Cardiometabolic and psychological effects of dual-release hydrocortisone: a cross-over study

Rosemary Dineen¹, Julie Martin-Grace¹, Khalid Mohamed Saeed Ahmed², Isolda Frizelle², Anjuli Gunness², Aoife Garrahy¹, Anne Marie Hannon¹, Michael W O'Reilly¹, Diarmuid Smith¹, John McDermott³, Marie-Louise Healy⁴, Amar Agha¹, Agnieszka Pazderska⁴, James Gibney², Chris J Thompson¹, Lucy-Ann Behan² and Mark Sherlock¹

¹Academic Department of Endocrinology, Beaumont Hospital/RCSI, ²Robert Graves Institute of Endocrinology, Tallaght University Hospital, ³Department of Endocrinology, Connolly Hospital, and ⁴Department of Endocrinology, St James Hospital, Dublin, Ireland

Correspondence should be addressed to M Sherlock
Email
marksherlock@beaumont.ie

Abstract

Background: Adrenal insufficiency (AI) is associated with increased cardiovascular morbidity and mortality and reduced quality of life (QoL). Optimum glucocorticoid (GC) dosing and timing are crucial in the treatment of AI, yet the natural circadian secretion of cortisol is difficult to mimic. The once-daily dual-release hydrocortisone (DR-HC) preparation (Plenadren®), offers a more physiological cortisol profile and may address unmet needs.

Methods: An investigator-initiated, prospective, cross-over study in patients with AI. Following baseline assessment of cardiometabolic risk factors and QoL, patients switched from their usual hydrocortisone regimen to a once-daily dose equivalent of DR-HC and were reassessed after 12 weeks of treatment.

Results: Fifty-one patients (21 PAI/30 SAI) completed the study. Mean age was 41.6 years (s.d. 13), and 58% ($n = 30$) were male. The median daily HC dose before study entry was 20 mg (IQR 15–20 mg). After 3 months on DR-HC, the mean SBP decreased by 5.7 mmHg, $P = 0.0019$ and DBP decreased by 4.5 mmHg, $P = 0.0011$. There was also a significant reduction in mean body weight (-1.23 kg, $P = 0.006$) and BMI (-0.3 kg/m², $P = 0.003$). In a sub-analysis, there was a greater reduction in SBP observed in patients with SAI when compared to PAI post-DR-HC. Patients reported significant improvements in QoL using three validated QoL questionnaires, with a greater improvement in PAI.

Conclusion: Dual-release hydrocortisone decreases BP, weight and BMI compared with conventional HC treatment, even at physiological GC replacement doses. Additionally, DR-HC confers significant improvements in QoL compared to immediate-release HC, particularly in patients with PAI, which is also reflected in the patient preference for DR-HC.

European Journal of
Endocrinology
(2021) **184**, 253–265

Introduction

Adrenal insufficiency (AI) is caused by the primary failure of the adrenal cortex (primary adrenal insufficiency (PAI), most commonly due to autoimmune adrenalitis) or due to disruption of the hypothalamic–pituitary–adrenal axis resulting in loss of stimulation of the adrenal cortex by adrenocorticotropin hormone (ACTH) (secondary adrenal insufficiency (SAI)) (1). All patients with AI receive

glucocorticoid (GC) replacement therapy, which aims to replicate physiological cortisol secretion and maintain health. However, despite the availability of GC replacement therapy for several decades, patients with AI have increased morbidity (2, 3, 4, 5), and impairment in quality of life (QoL) compared to the background population (6). Without the availability of reliable biomarkers, conventional

Clinical Study	R Dineen and others	Benefits of dual-release hydrocortisone in adrenal insufficiency	184:2	254
----------------	---------------------	--	-------	-----

GC replacement therapy can lead to temporary levels of supraphysiologic cortisol exposure (which in the long term can potentially lead to adverse metabolic effects) (7) or insufficient levels of circulating cortisol which places patients at risk from the consequences of hypoadrenalism, including adrenal crisis and impaired quality of life.

