

REVIEW

Inadequacies of glucocorticoid replacement and improvements by physiological circadian therapy

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Abstract

Patients with adrenal insufficiency need lifelong glucocorticoid replacement, but many suffer from poor quality of life, and overall there is increased mortality. Moreover, it appears that use of glucocorticoids at the higher end of the replacement dose range is associated with increased risk for cardiovascular and metabolic bone disease. These data highlight some of the inadequacies of current regimes.

The cortisol production rate is estimated to be equivalent to 5.7–7.4 mg/m² per day, and a major difficulty for replacement regimes is the inability to match the distinct circadian rhythm of circulating cortisol levels, which are low at the time of sleep onset, rise between 0200 and 0400 h, peaking just after waking and then fall during the day. Another issue is that current dose equivalents of glucocorticoids used for replacement are based on anti-inflammatory potency, and few data exist as to doses needed for equivalent cardiovascular and bone effects. Weight-adjusted, thrice-daily dosing using hydrocortisone (HC) reduces glucocorticoid overexposure and represents the most refined regime for current oral therapy, but does not replicate the normal cortisol rhythm. Recently, proof-of-concept studies have shown that more physiological circadian glucocorticoid therapy using HC infusions and newly developed oral formulations of HC have the potential for better biochemical control in patients with adrenal insufficiency. Whether such physiological replacement will have an impact on the complications seen in patients with adrenal insufficiency will need to be analysed in future clinical trials.

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Introduction

Patients suffering from adrenal insufficiency, whether primary or secondary, need to be on lifelong glucocorticoid replacement therapy. Population studies suggest that the incidence of adrenal insufficiency is increasing and the estimated prevalence of Addison's disease by 2030 is between 220 and 285 per million per year (1). The reported prevalence of secondary adrenal insufficiency is higher, between 300 and 450 per million, but this is likely to be an underestimate if undiagnosed hypopituitarism after brain injury is also considered (2). Despite replacement therapy, patients with adrenal insufficiency have higher mortality rates than the general population (3, 4), and suffer from impaired health-related quality of life (HRQOL) (5, 6), impaired bone health as evidenced by markers of bone turnover (7), and increased cardiovascular risk (8). The problem facing patients and clinicians is that all current therapies are inadequate since they are unable to provide appropriate

physiological replacement. Hydrocortisone (HC), the generic pharmaceutical name for cortisol, is the preferred replacement therapy for these patients, although it is not available in some countries (including some within Europe) (9, 10). Some clinicians favour use of prednisolone or dexamethasone, with doses based on equipotent anti-inflammatory effect (11), but doses that have an equipotent effect on the cardiovascular system are not fully established. Moreover, monitoring treatment remains a challenge, and is based on clinical assessment and biochemical parameters (12–14). Recently, efforts have focused on the development of newer formulations of HC to provide circadian glucocorticoid replacement therapy aimed to imitate more closely the normal physiological cortisol rhythm (15–17).

Here, we review the morbidity and mortality associated with adrenal insufficiency. We then discuss normal physiology of cortisol secretion and illustrate how current therapies remain inadequate. Finally, we summarise the state of the art in circadian cortisol therapy, and discuss areas that need further study.

Cardiovascular mortality and morbidity

In a recent study on 1675 patients with primary adrenal insufficiency in Scandinavia, mean age at diagnosis 37.3 years, with a follow-up period from initial diagnosis of 6.5 years, there was a mortality rate twofold higher than that of the background population (3). Deaths occurred from malignant ($n=73$), endocrine ($n=64$), respiratory ($n=45$) and infectious diseases ($n=12$), but the largest cause of death was cardiovascular disease ($n=239$). These data have been confirmed in a very recent study involving 3299 patients with primary autoimmune adrenal failure, where the leading cause of death was cardiovascular disease (18). Similarly, patients with secondary adrenal insufficiency have excess mortality. In 333 consecutive patients with hypopituitarism diagnosed between 1956 and 1987, the overall mortality was higher than the age- and sex-matched normal population, with vascular disease accounting for 60 deaths compared with the 31 expected (19).

