

Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency

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Summary

OBJECTIVE The objective of this study was to examine the variables determining hydrocortisone (HC) disposition in patients with adrenal insufficiency and to develop practical protocols for individualized prescribing and monitoring of HC treatment.

DESIGN AND PATIENTS Serum cortisol profiles were measured in 20 cortisol-insufficient patients (09–00 h cortisol < 50 nmol/l) given oral HC as either a fixed or 'body surface area-adjusted' dose in the fasted or fed state. Endogenous cortisol levels were measured in healthy subjects. Pharmacokinetic analysis was performed using P-Pharm software, and computer simulations were used to assess the likely population distribution of the data.

RESULTS Body weight was the most important predictor of HC clearance. A fixed 10-mg HC dose overexposed patients to cortisol by 6.3%, whereas weight-adjusted dosing decreased interpatient variability in maximum cortisol concentration from 31 to 7%, decreased area under the curve (AUC) from 50 to 22% ($P < 0.05$), and reduced overexposure to < 5%. Food taken before HC delayed its absorption. Serum cortisol measured 4 h after HC predicted cortisol AUC ($r^2 = 0.78$; $P < 0.001$).

CONCLUSIONS We recommend weight-adjusted HC dosing, thrice daily before food, monitored with a single serum cortisol measurement using a nomogram.

This regimen was prospectively examined in 40 cortisol-insufficient patients, 85% of whom opted to remain on the new thrice-daily treatment regimen.

All physicians will encounter patients with adrenal insufficiency. Hydrocortisone (HC), the generic pharmaceutical name for cortisol, is the preferred replacement therapy for these patients (Ten *et al.*, 2001; Arlt & Allolio, 2003). Some physicians use longer-acting steroids such as prednisolone or dexamethasone. However, there is no universal agreement regarding the appropriate dose, timing or monitoring of replacement therapy (Howlett, 1997). Chronic overtreatment theoretically may predispose to some complications associated with glucocorticoid excess such as osteoporosis (Peacey *et al.*, 1997). However, in hypopituitarism there is no evidence that conventional HC therapy results in an increased mortality (Tomlinson *et al.*, 2001). Undertreatment is potentially life-threatening, presenting with chronic fatigue and reduced resistance to illness (Axelrod, 2001; Arlt & Allolio, 2003). Therefore, optimization of HC replacement therapy is important.

Currently, HC doses prescribed for adults are based on cortisol production rate and the practicalities of taking oral HC. Original estimates of endogenous cortisol production (12–15 mg/m²/day) were high and resulted in a common overtreatment regimen of HC 20 mg in the morning and 10 mg in the evening. Current therapy, based on more accurate estimates of cortisol production; 6–11 mg/m²/day; (Linder *et al.*, 1990; Kraan *et al.*, 1998), is generally given as HC 10–20 mg/m²/day, allowing for incomplete oral bioavailability (Ten *et al.*, 2001). In a retrospective audit of patients from one centre, the recommendation was a fixed-dose, thrice-daily HC treatment regimen, regardless of patient size (Howlett, 1997). The smallest available oral HC tablet in the UK is 10 mg, making it difficult to administer doses that are not multiples of its quarter, although a 5 mg tablet is available in the USA.

Some clinicians use measurement of serum cortisol concentration to assess the adequacy of HC treatment (Feek *et al.*, 1981; Trainer & Besser, 1995). This may be important when determining whether symptoms of fatigue are due to HC underdosing. A variety of options have been recommended, from the measurement of peak and trough concentrations to intensive and inconvenient 6-h cortisol profiles. Patients are generally advised to take their first dose of HC on waking to simulate the normal circadian

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rhythm of cortisol (Krieger *et al.*, 1971). However, cortisol profiles after HC are measured later in the morning to fit with clinic routine and might therefore be assessed in either the fasted or the fed state. The effect of food on cortisol kinetics was studied in patients with adrenal insufficiency after a 25 mg dose of cortisone acetate, but observed increases in maximum concentration (C_{\max}) and area under the curve (AUC) were considered to be without clinical implications (Aanderud & Myking, 1981). However, another study in healthy subjects who were given high-dose HC (60 mg) showed that HC absorption was delayed and inconsistent in the nonfasting state (Barbhaiya & Welling, 1982).

We have performed a controlled study to examine variables that may influence HC disposition. Based on the findings, we provide improved dosage recommendations for replacement therapy. In addition, we propose a monitoring regimen based on the measurement of a single blood sample drawn in the clinic.