To mimic the physiological rhythm of endogenous cortisol, novel modified-release hydrocortisone preparations have been developed. The dual-release formulation of hydrocortisone (DR-HC), Plenadren®, has been licenced for use in clinical practice and is taken once daily in the morning. Plenadren® has been investigated in patients with Addison's disease showing improvements in cardiovascular risk factors, including a reduction in body weight, haemoglobin A1c and blood pressure, as well as a significant improvement in fatigue (8, 9). More recently, the DREAM study reported that 24 weeks of DR-HC treatment in patients with AI lead to reduced body weight, normalisation of the immune cell profile, reduced recurrent infections, and improved quality of life compared to patients on conventional glucocorticoid therapy (10).

In the initial phase III study by Johannsson *et al.* (8) and in the DREAM trial (10), which are the largest prospective trials investigating the DR-HC formulation (Plenadren®), the majority of study participants were receiving a mean daily dose of hydrocortisone ≥ 25 mg/day (68.2% of patients in the phase III trial (8), while the mean daily dose of hydrocortisone in the DREAM trial participants was 26.3 (s.d. 9.4) mg/day (11). Therefore, it is debated that the beneficial effects demonstrated in these studies may be explained by a reduction in total daily cortisol exposure from a relatively high dose of hydrocortisone replacement therapy (12). In a prospective study by Behan *et al.* higher doses of HC produced unphysiological cortisol exposure compared to a matched control group (13).

Several prospective studies investigating DR-HC have included patients who switched from differing glucocorticoid preparations (i.e. cortisone acetate, hydrocortisone, prednisolone or dexamethasone) (10, 14, 15). In the DREAM study, 57% of patients were switched from cortisone acetate to DR-HC. A presumed equivalence of 80% was used for these patients who were switched from cortisone acetate to DR-HC, which is not validated and therefore influences the interpretation of the results. Furthermore, there remains a paucity of data relating to DR-HC in patients with secondary AI, with the majority of studies including retrospective data (16, 17), or small study numbers (14, 15, 18, 19).

On this background, our study aimed to assess, in a prospective manner, the effect of changing from immediate-release hydrocortisone to once-daily DR-HC on cardiovascular risk factors and QoL in both primary and secondary AI patients who all switched from the same GC preparation, immediate-release hydrocortisone, and were on physiological GC replacement doses, (median daily HC dose of 20 mg (IQR 15–20 mg)).

Methods

Study design and population

We performed an investigator-led, open-labelled, multi-site, prospective study at two University Hospitals in Ireland (Tallaght University Hospital and Beaumont Hospital). Eligible patients were male and female patients aged ≥ 18 years, with a diagnosis of adrenal insufficiency, either PAI or SAI (basal cortisol <100 nmol/L, peak cortisol <400 nmol/L after stimulation) confirmed on dynamic testing at diagnosis, who were on conventional hydrocortisone replacement therapy, without any adjustment in hormone replacement for at least 3 months before study entry. Exclusion criteria included; age < 18 years; pregnancy; patients with acute medical or surgical illness; patients with advanced cardiac/pulmonary disease; patients with a terminal illness; patients on glucocorticoids for purposes other than adrenal insufficiency; patients on agents that interfere with corticosteroid metabolism including oral oestrogen-containing preparations due to the effect on corticosteroid-binding globulin (CBG) and thus total cortisol concentrations; and patients with known Type 1 or Type 2 diabetes mellitus requiring insulin therapy. The clinical characteristics of the patients are summarised in Table 1.

The study was approved by the Joint Research Ethics Committee of Tallaght University Hospital/St James's Hospital and the Beaumont Hospital Research Ethics Committee. Written informed consent was obtained from all patients before participation. All patients had an emergency kit and a steroid emergency card and received education regarding the management of an adrenal crisis.

This study was registered with ClinicalTrials.gov, NCT03282487.

Study intervention

The investigational medicinal product in this study is the DR-HC, Plenadren® which was prescribed according

Clinical Study	R Dineen and others	Benefits of dual-release hydrocortisone in adrenal insufficiency	184:2	255
----------------	---------------------	--	-------	-----

Table 1 Age, gender, duration and aetiology of AI in the study population.