The important adverse effects of even modest excess glucocorticoid dosing on cardiovascular risk has been assessed in a recent large Scandinavian study in 2424 patients with hypopituitarism (20). As a group those requiring glucocorticoid replacement had a higher waist circumference, total cholesterol, serum triglycerides and HbA1c. However, in those patients who received doses of glucocorticoid equivalent to HC 20 mg/day or less, metabolic end points did not differ from patients not requiring glucocorticoids. Moreover, all new cases of diabetes, stroke and myocardial infarction occurred in the glucocorticoid-treated groups. Further support for the negative effects of even low-level excess glucocorticoids comes from data studying the effects of exogenous glucocorticoids in the Scottish population, where doses of glucocorticoid above a dose equivalent of HC 30 mg were associated with subsequent cardiovascular events, including stroke and myocardial infarction (21).

Glucocorticoid replacement and glucose homeostasis

In terms of potential mechanisms for the observed adverse effects of glucocorticoids on cardiovascular risk, it is well established that high doses of glucocorticoids cause insulin resistance and diabetes, but whether this is true for low-dose glucocorticoid replacement is still a matter for debate. In normal subjects, glucose tolerance is relatively impaired in the afternoon and evening compared with the morning (22). An immediate effect of a small rise in serum cortisol is to inhibit insulin secretion, but leave circulating glucose unchanged, while, in contrast, peaks of serum cortisol exceeding the normal daily excursions (caused by doses of HC) are associated with a reduction in insulin sensitivity, which is apparent 4–6 h later, and may persist for more than

16 h (23). This is illustrated by administration of oral HC 50 mg; when given at 0500 h the delayed hyperglycaemic effect is minimal, whereas when given at 1700 h there is a much more pronounced increase in insulin secretion and with a 30% decrease in insulin clearance (24). Therefore, 24-h physiological cortisol rhythmicity may be partly responsible for the normal diurnal variation in glucose tolerance and providing physiological HC replacement may be crucial to maintain the homeostasis of daily glucose control. However, when more usual replacement doses are given the data are less clear cut. On the one hand, hypopituitary patients on conventional replacement showed higher total plasma glucose and insulin when given glucocorticoid before an oral glucose tolerance test (OGTT), compared with when it was given after the OGTT, with the difference in glucose exposure correlating with the maximal cortisol level (8). On the other hand, over a 4-week observation period in patients suffering from primary adrenal insufficiency, no significant difference was observed in fasting plasma insulin, insulin resistance or β -cell function when taking either HC 10 mg morning/5 mg mid-day or HC 10 mg morning/5 mg mid-day/5 mg evening or dexamethasone 0.1 mg/15 kg body weight at breakfast, although values for the dexamethasone tended to be higher (25). Furthermore, when comparing low-dose oral HC replacement therapy (15 mg at 0800 h, 5 mg at 1700 h) to a physiological HC infusion, endogenous glucose production was similar (26). Overall, these data suggest that lower levels of glucocorticoid have fewer adverse effects, but that even modest excursions outside normal physiology cause an adverse metabolic profile.

Although it is important to debate the potential effects on the cardiovascular system of long-term over-replacement with glucocorticoids, under-replacement also needs to be avoided. In a cohort of 6107 patients with pituitary disease studied from 1963 to 1996, and providing 105 797 person years of follow-up, there were 433 deaths from all causes. The overall risk of death was four times the normal population. Importantly, one of the most striking risk factors was adrenal insufficiency: out of the 35 subjects found dead or comatose by families or friends, 30 (86%) probably died from unrecognised or inadequately treated adrenal insufficiency (4).

Poor health-related quality of life

HRQOL is consistently impaired in patients with Addison's disease. Scores on the SF-36 quality-of-life questionnaire in 79 patients with Addison's disease showed that general health and vitality perception were low, while total fatigue, physical fatigue and mental fatigue were all high, compared with normal (6). A significant number of patients in the 18–67 age group were out of work due to disablement, while

HRQOL in patients on treatment was found to be comparable with that of congestive heart failure. In a survey from the Netherlands, 50% of patients with primary adrenal insufficiency considered themselves unfit to work and 30% needed household help (27). Similar findings have been found in patients with secondary adrenal insufficiency with SF-36 scores significantly lower in seven out of eight dimensions, and significantly higher levels of anxiety and depression, compared with normal individuals (5).

Whether poor quality of life is caused by non-physiological replacement of glucocorticoids is unknown, but published data for patients on conventional replacement therapy is that morning fatigue is a particular feature: well being is lowest just before the first dose of morning glucocorticoid, rising to a maximum at lunch time, and then falling gradually towards the evening, with HRQOL better on thrice rather than twice-daily HC (13). Similarly, a twice-daily regimen of HC appears to be better than once daily (28).