Subjects and methods

Subjects

We studied cortisol pharmacokinetics in two groups of adrenal-insufficient patients and a group of healthy subjects. The introduction of a new HC regimen was then monitored prospectively. The studies were approved by the North Sheffield Local Research Ethics Committee, and participants gave written informed consent. All patients in the pharmacokinetic studies had primary or secondary adrenal insufficiency (hypothalamic–pituitary disease not adrenal suppression due to exogenous glucocorticoids) with a 09:00 h serum cortisol level off treatment < 50 nmol/l. The results of renal and liver function tests were normal. Healthy controls were matched to the second group of patients for gender, age, height, weight and body-surface area (BSA) within 10% of individual patients. Patients on oestrogen replacement were studied after having stopped this therapy for 6 weeks. No patient was taking any medication known to alter cortisol metabolism.

Study 1: Pharmacokinetics of HC after a fixed 10 mg oral dose

Ten patients [five males, five females; four primary hypoadrenalism; age 32–72 years; weight 57.6–99.8 kg; body mass index (BMI) 21.7–35.8 kg/m²] attended the investigation unit on three occasions. They discontinued HC replacement from noon on the day prior to the study and fasted from midnight. On the first and third occasions, patients were given breakfast 3 h after their HC and, on the second occasion, they received a standard breakfast 20–30 min before receiving HC. On each of the 3 study days the patients received 10 mg of HC (Hydrocortone™, Merck, Sharp & Dohme) orally, between 08:00 and 09:00 h. Peripheral venous blood samples were drawn immediately before dosage and at

20, 40, 50, 60, 70, 80, 90, 100, 120, 180, 240, 300 and 360 min after dosage.

Study 2: Pharmacokinetics of HC after individually tailored oral doses

We studied a further group of 10 patients (six males, four females; six primary hypoadrenalism; age 46–68 years; weight 56.6–112.4 kg; BMI 24.4–35.5 kg/m²) after giving them HC doses of 5.5 mg/m² BSA (to the nearest practical dose unit) at 08:30 h, 1 h before breakfast. We derived the dose to minimize intersubject variability in HC kinetics based on analysis of the Study 1 data. A tablet cutter was used to adjust the HC dose in 2.5 mg quanta, that is quarters of 10 mg tablets. Thus, the absolute dose ranged from 7.5 to 12.5 mg. Blood sampling was as in Study 1. We measured serum concentrations of endogenous cortisol in seven healthy subjects (three males, four females; age 44–68 years; weight 61–87 kg; BMI 23.2–28.7 kg/m²) at the same time points as the patients but without ingestion of HC.

Prospective monitoring of a weight-related HC treatment regimen

Based on the data from Studies 1 and 2, we developed a new HC treatment and monitoring regimen (Table 3). This was tested prospectively in a further 40 adrenal-insufficient patients (20 males, 20 females; age 17–78 years; weight 55.0–122.6 kg). The patients were instructed to use a tablet cutter to divide the 10 mg HC tablets into quarters. A week after changing the HC regimen, patients attended for a single blood sample approximately 4 h after their morning dose of HC. They were questioned specifically about fatigue, dizziness and nausea before and after any change in HC dose.

Data analysis

Kinetic analysis of the serum cortisol concentration–time profiles in the patients was carried out using a user-defined model within the software package P-Pharm (version 1.5, InnaPhase, France), assuming monoexponential disposition, first-order absorption, and a baseline correction to account for any endogenous levels of cortisol (Barbhaiya & Welling, 1982; Toothaker *et al.*, 1982; Heazelwood *et al.*, 1984; Derendorf *et al.*, 1991). Values of oral clearance (CL/F), volume of distribution (V/F), apparent absorption rate constant (k_a) and absorption lag time (t_{lag}) were obtained from the model fitting, and were used to derive other parameter values. Bias in dosing was assessed as the percentage difference in AUC values in patients compared to the mean AUC of endogenous cortisol in the healthy subjects over the same time period. Variability in serum cortisol concentration–time profiles in patients was expressed by the coefficient of variation (CV). Analysis of

Table 1 Variability (CV) and bias (percentage difference from healthy matched controls of AUC) for patients on different hydrocortisone regimes

HC regime	Variability in C_{\max} (%)	Variability in AUC (%)	% Bias (AUC)
Fixed 10 mg, fasted	31	50	6.3
Fixed 10 mg, fed	36	45	24.5
BSA-adjusted (5.5 mg/m ²), fasted	10*	24**	7.4
Weight-adjusted (0.12 mg/kg), fasted†	7*	22**	4.6

HC, hydrocortisone; BSA, body surface area; AUC, area under the curve; C_{\max} , peak serum cortisol level.