Characteristics	Values
Primary AI, <i>n</i>	21
Age (years) mean (s.d.)	41.05 (13.35)
Male: Female	9:12
Duration of disease (years) mean (s.d.)	9.8 (9.2)
Aetiology	
Autoimmune	
Isolated	9
Isolated with coeliac disease	1
Isolated with vitamin B12 deficiency	1
APS2 with hypothyroidism	7
Bilateral adrenalectomy	
VHL- bilateral pheochromocytoma	1
Carney complex- PPNAD	1
BMAH	1
Secondary AI, <i>n</i>	30
Age (years) mean (s.d.)	47.5 (12.77)
Male: Female	22:8
Duration of disease (years) mean (s.d.)	12.2 (7.5)
Aetiology	
Isolated ACTH	2
Craniopharyngioma	5
NFPA	14
Germinoma	2
Parasellar meningioma	1
Apoplexy	1
Macroprolactinoma	2
ACTH-dependent Cushing's (in remission)	2
Congenital hypopituitarism	1

ACTH, adrenocorticotrophic hormone; AI, adrenal insufficiency; APS, autoimmune polyglandular syndrome; BMAH, bilateral macronodular adrenal hyperplasia; NFPA, non-functioning pituitary adenoma; PPNAD, primary pigmented nodular adrenocortical disease; VHL, Von Hippel Lindau disease.

to the Summary of Product Characteristics (SmPC). The dose of Plenadren® prescribed was equal to the total daily dose of the patients' usual conventional hydrocortisone before study entry. Plenadren® is available in 5 and 20 mg tablets only, hence all patients received their dosage using these formulations. Patients were instructed to take the Plenadren® tablets orally in the fasting state upon waking. In the event of intercurrent illness, recommendations were given to double the daily dose requirement (second dose 8 h after the first dose) or tripled (6 and 12 h after the first dose).

After screening for eligibility and informed consent, patients presented for Visit 1. Thereafter, if biochemical investigations were within the normal reference range, patients were switched from immediate-release HC to the daily dose equivalent of once-daily DR-HC, as per the SmPC, for 12 weeks. At the end of the intervention treatment period, patients presented for Visit 2, thereafter patients were switched back to their usual immediate

release HC regimen, as Plenadren® is currently not available in clinical practice in Ireland, and were followed up in the outpatient clinic according to the standard surveillance protocol of the clinic.

Study procedures

At baseline and 12 weeks after DR-HC, patients presented after an overnight fast at 08:00 h. Blood pressure was obtained as per NICE guidance, Hypertension in Adults: diagnosis and management (20). Heart rate (b.p.m.), body temperature (°C), respirations (breaths per minute), height (cm), waist and hip circumference (cm) were measured and recorded. Body composition analysers (Tanita® BC418MA for patients recruited in Tallaght University Hospital; and Tanita® DC360S for patients in Beaumont Hospital) were used to calculate BMI, body fat percentage (%), body fat mass (BFM) (kg), fat-free mass (FFM) (kg), muscle mass (kg), total body water percentage, and basal metabolic rate.

Fasting laboratory investigations were performed including routine renal/bone/liver profiles (sodium, potassium, urea, creatinine, calcium, alkaline phosphatase (ALP), magnesium, alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), bilirubin) serum albumin, fasting total cholesterol, HDL- and LDL-cholesterol, triglycerides, haemoglobin A1c, C-reactive protein and full blood count using in-hospital assays.

All study participants completed three validated QoL questionnaires; the Short Form-36 Health Survey (SF-36) (21), the Addison's Disease-specific, AddiQoL questionnaire (22), and the Nottingham Health Profile (NHP) (23). The SF-36 aims to assess general well-being over the preceding 4 weeks by evaluating responses to statements through 8 domains of health. Scores are coded and transformed to a scale of 0–100 with higher scores indicating a better QoL (21). The AddiQoL questionnaire has been validated for patients with PAI is a 30-item questionnaire (22). Positive items have scores from 1 to 6; negative QoL statements were reversed for questionnaire scoring (6 to 1). The scoring was converted to points: 6=4 points; 5 and 4=3 points; 3 and 2=2 points, 1=1 point. The algebraic sum of points was calculated. Higher points indicate a better QoL. The NHP contains 38 yes/no questions over 6 health domains. Each question is weighted and the sum of each domain is 0–100 with higher scores indicating worse QoL (23).

To strengthen the QoL assessment, we recruited healthy age- and BMI-matched controls from similar socio-economic background to our patient population, to complete the same QoL questionnaires.