Sleep disturbances

The cortisol rhythm and the sleep–wake cycle have independent pulse generators in the suprachiasmatic nucleus (SCN), but there is a bidirectional relationship such that any sleep–wake transitions may modulate the effects of cortisol circadian rhythmicity, and vice versa (29). At sleep onset, and during the initial hours of sleep, cortisol levels are low, a period mostly associated with slow-wave sleep (SWS), while there is a predominance of time spent in rapid eye movement (REM) sleep in the second half of the night when cortisol levels are increasing prior to and after waking. Delta wave activity (deep sleep) cannot develop unless corticotrophic activity is low; inhibition of CRH release results in decreased sympathetic activity and cortisol production. Increased cortisol levels at night are significantly associated with light sleep and wakefulness (30, 31).

The problems of sleep are illustrated in 60 patients in adrenal insufficiency, where 34% reported weekly sleep disturbances (difficulties falling asleep in 13%; repeated awakenings in 14%; and early morning awakenings in 20%) (32). Early morning awakening, the most common complaint, could be related to abnormalities in the hypothalamo–pituitary–adrenal (HPA) axis despite these patients being on treatment. During daily activities, 40% of patients were tired more than once a week, but the scores of the Epworth sleepiness scale questionnaire were not higher than normal. This confirmed the presence of increased daytime fatigue in patients with Addison's disease, but no more daytime sleepiness than normal.

The effect on REM sleep has been assessed in ten HC-deprived patients with Addison's disease, where there was an increase in REM sleep latency (145 min) and diminished time spent in REM sleep, whereas HC at bedtime resulted in a REM latency of 70.7 min (33).

The REM latency in normal individuals is around 103 min (34). Moreover, the absence of HC resulted in a decrease in sleep continuity, while HC replacement resulted in a more consolidated sleep pattern. This may be related to either absolute cortisol levels or possibly to a reduction in the levels of CRH or ACTH. However, there is an optimum to be attained since high doses of exogenous glucocorticoids in normal individuals reduce REM sleep (35), and patients on higher doses of nocturnal glucocorticoid frequently report sleep disturbance.

Effects on SWS are variable and may be related to the dose of corticosteroids and the differential effect on binding to high-affinity mineralocorticoid receptors in the hippocampus and amygdala (CRH suppression) or low-affinity glucocorticoid receptors (GRs) in the amygdala (CRH stimulation) (31). Thus, it is possible that more physiological cortisol replacement could achieve sleep indices closer to normal values in patients with adrenal insufficiency.

Defects in bone metabolism

Bone loss secondary to suppression of osteoblastic function, evident by lower osteocalcin levels, may also occur with increasing HC doses. Serum osteocalcin levels significantly decrease with an increase in HC doses (7). In 19 patients whose mean glucocorticoid dose was reduced from 29.5 to 20.8 mg over ~3.5 months, the median osteocalcin concentration increased significantly from 16.7 to 19.9 µg/l. Therefore, small changes in cortisol replacement therapy may have effects on bone turnover with higher doses more likely to have an adverse effect on bone formation (36). Despite this, no specific changes have been observed in circulating bone alkaline phosphatase, another marker of bone formation, in those on glucocorticoid replacement therapy (37).

Effects on bone density (BMD) are debatable, especially as different studies have shown conflicting results. The BMD at the lumbar spine in 15 patients on glucocorticoid replacement (mean daily dose cortisone acetate 36.6 mg) for more than 5 years varied within the normal reference range, and also did not differ significantly from matched controls (38), with the suggestion that patients on currently recommended low-dose HC regimes do not need BMD screening. By contrast, in 91 patients with Addison's disease, who had been receiving glucocorticoid replacement therapy for an average of 10.6 years, a significant negative linear correlation was shown between HC dose per kilogram of body weight and BMD in the lumbar spine in men but not in women (39). The difference in gender could be explained by the women being pre-menopausal or post-menopausal oestrogen replacement therapy.

Circadian variation of bone remodelling is shown by levels of markers of bone resorption (urinary excretion of urinary cross-linked N-telopeptide of type 1 collagen

(NTx) (40) and pyridinium cross-links (41, 42)) and formation (serum osteocalcin, respectively (43, 44)); peak levels occur at night with a nadir in the afternoon. The levels of osteocalcin fall following the rise in serum cortisol, with a latency ~ 4 h (45). Reproducing the cortisol circadian rhythm using HC infusions maintained the circadian rhythm of osteocalcin, whereas with a constant HC infusion the afternoon nadir of serum osteocalcin was eliminated (46). These data indicate that the circadian variation in osteocalcin is under the control of the endogenous circadian variation in serum cortisol. Thus, it is possible that circadian replacement cortisol therapy could provide a treatment that interacts with bone physiology more effectively.