* $P < 0.001$ vs. fixed dose. ** $P < 0.05$ vs. fixed dose. †If weight adjustment was assumed.

variance (ANOVA) was used to assess the effect of food intake in Study 1, accounting for repeat individual measurements in the fasting state. BSA, weight, height, BMI, dose of HC, gender and age were also investigated as covariables. All statistical analyses were carried out using SPSS version 10.0 (SPSS Inc, USA).

Initial analysis of the data from Study 2 showed that, if the dose had been adjusted for weight (0.12 mg/kg), the interpatient variability in C_{\max} and AUC would have been lower. Owing to the discrete nature of dose increments (multiples of 2.5 mg), nine of the 10 patients who had taken the BSA-adjusted HC dose would still have required the same dose if this had been weight-adjusted. Only one of the 10 patients would have required a reduction in the HC dose (from 12.5 mg to 10.0 mg) to be in the nearest weight-adjusted dose range. Therefore, in the part of the analysis relating to body weight-adjusted dosage, we normalized the serum cortisol levels of this patient to a 10.0 mg dose assuming concentration–dose proportionality.

To assess the optimal dosage regimen of HC in patients with adrenal insufficiency, simulations were carried out using the Solver tool in Microsoft Excel™, with the aim of minimizing the residual sum of squares between the simulated 24-h serum HC profile and measured 24-h profiles reported in the literature (Chakraborty *et al.*, 1999). Constraints on the simulated dosage regimen were a maximum of three doses between 06.00 and 22.00 h and a minimal 2.5 mg increment of HC dosage (compatible with quartering of the available 10 mg tablet).

Based on the results of Studies 1 and 2, Monte Carlo simulations were carried out in virtual patients ($n = 1000$; 32–72 years), using demographic information available for the UK population (Prescott-Clarke & Primates, 1996), to construct a nomogram showing the likelihood of the expected serum cortisol concentration at 2.5–5 h after early morning intake of HC. Mathcad (Version 6; MathSoft, Edinburgh) was used to generate random numbers and to run the simulations.

Assay

Serum was separated from the blood samples immediately after collection, and stored at -20°C until assay. Cortisol concentrations were measured using an ACS:180 automatic chemiluminescence

system (Kiron Diagnostic Corporation, East Walpole, USA). The intra- and interassay CVs of the method were less than 7.6%.

Results

Variables affecting cortisol kinetics

In Study 1 there was considerable intersubject variability in C_{\max} and AUC values in patients receiving a fixed 10 mg oral dose of HC taken in the fasted state (Fig. 1a; Table 1). In contrast to intersubject variability, within-subject variability was low, and the two mean cortisol profiles measured in the fasted state were superimposable (Fig. 1b). Food intake prior to HC ingestion prolonged its absorption half-life (mean \pm SEM fed vs. fast, 43 ± 12 vs. 15 ± 4 min; $P = 0.002$) and decreased its oral clearance (0.226 ± 0.031 vs. 0.270 ± 0.027 l/min, $P = 0.05$). In Study 2 the intersubject variability in C_{\max} and AUC values was significantly decreased when a BSA- or weight-adjusted dose of HC was assumed (Fig. 1c; Table 1). Weight, height and BSA were major variables affecting HC kinetics, and HC dose also made a significant contribution (Table 2); however, age and gender had no significant effect. Of these covariates, weight had the greatest effect on HC clearance.

Table 2 Stepwise multiple linear regression analysis of patient variables with parameters of HC disposition

Parameter	Covariate	P -value of each covariate	r^2
HC clearance	Weight	< 0.001	0.380
	Dose	0.042	
Oral volume of distribution	Height	< 0.001	0.421
	Dose	0.033	
C_{\max}	BSA	< 0.001	0.604
	Dose	< 0.001	

HC, hydrocortisone; C_{\max} , peak serum cortisol level; BSA, body surface area. Variables tested: age, gender, weight, height and BSA.