Outcomes

The primary efficacy outcome was bodyweight changed from baseline to 12 weeks.

Assuming a s.d. of 1.3 kg for bodyweight change, based on published data (8), and 1 kg as the minimal clinically relevant difference between treatments, we estimated that a sample size of 54 would be needed to provide 80% power to detect a 1.0 kg difference in the primary outcome, with a two-sided significance level of 0.05, assuming that 20% of patients would drop out of the study. Change from baseline was calculated as the value at 12 weeks minus the baseline value.

Secondary outcomes included a change from baseline to 12 weeks in metabolic profile (assessed by measurement of blood pressure, HbA1c, fasting serum lipids, BMI, waist circumference) and quality of life. Safety was monitored throughout the study and included the recording of adverse events, adrenal crises and symptoms suggestive of hypoadrenalism. An adrenal crisis was defined as per guidelines (24).

Statistical analysis

The normality of quantitative variables was tested with the Shapiro–Wilk test. The baseline characteristics of the groups are presented as mean (s.d.) or median (interquartile range) as appropriate. The differences between the post-treatment and baseline data were evaluated with paired *t*-tests in a single group for quantitative variables and chi-square for categorical variables or the appropriate non-parametric test. To assess whether the effect in SAI differs from PAI, a formal interaction test was performed.

QoL questionnaires were coded for analysis by the investigators, and the investigators were blind to the study to reduce the risk of bias during the analysis of the results. Investigators were blinded to the study ID and study visit matching each questionnaire. Analysis of QoL involved calculating age and gender-specific mean and s.d. score values from the normally distributed healthy control data to produce age and gender-specific Z-scores for each patient before and after DR-HC. The Z-score reveals how many units of the s.d. each subject is above or below the mean. The Z-score was calculated as follows: $Z = (x - \mu) / \sigma$, where x = individual QoL value, μ = mean QoL value of controls of equal gender and age and σ = s.d. of QoL value of controls of equal gender and age. The Z-score was calculated for each domain in SF36, NHP and AddiQoL. A higher score is associated with worse QoL in the NHP, therefore, a positive Z score denotes worse QoL

compared to healthy controls. In the SF36 and AddiQoL, a higher score indicates better QoL and therefore a negative Z score denotes decreased QoL compared to healthy controls. Significance was defined for *P*-values less than 0.05. Statistical analysis was performed using GraphPad Prism version 8.2.0 for Windows, GraphPad Software.

Results

Baseline demographic and metabolic parameters

From September 2017 to March 2019, 150 patients were screened for eligibility. A consort diagram of the study population is outlined in Fig. 1. Fifty-eight patients were entered into the study. Two patients completed Visit 1 but did not commence the study drug. A further 5 patients withdrew from the study (4 had an adverse event and 1 declined to attend for follow-up) therefore, a total of 51 patients completed the study (i.e. with available data from both Visit 1 and Visit 2); 21 patients with PAI and 30 patients with SAI. The mean age of patients with PAI and SAI was similar (Table 1). There was a predominance of female patients in the PAI group and a predominance of men in the SAI. Disease duration and aetiology of AI in the study population are outlined in Table 1.

At study entry, patients with SAI had a significantly higher mean (s.d.) weight (94.8 kg (25.1) vs 76.4 kg (18.2), $P = 0.006$), BMI (31.5 kg/m² (7.3) vs 26.8 kg/m² (6.7), $P = 0.0023$) and waist circumference (106.4 cm (19) vs 88.5 cm (14), $P = 0.0009$) compared to patients with PAI, however, there were more men in the SAI group which may account for the observed differences (Table 2). Comparison of blood pressure and lipid characteristics of patients with PAI and SAI are presented in Table 2. Both PAI and SAI groups had similar mean blood pressure at baseline, however, a higher proportion of SAI patients were receiving anti-hypertensive therapy ($P = 0.03$). A higher proportion of SAI patients were receiving statin therapy ($P = 0.015$). Patients with PAI were on a higher median daily dose of hydrocortisone replacement compared to SAI patients (20 mg (IQR: 20–25 mg) vs 17.5 mg (IQR: 15–20 mg), $P = 0.0034$), and were more likely to receive thrice daily hydrocortisone than patients with SAI (Table 2).