Taken together, these findings suggest that patients should be maintained on the lowest possible HC replacement doses, so as to avoid impaired bone health and the likelihood of development of osteoporosis and its consequences in the long term. It is important to stress, however, that this is a recommendation based on our current knowledge, and that the influence of glucocorticoid replacement on bone health and fracture risk is not fully established, and more work is needed in this area.

Normal cortisol physiology

Cortisol circadian rhythm

Cortisol has a distinct circadian rhythm that is well established and has been analysed in fine detail (47). Cortisol reaches the lowest levels at around midnight. These then start to rise at ~ 0200 – 0300 h and reach a peak in the morning after waking. Following this, the levels slowly decrease back to the nadir to complete the cycle over 24 h (48). This rhythm is characterised by a constant and reproducible pattern under stable physiological conditions (49).

The regulation of cortisol is critically determined by the activity of the HPA axis, which receives input from the central 'master' pacemaker in the SCN via the circadian release of CRH from the paraventricular nucleus. CRH release is also influenced by a wide variety of physical and emotional stressors, and in turn stimulates the release of ACTH from the corticotroph cells in the anterior pituitary (in synergy with vasopressin), and thence cortisol from the adrenal cortex. In turn, cortisol exerts inhibitory effects at pituitary and hypothalamic levels, in a classical negative feedback loop but does not seem to feedback on the SCN (50), and the GR appears to be absent in this structure.

The adrenal gland contains a circadian clock regulated via the splanchnic nerve, which defines a time window during which the adrenal most effectively responds to ACTH (51). Clock genes in the zona glomerulosa and zona fasciculata and entire metabolic

pathways relevant to the adrenal gland, such as those responsive to steroid metabolism in the liver, are transcriptionally regulated by the circadian clock (52). Clock genes in the adrenal gland show a 6-h phase delay relative to the SCN (53, 54).

Thus, there is a tightly co-ordinated interplay between the production of glucocorticoids and the responsiveness of target tissues, which is lost in adrenal insufficiency.

Cortisol production rate

A number of cortisol secretory episodes occur during the 24 h of the day, making it possible to describe four different unequal temporal phases. These phases are represented by: (i) a period of minimal secretory activity, during which cortisol secretion is negligible and occurs 4 h before and 2 h after sleep onset; (ii) a preliminary nocturnal secretory episode at the 3rd to 5th hours of sleep; (iii) a main secretory phase of a series of three to five episodes occurring during the 6th to 8th hour of sleep and continuing through the 1st hour of wakefulness; and (iv) an intermittent waking secretory activity of four to nine secretory episodes found in the 2nd to 12th-hour waking period (47). Using stable isotopic methodology, the daily cortisol production rate is ~ 5.7 – 7.4 mg/m² per day or 9.5–9.9 mg/day (55–57), less than previous estimates of 12–15 mg/m² per day. Cortisol production rates in children and adolescents are very similar.

Evolution of glucocorticoid replacement therapy

It has been established for many years that adrenal insufficiency is not compatible with life (58). In 1933, initial studies on adrenalectomised dogs revealed a progressive decrease in blood volume with a progressive fall of blood pressure until death. Blood volume and blood pressure changes appeared within 24–72 h after discontinuation of injections of adrenal cortex extract, and before any symptoms of adrenal insufficiency were evident. Following administration of adequate amounts of 'cortical hormone' blood volume, blood pressure and blood constituents all returned to normal. In 1937, 11-deoxycortisol was synthesised, and by 1940 cortisone and HC had been isolated by Kendall and Reichstein. The first published report of the efficacy of cortisone in the treatment of rheumatoid arthritis appeared in 1949, and had such an enormous impact on the scientific community that the Nobel Prize in Medicine was jointly awarded to Philip Hench, Edward Kendall and Tadeus Reichstein, just one year later in 1950. In that same year, George Widmer Thorn and P H Forsham were the first to use cortisone acetate in Addison's disease, where the treatment had to be supplemented with sodium chloride or deoxycortone

acetate to achieve a satisfactory electrolyte balance (59). In November 1950, Merck made cortisone available to physicians in the US (60). Since then patients with adrenal insufficiency have been treated with glucocorticoid, and since the introduction of fludrocortisone in the 1950s, replacement therapy has remained virtually unchanged (10).