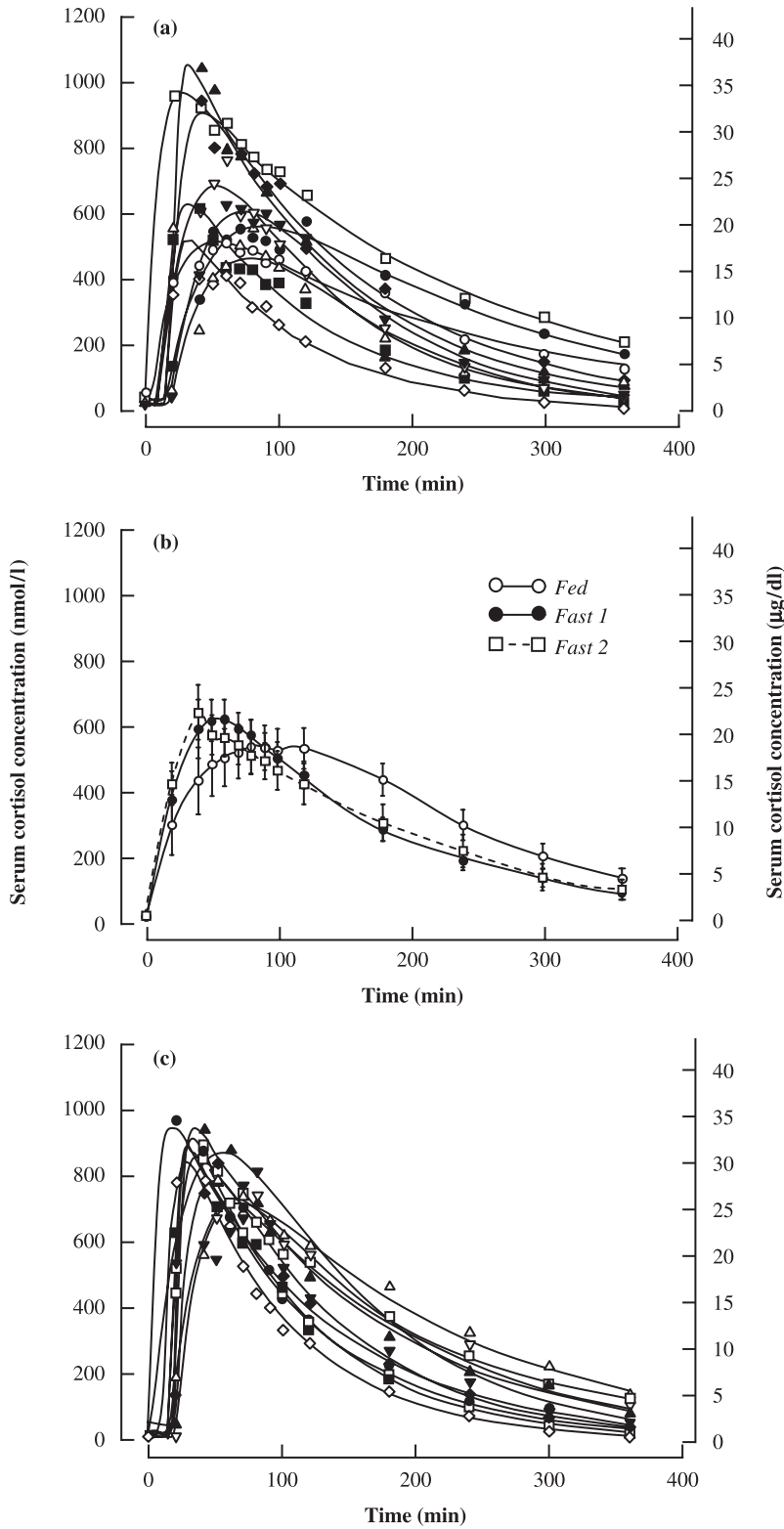


Fig. 1 (a) Serum cortisol concentrations in 10 fasted patients after taking a fixed dose of 10 mg hydrocortisone; (b) mean serum cortisol concentrations following a fixed dose of 10 mg hydrocortisone, in fasting and fed states; and (c) serum cortisol concentration in 10 fasted patients after taking a weight-adjusted (0.12 mg/kg) dose of hydrocortisone. Divide serum cortisol concentration in nmol/l by 27.59 to get µg/dl.

Fig. 2 Range of area under the curve (AUC) values according to study groups. The mean AUC value is shown as a solid line in each group and individual data are shown as filled circles. The shaded area represents the 95% confidence intervals (CI) for observations in the healthy control group with their mean value being represented by the continuous line.