Post 12 weeks of dual-release hydrocortisone therapy

Effect on blood pressure

After 12 weeks of DR-HC treatment, we observed a significant reduction in systolic blood pressure (−5.7 mmHg, $P = 0.0019$)

Figure 1

Consort diagram of the study population.

(Fig. 2A) and diastolic blood pressure (-4.5 mmHg, $P=0.0011$) (Fig. 2B) within the entire study population ($n = 51$). These observed reductions in SBP and DBP remained significant when adjusted for anti-hypertensive therapy (SBP adjusted $P = 0.009$, DBP adjusted $P = 0.005$). When comparing blood pressure reduction between patients with PAI and SAI, we observed a significant reduction in SBP and DBP in patients with SAI compared to patients with PAI (Fig. 2C, D, E and F).

Effects on body weight, BMI, body composition and waist circumference

We observed a significant reduction in mean body weight (-1.23 kg, $P = 0.006$), within the entire study population ($n = 51$) after 12 weeks of DR-HC (Fig. 3A). This translated to a significant reduction in BMI (-0.3 kg/m², $P = 0.003$) (Fig. 3B). There was a reduction in overall waist circumference (WCM) among the study group (-1 cm, $P = 0.07$) but this was not significant (Fig. 3C). Figure 3 also illustrates the observed reductions in body weight, BMI and WCM among the disease subgroups, PAI and SAI. Following 12 weeks of DR-HC, we observed a reduction in mean body weight in patients with SAI (-1.48 kg (s.d. 3.6), $P = 0.03$), compared to patients with PAI (-0.9 kg (s.d. 2.2),

Table 2 Patients with PAI ($n = 21$) and SAI ($n = 30$) at baseline. Data expressed as mean (S.D.) unless otherwise stated.

	Primary AI ($n = 21$)	Secondary AI ($n = 30$)	P value
Age (years)	41.1 (13.4)	47.5 (12.8)	0.08
Weight (kg)	76.4 (18.2)	94.8 (25.1)	0.006
BMI (kg/m ²)	26.8 (6.7)	31.5 (7.3)	0.002
WCM (cm)	88.5 (14)	106.4 (19)	0.0009
SBP (mmHg)	125.6 (15.7)	125.3 (14.7)	0.93
DBP (mmHg)	75.7 (9)	78.4 (10)	0.34
HR (b.p.m.)	71.7 (11.3)	71.8 (9.5)	0.99
Anti-hypertensive therapy (n)	0	6	0.03
Statin therapy (n)	1	10	0.015
Total Cholesterol (mmol/L)	4.88 (0.97)	4.9 (1.01)	0.83
LDL cholesterol (mmol/L)	2.73 (0.7)	2.95 (0.94)	0.38
Triglycerides (mmol/L)	0.79 (0.26)	1.1 (0.63)	0.05
HDL cholesterol (mmol/L)	1.79 (0.47)	1.48 (0.47)	0.02
HC replacement dose (mg/day)	20 (20–25)	17.5 (15–20)	0.003
Median (IQR)			
Replacement regimen			
BID	12	30	<0.0001
TID	9	0	<0.0001

Significance, $P < 0.05$.

BID, twice daily; DBP, diastolic blood pressure; HC, hydrocortisone; HR, heart rate; LDL, low-density lipoprotein; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; SBP, systolic blood pressure; TID, thrice daily.

$P = 0.07$) (Fig. 3A), however, patients with PAI did have a significant reduction in mean BMI (-0.34 kg/m², $P = 0.04$) (Fig. 3B). Patients with SAI also had a significant mean reduction in waist circumference (-2.7 cm, $P = 0.014$) (Fig. 3C). We did not find any significant differences in bioimpedance analysis post-DR-HC therapy among the study population (Supplementary Table 1, see section on supplementary materials given at the end of this article). However, we did observe a positive correlation between the reduction in body weight and the reduction in fat mass (kg) in the study population post-DR-HC ($r=0.67$ (95% CI 0.31–0.75), $P < 0.0001$) and a trend towards a positive correlation between the reduction in body weight and the reduction in SBP observed in the patient population, but this was not statistically significant ($r=0.27$ (95% CI 0.02–0.5), $P = 0.06$).