Current treatment of adrenal insufficiency

Different regimens and doses

HC is now the most commonly used glucocorticoid for adrenal insufficiency. Traditionally, the dose of HC was two-thirds in the morning and one-third in the evening to try and replicate cortisol circadian rhythm, usually 20 mg in waking and 10 mg in the evening (61). Newer estimates of the cortisol production rate (see above) indicate that 15–20 mg total daily HC is required. Unfortunately, HC has a short plasma half-life and patients taking this tablet wake with undetectable cortisol levels, thus achieving peak cortisol levels an hour after dosing (14, 62). The pharmacokinetics of 20 mg HC has been studied after i.v. and oral administration. After i.v. administration, HC is eliminated with a total body clearance of 18 l/h and a half-life of 1.7 h. The volume of distribution is 34 l. Oral bioavailability averages 96%. This predicts very low levels of cortisol by mid-afternoon. The pharmacokinetics of immediate release HC makes it impossible for physicians to replicate physiological cortisol release. A number of research studies have explored different HC regimes to try and identify the best doses and patterns of treatment. Patients on a thrice-daily regimen show levels of cortisol, which are much more constant and better imitate physiological cortisol rhythm when compared with those on a twice-daily regimen (13). The use of weight-adjusted dosing before food showed decreased inter-patient variability in maximum cortisol concentration from 31 to 7%, and reduced over-exposure to <5%, and thrice-daily weight-adjusted dosing has been recommended as the preferred HC regime (14). It is a clinical experience, however, that patient compliance with thrice-daily dosing is far from absolute for many patients.

Another glucocorticoid, still preferred in some European countries, is cortisone. Originally, cortisol deficiency was more commonly treated with cortisone acetate (25 mg in the morning and 12.5 mg in the evening), but this drug is now less frequently used and needs to be converted to HC by the enzyme 11 β hydroxysteroid dehydrogenase (11 β HSD1) type 1 to become active. On the other hand, when compared with HC, it shows a lower serum cortisol peak and possible delayed clearance of cortisol (63, 64) properties that may be advantageous.

Some clinicians, more commonly in the US, have favoured use of equipotent doses of prednisolone or dexamethasone for more stable glucocorticoid effects throughout the day. Prednisolone has an intermediate duration of action and more anti-inflammatory effects than mineralocorticoid activity, while dexamethasone has no mineralocorticoid effect but mainly has anti-inflammatory effects with a long half-life of 36–72 h. Once- or twice-daily dosing is used for these drugs. As they are long-acting, with more powerful effects on the GR, there is an increased risk of excess exposure that may have long-term adverse consequences. Besides, surveillance of therapy is difficult (10, 65). Furthermore, it is likely that the dose equivalents of glucocorticoids calculated from classical anti-inflammatory experiments (66, 67) are not equivalent for cardiovascular effects. This may be due to the different mechanism of action of the ligand-bound GR for anti-inflammatory and metabolic effects. The classical actions of the activated GR are mediated by binding DNA in promoter regions of genes and causing either transactivation or transrepression (68). Many of the metabolic effects of glucocorticoids are mediated by these means. By contrast, many of the anti-inflammatory effects of glucocorticoids are mediated by mechanisms other than DNA binding, such as sequestration of NF κ B in the cytoplasm (69). A further layer of complexity is added by wide inter-individual variability in sensitivity to glucocorticoids and even intra-individual variability in different tissues (70, 71). Part of the explanation may come from GR polymorphisms that appear to be associated with altered metabolic phenotypes (72, 73). Such altered sensitivity could clearly have a major impact over a lifetime of exposure in patients with adrenal insufficiency. Nevertheless, if it were possible to have confidence in the appropriate dose equivalents for the use of these synthetic glucocorticoids and if the dose could be easily varied and administered, and the effects adequately monitored, then their use may have advantages with potentially fewer daily doses.

Difficulties with monitoring HC replacement

There is no universal agreement regarding appropriate monitoring of HC replacement to determine the most appropriate replacement dose for individual patients. Some endocrinologists are in favour of adjusting HC doses guided by clinical features (38, 74). In 46 patients with adrenal insufficiency on a median dose of 37.5 mg cortisone acetate, serum cortisol correlated significantly with a clinical score assessing the adequacy of replacement, but there was no significant difference between those deemed under- or over-replaced patients (38). By contrast, others advocate the use of HC day curves (12, 75). These are inconvenient to perform, but may have particular merit in situations where patients are on drugs that interact with HC through enzyme

induction or inhibition resulting in lower or higher cortisol levels respectively (see below). A simple, practical and effective way of monitoring cortisol is to measure a single serum cortisol 4 h after dosing, and to compare this to a dosing nomogram that allows prediction of the cortisol and hence total cortisol exposure (14).