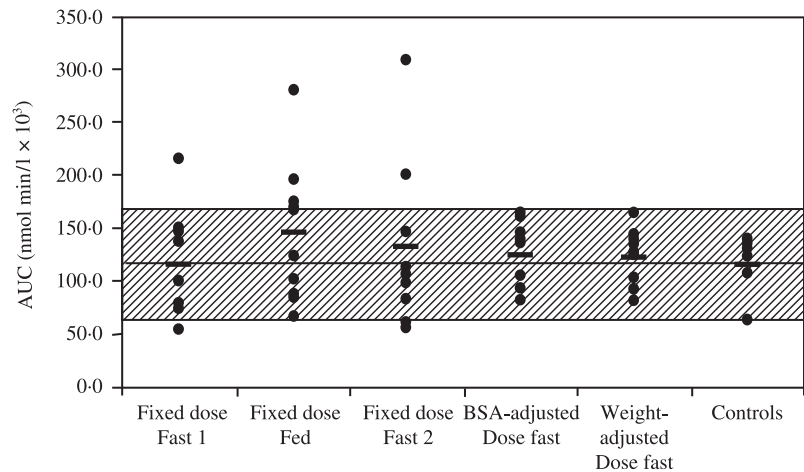


Table 3 Suggested hydrocortisone dosing regime using 10 mg HC (Hydrocortone, Merck Sharp & Dohme) and dividing tablets into 2.5 mg quanta using a tablet cutter

Patient weight (kg)	Total dose per day (mg)	First morning dose (mg)	Second midday dose (mg)	Third evening dose (mg)
50–54	10.0	5.0	2.5	2.5
55–74	15.0	7.5	5.0	2.5
75–84	17.5	10.0	5.0	2.5
85–94	20.0	10.0	7.5	2.5
95–114	22.5	12.5	7.5	2.5
115–120	25.0	15.0	7.5	2.5

HC exposure in patients relative to controls

The serum cortisol profiles after HC administration in Studies 1 and 2 were compared to the mean profile of endogenous cortisol in our control subjects. The effects of using different fixed doses (7.5–12.5 mg) were simulated using the observations on the 10 mg dose. Treatment with a 10 mg fixed dose of HC in the fasting state was associated with a 6.3% overexposure of patients to cortisol compared to that in our controls, and this was even greater in the fed state (24.5%). The AUC of exogenous HC in patients compared to the endogenous AUC in healthy control subjects indicated the least bias when dosage was adjusted for weight (4.6%) and BSA (Fig. 2; Table 1).

Single point prediction of AUC

Correlation coefficients for the observed AUC values in Study 1 patients and those predicted from their serum cortisol concentrations at specific times were: 240 min ($r = 0.885$, $P < 0.001$), 40 + 240 min ($r = 0.912$, $P < 0.001$), 60 + 180 + 240 min ($r = 0.950$, $P < 0.001$), and 40 + 60 + 180 + 240 min ($r = 0.950$, $P < 0.001$). Thus, 78% of the variability in AUC was explained by the serum cortisol concentration at 240 min. The predicted AUC based on the serum cortisol value from this sample point was

concordant with observed values both in the original set (30 samples from 10 patients in Study 1) and in the independent group of 10 patients in Study 2 ($r^2 = 0.78$).

Design of optimal HC treatment regimens

The data used for the above analysis refer to the first morning dose of HC. The total daily dose and regimen of administration were estimated using 24-h cortisol profiles reported in the literature (Chakraborty *et al.*, 1999), and the pharmacokinetic parameters defined by our study. The results show that thrice-daily administration given on a weight-related basis provides optimal replacement within the constraints of the current HC formulation (Table 3 and Fig. 3a). Patients have their lowest cortisol level first thing in the morning, at the time of highest endogenous cortisol levels. It is evident from the simulated profiles that it is not possible to mimic normal cortisol profiles with the current formulations of HC.

Nomogram to adjust dosage based on serum cortisol concentration

The predicted population distribution of the serum cortisol concentration–time profile from 150 to 300 min after a 0.12 mg/kg