Effect on fasting lipids, HbA1c and haematology parameters

No differences in fasting cholesterol or HbA1c were observed after the 12 weeks of DR-HC. We observed a small but significant increase in mean fasting triglycerides after 12 weeks of DR-HC therapy ($+0.1$ mmol/L (0.02), $P = 0.03$). Due to a complementary *in-vivo* component of our study (where the patient received an overnight tablet of dexamethasone) fasting glucose and insulin could not be interpreted accurately.

Figure 2

Blood pressure on conventional immediate release HC (visit 1) and 12 weeks after dual-release hydrocortisone (visit 2). (A) SBP pre and post 12 weeks of DR-HC in the entire study population. (B) DBP pre and post 12 weeks of DR-HC in the entire study population. (C) SBP pre and post 12 weeks of DR-HC in patients with PAI. (D) DBP pre and post 12 weeks of DR-HC in patients with PAI. (E) SBP pre and post 12 weeks of DR-HC in patients with SAI. (F) DBP pre and post 12 weeks of DR-HC in patients with SAI. SBP, systolic blood pressure; DBP, diastolic blood pressure; DR-HC, dual-release hydrocortisone; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency.

There was a significant reduction in the mean total white cell count (WCC) between baseline and post 12 weeks of DR-HC ($7.03 \times 10^3/\mu\text{L}$ vs $6.56 \times 10^3/\mu\text{L}$, $P = 0.005$), with a significant reduction in neutrophil count ($5.06 \times 10^3/\mu\text{L}$ vs $4.63 \times 10^3/\mu\text{L}$, $P = 0.002$), but not in lymphocyte count.

We observed a small but significant reduction in the mean concentration of the liver enzyme, alanine aminotransferase (-2.5 mmol/L , $P = 0.04$) following 12 weeks of DR-HC. No statistical changes occurred in the concentration of bilirubin, alkaline phosphatase and gamma-glutamyl transpeptidase post 12 weeks of DR-HC therapy. Similarly, no statistically or clinically relevant changes were observed in other haematology parameters such as haemoglobin, haematocrit, platelet count, and in routine biochemistry including electrolytes, and bone profile.

Effect on quality of life (QoL)

In the SF-36, there was a significant improvement reported among the study population after 12 weeks of DR-HC in the physical and emotional role domains, in addition to a significant improvement in the domains of vitality, and mental health (Table 3). The AddiQoL was also assessed among the entire study cohort before and after DR-HC, and there was a significant improvement in mean QoL scores across all domains including; fatigue, symptoms, emotions and miscellaneous which includes sleep, sexuality and impact of intercurrent illness (Table 3). In the NHP, lower scores indicate better QoL. Patients reported significant improvement in energy levels after 12 weeks of DR-HC therapy (Table 3).

Using calculated Z scores (the s.d. from the mean of the normative population), we observed the same significant differences between Visit 1 (when patients were on conventional hydrocortisone) and Visit 2 (after 12 weeks of DR-HC), as outlined previously, which are illustrated in Fig. 4. In the SF-36 there was a reduction in the negative Z score in the physical role ($P = 0.001$), emotional ($P = 0.02$) role, vitality ($P = 0.0014$), and mental health ($P = 0.03$), after DR-HC compared to controls, signifying an improvement. Similarly, there was a reduction in the negative Z score in all domains of the AddiQoL after DR-HC, reflecting an improvement in QoL. In the NHP, we observed only a significant improvement post-DR-HC in the energy level domain (highlighted by a decrease in the positive Z value).

When examining results by disease group, we observed greater improvement in QoL post-DR-HC in patients with PAI compared to patients with SAI (Fig. 5). Patients with PAI reported significant improvement in all domains of the AddiQoL (Fig. 5D), in addition to an improvement in the

Figure 3

Change in (A) weight, (B) BMI and (C) waist circumference (WCM) in the study patients from baseline to 12 weeks post-dual-release hydrocortisone. Whole group = 51 patients; Primary adrenal insufficiency (PAI) = 21 patients; Secondary adrenal insufficiency (SAI) = 30 patients. Data expressed as mean (S.E.M.) unless otherwise stated, * P value < 0.05, ** P value < 0.01. WCM, waist circumference; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency.

physical role domain ($P = 0.005$), vitality ($P = 0.003$), and mental health ($P = 0.04$) in the SF-36 (Fig. 5A). For patients with SAI, all mean QoL scores improved post-DR-HC but only the domains of bodily pain ($P = 0.04$) and the emotional role ($P = 0.016$) in the SF-36 were significant (Fig. 5D).