Urinary-free cortisol levels have been used as an indicator of overall cortisol replacement (36, 76). The problem with this approach is that saturation of cortisol-binding globulin is rapid after oral HC (77), with the free cortisol then being filtered in the kidney and the potential for spurious results. Moreover, fluctuations of cortisol throughout the day are difficult to detect and are not ideal to diagnose under replacement.

Salivary cortisol measurements have also been used to detect abnormal levels of glucocorticoids (78, 79). This is a feasible way of monitoring cortisol levels but some studies show wide inter-individual variability in plasma and salivary profiles of cortisol, and a poor correlation between salivary and plasma measurements has been shown in patients with adrenal insufficiency (80). In others, the correlation is far better and this approach used for monitoring (81).

Overall, clinical assessment of patients on glucocorticoid replacement therapy remains crucial, but the optimum means of achieving this and the optimum means of biochemical monitoring remain open for debate.

Hormonal and drug interactions

Interconversion between active cortisol and inactive cortisone is driven by the isoenzymes, 11 β HSD types 1 and 2 (82). The type 1 isoenzyme expressed mainly in visceral adipose tissue, liver and gonads, converts exogenous or endogenous cortisone to cortisol, hence is essential to expose local tissues to glucocorticoids (83). The GH-IGF1 axis may inhibit 11 β HSD type 1 expression (84). GH therapy in patients with hypopituitarism on stable HC therapy reduces the mean cortisol peak and total cortisol exposure (85). GH therapy reduces the mean ratio of Fm/Em (ratio of urine cortisol to cortisone metabolites) bringing patients with hypopituitarism on HC treatment closer to physiological glucocorticoid exposure. Mean serum cortisol levels also fall in all subjects, this finding is more significant in patients on cortisone acetate indicating that patients on this drug may be more susceptible to the effects of GH on 11 β HSD type 1 (86). Thus, caution is advised when introducing GH treatment in patients on cortisol replacement, especially if on cortisone acetate, and all should be monitored for symptoms of impending adrenal insufficiency.

Oral oestrogens increase total cortisol levels by increasing cortisol-binding globulin (CBG) levels with no effect on free cortisol levels. Transdermal oestrogens,

which avoid the first-pass hepatic effect, do not significantly affect CBG levels. No change in HC doses is required for patients on oestrogen therapy, but measured total serum cortisol levels may be higher, and oestrogen needs to be stopped for 6 weeks prior to any assessment of the HPA axis, or alternatively, salivary cortisol measurements may be used (87).

Cortisol metabolism occurs principally by enzymatic reduction (5 β -reductase, 5 α -reductase – rate limiting; 3 α -HSD) and oxidation (11 β HSD1) but also by 6 β -hydroxylation, a reaction catalysed by cytochrome P450 3A4 (88, 89). Drug–drug interactions therefore occur between glucocorticoids and drugs that induce or inhibit the activity of the CYP3A4 (90), such as anti-convulsant medication (enhanced effect and hence lower cortisol levels) or anti-retroviral medication (reduced effect and hence higher cortisol levels). Furthermore, glucocorticoids are able to induce cytochrome P450 at the pre-translational level by exerting an effect directly on hepatocytes. CYP3A4 mRNA and protein have been shown to be upregulated by exposure to dexamethasone (91–93). Close monitoring of cortisol levels is essential in these scenarios to avoid decreased or increased cortisol exposure and consequent side effects (Table 1).

Circadian glucocorticoid therapy

In patients with adrenal insufficiency, it is evident that increased mortality and morbidity are still a problem and current replacement regimes are not adequate. Studies on circadian replacement have demonstrated potential to produce better results using formulations that more closely mimic this rhythm. One option is to wake at 0300 h to take immediate-release HC, a strategy that resulted in a significant improvement in 17 OH-progesterone, testosterone and individual

Table 1 Drug interactions for hydrocortisone.