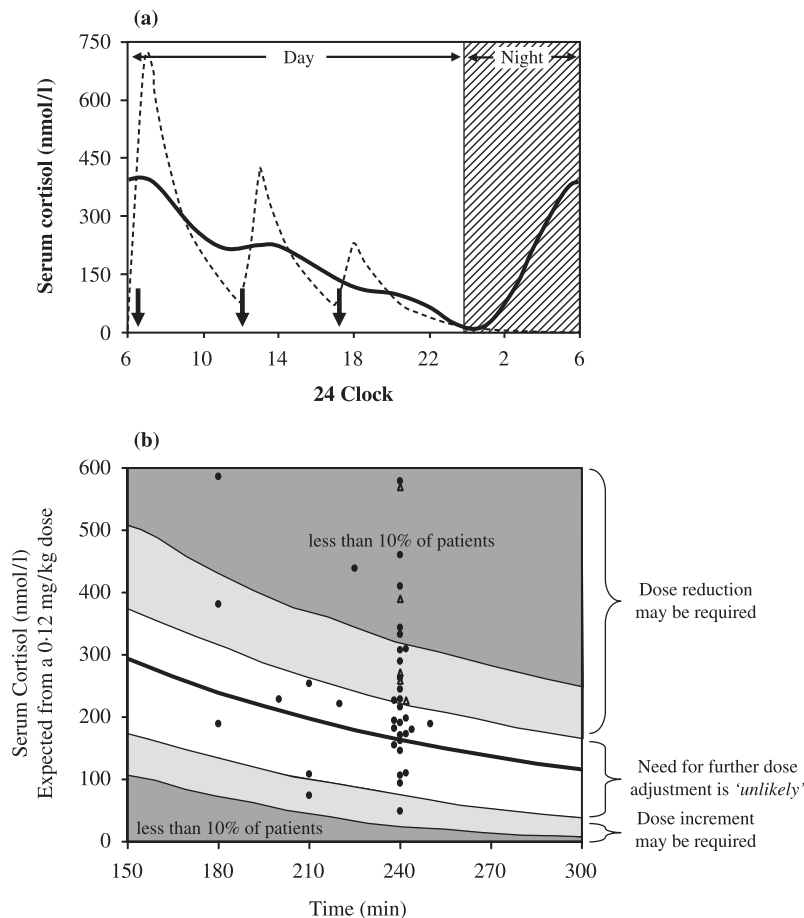


Fig. 3 Circadian rhythm of serum cortisol in normal subjects from published data (solid line): (a) simulated cortisol profile for a patient (broken line) following thrice-daily hydrocortisone administration (10 mg at 06:00 h, 5 mg at 12:00 h and 2.5 mg at 18:00 h, shown as solid arrows); (b) nomogram for individual adjustment of hydrocortisone dosage based on serum cortisol estimation 2.5–5 h after a morning HC dose taken on an empty stomach. (The lines represent the 10th, 25th, 50th, 75th and 90th centiles, the closed circles represent the single cortisol level of each patient on the weight-related HC regime, and the open triangles are the repeat cortisol levels from a full cortisol profile of patients who had an initial level outside the 10th–90th centiles of the nomogram. Two patients with serum cortisol values of 776 nmol/l at 240 min and 641 nmol/l at 270 min, respectively, are not shown in the nomogram as the values were outside the borders of the nomogram. These data are discussed in the text.) Divide serum cortisol concentration in nmol/l by 27.59 to get $\mu\text{g/dl}$.

dose of HC is shown in Fig. 3b. This nomogram is designed to allow adjustment of an individual's HC dosage using a single serum sample. Thus, a cortisol level falling within the 10th to 90th centiles indicates that the HC dose taken by the patient would result in the predicted cortisol profile (AUC). Cortisol levels below the 10th centile indicate that the patient may require further investigation with regard to possible malabsorption and the HC dose may need to be increased. By contrast, if a cortisol level is above the 90th centile, the HC dose may need to be reduced.

Prospective testing of the new HC treatment regimen

A further 40 patients have been prescribed the weight-related HC regimen according to the dose scheme shown in Table 3. Consequently, 31 (77.5%) patients had a reduction in total daily HC dose, ranging from 2.5 to 17.5 mg, three (7.5%) patients had an increment in HC dose of 2.5 mg and for the remaining patients there was either no dose change or they were starting HC therapy. Thirty-nine (97.5%) patients have had their serum cortisol level

measured at approximately 3–5 h after their morning dose of HC and the values are plotted in Fig. 3b. Thirty (76.9%) patients had serum cortisol levels within the 10th to 90th centiles of the nomogram, and in each of the nine (23.1%) patients with cortisol levels outside these limits the levels were above the 90th centile. One patient reverted to his previous higher dose prior to monitoring of his serum cortisol because he felt unwell. Six of the nine patients whose serum cortisol level was above the 90th centile of the nomogram had their cortisol profile measured. The shapes of these were similar to those observed in the patients who took part in the pharmacokinetic study. In four patients, their repeat 4-h cortisol level was within the 10th to 90th centile, whereas in the other two, although there was a reduction in their serum cortisol level, it remained above the 90th centile.

