisone (12). Deaths from infections are higher in adrenal insufficiency, and adrenal crisis still accounts for 10% of the mortality (25). In our study, the safety profile was overall similar between standard therapy and hydrocortisone although there was one adrenal crisis in the prednisolone group and none on MRHC. In the extension study on MRHC, the incidence of adrenal crisis was at the low end of that reported in the literature (26, 27).

The limitations of this study include the relatively short duration of the randomised study for looking at the impact of glucocorticoid on clinical and metabolic outcomes; long-term studies are required to study the impact of changing glucocorticoid dose. The current guidance for glucocorticoid use in CAH is to use the lowest dose of glucocorticoid required to control androgens, and the recommendation is not to normalise 17OHP as this generally results in overtreatment with standard glucocorticoid therapy (6). For this reason, it has been recommended that optimal control of CAH is 17OHP < 36 nmol/L, approximately three times the upper limit of the 17OHP reference range. Our results show that some (43%), but not the majority, of patients with CAH can have 17OHP controlled within the reference range on a dose of MRHC within the current guideline range for hydrocortisone. To reduce the dose of glucocorticoid to less than a replacement dose would increase the risk of adrenal crisis. Thus, future studies and guidelines will need to revise their advice regarding the parameters for optimal control of CAH.

In conclusion, our study shows that MRHC reduces morning 17OHP compared to prednis(ol)one. When the MRHC dose was titrated by clinicians, the median daily dose was 20 mg.

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