Drugs that accelerate metabolism by induction of CYP3A4
Phenobarbital
Phenytoin/fosphenytoin
Carbamazepine
Primidone
Rifampin
Rifapentine
Ethosuximide
Pioglitazone
Drugs that impair metabolism by inhibition of CYP3A4
Aprepitant/fosaprepitant
Itraconazole
Ritonavir
Fluoxetine
Diltiazem
Cimetidine
Drugs that increase CBG and may falsely elevate cortisol results
Oestrogens
Mitotane

urinary 17-ketosteroids in five patients with congenital adrenal hyperplasia (CAH). This was not achieved by giving higher or later evening doses (94). This is, however, not a practical solution for the majority of patients with adrenal insufficiency, and taking doses of longer acting glucocorticoids at night is associated with impaired sleep (35).

Physiological hormone replacement, using sustained formulations of HC, should be the safest, most effective and practical solution. Over the past few years, interventions introducing circadian cortisol therapy, using HC infusions and modified-release oral formulations have shown that these treatments could imitate physiological cortisol rhythm, and hence potentially result in improved therapy for patients with adrenal insufficiency.

Circadian HC infusions

In a proof-of-concept study, circadian i.v. infusions of HC imitating the normal cortisol rhythm, delivered by a programmable pump, were used to assess whether these could improve ACTH and androgen levels in two patients with Addison's disease and two patients with CAH (Fig. 1). In the patients with CAH, very high plasma ACTH and 17-hydroxyprogesterone levels were present before the morning dose and at the end of conventional HC treatment, in contrast to significantly lower levels of both ACTH and 17-hydroxyprogesterone after circadian infusion (17) (Fig. 2). These findings were corroborated by another study on seven patients with adrenal insufficiency, where continuous s.c. hydrocortisone infusions (CSHI) were evaluated. Morning ACTH levels were reduced from high (>39 pmol/l) to near normal levels (<18 pmol/l). The glucocorticoid dose could be reduced in most patients and all were satisfied with the treatment. All mean SF-36 scores of all subscales improved, such that two patients continued

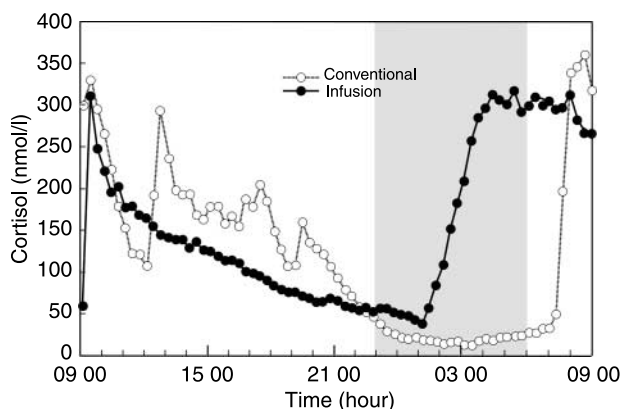


Figure 1 Comparison of mean serum cortisol levels in patients with Addison's disease and congenital adrenal hyperplasia (CAH) during conventional oral replacement therapy and during circadian i.v. infusion of hydrocortisone (adapted from *Clinical Endocrinology* 2006 65: 45–50 (16)).

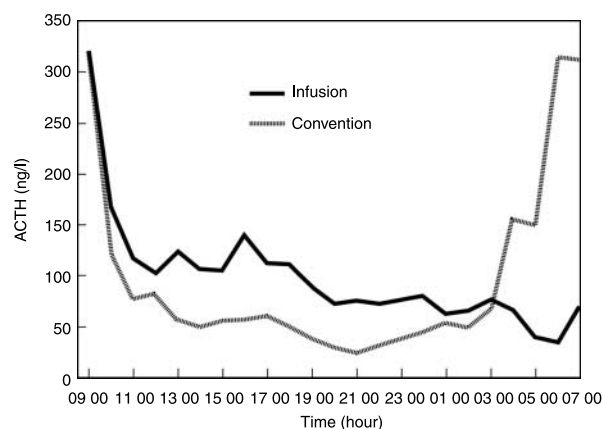


Figure 2 Comparison of mean serum ACTH levels in patients with Addison's and congenital adrenal hyperplasia (CAH) during conventional replacement therapy and during circadian infusion of hydrocortisone (to convert from ng/l to pmol/l: $\times 0.22$; adapted from *Clinical Endocrinology* 2006 65: 45–50 (16)).

CSHI permanently (95). With the caveat that these are very small, open uncontrolled studies, with the potential for a clear placebo effect, the results suggest that circadian administration of HC could provide better biochemical control in CAH and improved HRQOL in adrenal insufficiency. HC infusions are, however, very cumbersome and will not be a practical solution for the vast majority of patients. These factors have prompted the development of oral modified-release formulations.