The patients were asked whether they wished to continue with the new, weight-related HC regimen or revert to their previous regimen. Six (15%) patients asked to revert to their previous HC regimen, all of whom had originally been on a higher total daily HC dose.

Discussion

Body weight and BSA are important variables determining HC clearance such that prescribing a fixed dose to all patients results in greater under- and overtreatment (bias) compared to weight-adjusted dosing (bias < 5%). A weight-adjusted HC dosage of 0.12 mg/kg for the morning dose produces serum cortisol profiles with less interpatient variability and is associated with AUC values similar to those of endogenous cortisol in matched controls over the same study period (08.00–14.00 h). It is important to note that endogenous cortisol levels reach their highest levels within 30 min of waking and therefore this comparison does not take into account the early morning peak. However, the thrice-daily hydrocortisone replacement regimen we describe recommends taking the first dose of hydrocortisone on waking and, because of the pharmacokinetics of HC, the peak cortisol following the first dose is likely to be higher than the predicted endogenous early morning cortisol peak although the trough level before the next dose will be lower than the predicted endogenous level (Fig. 3a). Characterization of full serum cortisol profiles after a single HC dose is carried out in some clinics (Trainer & Besser, 1995). However, this approach is expensive, inconvenient and time-consuming. Based on our data, a single measurement of cortisol at 240 min following weight-adjusted HC ingestion can predict cortisol AUC reliably in the majority of patients. In a few patients the measurement of full cortisol profiles may still be necessary. However, the dosage regimen that we recommend should decrease the number of such studies allowing greater patient convenience and cost-saving. In addition, it should be recognized that a reduction in HC dose may result in an increased requirement for fludrocortisone. We accept that using current preparations of hydrocortisone it is not possible to replicate normal physiological cortisol secretion and our protocol is an attempt to optimize replacement with the current HC preparations available.

The peak morning serum cortisol concentration in healthy individuals is usually between 400 and 800 nmol/l, and the nadir during the day is greater than 100 nmol/l (Krieger *et al.*, 1971; Ross *et al.*, 1991). However, conventional HC therapy regimens commonly result in higher peaks and lower troughs (Scott *et al.*, 1978; Howlett, 1997). We have modelled an HC replacement regimen to provide cortisol profiles as close to physiological levels as practical within the constraints of the current HC preparation (Fig. 3a; Table 3). On this basis, we recommend a thrice-daily treatment regimen of HC taken before food. This regimen does require a high level of compliance and may not be suitable for all patients, although previous studies have reported that over 50% of patients may take their HC thrice daily (Howlett, 1997). A previous study suggested that feeding has little impact on clinical outcome, despite the demonstration that it alters cortisone absorption (Aanderud & Myking, 1981). We would challenge this statement and argue for taking HC in the fasted

state for two main reasons; first, absorption of HC is delayed in the fed state and the aim in the morning is to achieve a peak level as quickly as possible; second, feeding increases variability in HC absorption. Our studies have only examined the effect of delaying breakfast by 1–3 h. In practice, we advise patients to take their first dose of HC on waking, and for most patients this is timed for at least 15–60 min before food, although we recognize that we have not specifically tested this regimen.

Cortisol, although secreted in the unbound state, binds to plasma proteins, cortisol binding globulin (CBG, transcortin) and, to a lesser extent, albumin (Hammond, 1990). Under basal conditions about 5–10% of circulating cortisol is free, about 75% is bound to CBG, and the remainder is bound to albumin. However, it is the free level that is sensed and regulated by the corticotrophin (CRH)–ACTH axis. Normal CBG has a cortisol-binding capacity of approximately 25 µg/dl; increases in total plasma cortisol concentrations above 550 nmol/l exceed the binding capacity of CBG and result in rapid increases in levels of free cortisol concentration (Tunn *et al.*, 1992). The cortisol-binding capacity of albumin is greater than that of CBG, but its affinity is lower. In normal individuals there are circadian fluctuations in the capacity of CBG for cortisol, which are lost in patients on chronic replacement (Angeli *et al.*, 1978). Animal studies have suggested CBG levels peak at around 18.00 h (Hsu & Kuhn, 1988), and it has been suggested that an evening dose of HC may have delayed clearance (Charmandari *et al.*, 2001). It is possible that when HC is given as a more physiological replacement, the circadian rhythm of CBG will return and this will need to be accounted for in refined HC treatment regimens. Our thrice-daily replacement regimen aims to keep the peak cortisol low while attempting to replicate the normal circadian rhythm of cortisol, although it can be seen that especially after the first morning dose of HC the peak exceeds 550 nmol/l.

Our recommended total daily HC dose (15 mg HC) for a 70 kg patient (175 cm height) is approximately 8.1 mg/m²/day, which is similar to the estimated cortisol production rate (Linder *et al.*, 1990). Clinicians generally give a higher replacement dose assuming incomplete absorption and first-pass hepatic metabolism (Ten *et al.*, 2001). There have been contradictory reports regarding the extent of the oral bioavailability of cortisol. Early studies suggested that this was very variable, ranging from 26 to 91% (mean 54 ± 6.9%) (Heazelwood *et al.*, 1984), but more recently, two separate groups reported that the absorption of HC is rapid and its oral bioavailability is almost complete (94–96%) (Derendorf *et al.*, 1991; Charmandari *et al.*, 2001). Our proposed treatment regimen is based on pharmacokinetic studies performed using an early morning dose of HC. Although HC bioavailability in the evening is likely to be the same, clearance may be lower at this time (Charmandari *et al.*, 2001). Our recommended total daily and individual HC doses are lower than those currently used by many clinicians and are based on the principle that HC

replacement therapy should replicate normal physiology. It is possible that, because current preparations of HC do not allow normal physiological replacement (cortisol levels are low first thing in the morning), patients require suprphysiological levels of cortisol at other times of the day. We suggest that changes in HC replacement require careful monitoring, including specific questioning about fatigue. Patients also need appropriate advice on increasing their HC dose when unwell.

Changes in cortisol metabolism with increasing BMI have been described (Stewart *et al.*, 1999) and may be a consequence of enhanced A-ring reductase activity as well as decreased 11-beta-hydroxysteroid dehydrogenase type 1 reductase activity. Both these mechanisms may serve to decrease cortisol half-life. This fact and our results emphasize the need to increase HC replacement with increased body weight.

We were concerned that our new treatment regimen would underdose patients. Based on 4-h cortisol sampling, this does not appear to be the case as all patients had 4-h cortisol values above the 10% confidence interval. In practice, patients are usually encouraged to take their first dose of HC on waking in the fasted state, whereas cortisol profiles are measured later in the morning, often in the fed state. We recommend that patients take their HC on waking in the fasted state, note the time, and then provide a blood sample 3–5 h later for monitoring of HC handling according to the nomogram shown in Fig. 3b. We have tested the nomogram on 40 patients who have been converted to the weight-related HC regimen, and found that 76.9% of them had 4-h cortisol levels within the 10th–90th centile, and 23.1% had cortisol levels above the 90th centile. Thus, our concern that the change in regimen could result in underdosing patients was unfounded. The finding that some patients had cortisol values above the 90th centile could reflect the possibility that some of our patients retain a degree of basal cortisol secretion. We do not perceive this to be a major contraindication to our regimen as the majority of patients had a dose reduction in HC. In addition, the ACTH drive during the day is likely to be suppressed after the first morning dose of HC. It is important to recognize that different assays for cortisol may give different results and this is particularly relevant for older assays and should be taken into account if using the nomogram with a different cortisol assay to that reported in this manuscript.

All our modelling predictions are based on data from the first morning dose of HC. However, this will always be the largest dose taken during the day, and changes in the first morning dose will have the greatest impact on the total daily dose of HC. Most of our patients preferred the weight-related treatment regimen, although six (15%) asked to revert to their previous HC regimen with an increased total daily dose of HC.

HC is generally regarded as the preferred replacement therapy for adrenal insufficiency over dexamethasone and prednisolone. The latter were prescribed to 11% of patients in one study,

although most of these patients had congenital adrenal hyperplasia (Howlett, 1997). It is not possible to compare HC, prednisolone and dexamethasone directly because of differences in potency, selectivity for glucocorticoid and mineralocorticoid receptors, and kinetics. Prednisolone and dexamethasone may be used to provide a longer duration of action but they cannot reproduce the normal circadian rhythm of cortisol. Optimal HC replacement would be provided by a controlled release preparation, as suggested for the treatment of congenital adrenal hyperplasia (Cutler, 1996). It should be recognized that our regimen is based on pharmacokinetics in an open study using unvalidated tools for assessing patient preference, and longer-term controlled studies will be required to evaluate its clinical benefits and safety.

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