Oral delayed and sustained release formulations of HC

One concept is to have a delayed and sustained release formulation that could be taken at night, to allow the gradual build-up of serum cortisol from 0200 to 0300 h, and the patient to wake with physiological peak levels. The hope would be to reduce early morning fatigue in patients with adrenal insufficiency and improve biochemical control in those with CAH. A modified-release HC tablet aimed at achieving these goals and consisting of an insoluble barrier coat covering all but one face of the tablet, with a slowly eroding layer retarding release from an inner drug containing layer, was tested in a pilot study of six healthy males whose endogenous cortisol had been suppressed by dexamethasone (15). The dose was administered at 2200 h. Two formulations with predicted delayed release of 2 and 4 h were studied. The measured serum cortisol showed delayed release, as expected, of 2 and 4 h, with median peak cortisol concentrations at 4.5 and 10 h respectively. The profiles indicated a good match to the normal circadian profile overnight, but lower cortisol levels than normal after 1200 h on day 2, suggesting that it would not be suitable for just once daily nocturnal dosing (Fig. 3). Thus, this formulation has the potential to achieve its

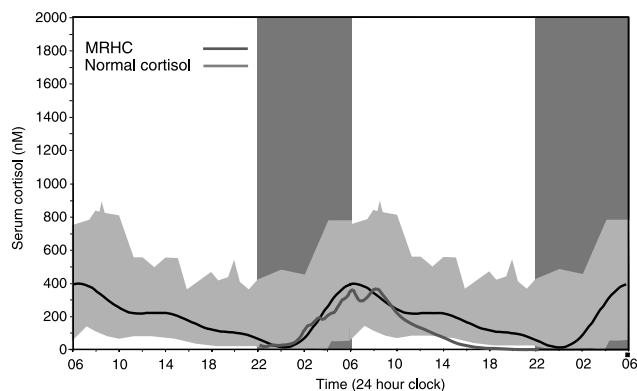


Figure 3 Concentration–time profile for modified-release hydrocortisone (MRHC), 30 mg given at 2200 h showing delayed and sustained release characteristics: dark grey is mean cortisol level for subjects administered MRHC, black line is mean cortisol level in normal subjects and light grey area is range of cortisol levels in normal subjects (adapted from *Clinical Endocrinology* 2008 68: 130–135 (14)).

goals, but formal assessment in an appropriately designed trial in patients is needed.

Another formulation with combined immediate and extended release characteristics has also been developed (16), with the concept to allow once daily morning dosing. In a study to determine single-dose pharmacokinetics and dose proportionality, it was shown that the time to reach a clinically significant serum concentration of cortisol (>200 nmol/l) was within 25 min and a peak of 400–450 was obtained within 50 min after the 20 mg tablet. Serum cortisol levels remained above 200 nmol/l for ~ 6 h; thereafter, whereas all serum concentrations 18–24 h after intake were below 50 nmol/l. Thus, this has the potential for once-daily dosing, but does not address the issue for patients with adrenal insufficiency of waking with low levels of serum cortisol, although peak serum cortisol levels are achieved rapidly. These are, however, unpublished data and the full results are awaited.

In summary, these new drug delivery technologies have shown that it may be possible to simplify and improve glucocorticoid replacement, with the potential for less adverse effects and improved compliance. It is important to stress that it is yet to be established whether such therapies will result in improvements for patients with adrenal insufficiency, and clearly further studies are needed.

Conclusion

Over the past 60 years, glucocorticoid replacement therapy has had an important impact in the lives of patients with adrenal insufficiency. Yet problems remain. It is evident that although glucocorticoid-related side effects such as increased cardiovascular risk

and metabolic bone problems are less likely on low-dose HC replacement therapy, these may occur on higher doses. Glucocorticoid dose equivalences used by most physicians are mainly related to their anti-inflammatory effects and are not related to other therapeutic or adverse effects, and this is an area needing further investigation. Monitoring therapy and adjusting doses are problematic for all patients and physicians. Identifying biomarkers or monitoring treatment will be of the utmost importance for both clinical practice and research.

Patients with adrenal insufficiency suffer from impaired quality of life and increased mortality. Physiological, circadian cortisol replacement for these patients, while never being able to fully replicate all aspects of an intact HPA axis, offers the prospect of improved biochemical control and quality of life, and further developments and research are needed in this area.

Declaration of interest

M D & J N-P have nothing to declare. R J R has equity interests in Diurnal Ltd.

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