Patient preference for either once daily DR-HC or conventional therapy was assessed at the end of the study, and 100% of patients chose to continue DR-HC if given the option.

Adverse events

No deaths occurred during the study. Three patients withdrew from the trial after reporting adverse events including fatigue and nausea, all occurring within 2 weeks of commencing the treatment. Two patients were hospitalised and treated with intravenous steroids with acute adrenal insufficiency triggered by infectious disorders (one case of bacterial gastroenteritis and one case of pneumonia). These two cases were deemed serious due to hospitalisation and occurred at least 4 weeks after DR-HC commencement. The patient with gastroenteritis continued DR-HC for the remainder of the study without adverse effects, while the patient with pneumonia discontinued the intervention.

The percentage of days when increased hydrocortisone use reported during the 3 months of DR-HC therapy was low (5% of study days), similar to that reported in a recent study by Schöfl *et al.* (25).

Discussion

Our prospective study shows that in patients with adrenal insufficiency (both PAI and SAI), the switch from conventional HC replacement therapy, at physiological replacement doses, to once-daily DR-HC is associated with significant improvements in blood pressure, body weight, BMI and QoL.

Similar to previous studies (9, 10, 14), we observed a significant reduction in weight and BMI in the entire study cohort, with an additional reduction in waist circumference observed in patients with SAI. This reduction in body weight may be related to the reduction in the 24-h exposure and supraphysiological peaks of circulating cortisol with DR-HC compared to immediate-release HC, as shown in previous pharmacokinetic studies (8, 26, 27). In the study by Johannsson and colleagues (8), the reduced area under the curve (AUC) of circulating cortisol obtained with DR-HC compared with immediate-release HC regimen was predominantly due to lower cortisol concentrations in the afternoon and evening. Studies have shown that treatment with immediate-release HC is associated with supraphysiological cortisol exposure in the late afternoon and evening (13). DR-HC displays a similar cortisol time-exposure profile to the endogenous cortisol profile, avoiding the fluctuations in cortisol concentration that occur with conventional hydrocortisone therapy (8).

We observed a mean reduction in SBP of -5.7 mmHg and DBP of -4.5 mmHg post 12 weeks of DR-HC. Our study population were receiving a lower median daily HC dose of 20 mg at study entry compared to previous studies reporting a similar BP reduction (8), demonstrating that the beneficial effect on BP is not only observed at higher mean daily HC doses, as previously debated (12). Importantly, earlier studies that have focused on simply a reduction in the daily cumulative HC dose using immediate-release hydrocortisone failed to demonstrate any benefit on BP (28, 29, 30). We observed a greater reduction in BP in patients with SAI compared to patients with PAI post-DR-HC, which has not been previously reported. Some patients with SAI may have partial ACTH deficiency, with higher circulating endogenous cortisol levels than patients with PAI. These patients may, therefore, be over-replaced on similar doses of HC replacement to patients with PAI. However, the patients in our study had evidence of severe ACTH deficiency confirmed on dynamic testing at diagnosis and were on a median daily HC dose of 17.5 mg (IQR 15–20 mg), therefore were unlikely to be over-replaced before initiation of DR-HC.

Clinical Study	R Dineen and others	Benefits of dual-release hydrocortisone in adrenal insufficiency	184:2	260
----------------	---------------------	--	-------	-----

Table 3 Absolute quality of life scores in patients with adrenal insufficiency at baseline, on conventional immediate release hydrocortisone (Visit 1), after 12 weeks of dual-release hydrocortisone (Visit 2), and age and BMI-matched healthy control population from a similar socio-economic background. Data expressed as mean (S.D.)

	QoL in patients with AI on conventional HC compared to healthy controls			QoL in patients with AI before (Visit 1) and after 12 weeks of DR-HC (Visit 2)			Effect size Cohens <i>d</i> (95% CI)
	(Visit 1§)	Controls	<i>P</i> value	Visit 1	Visit 2	<i>P</i> value	
Short Form-36 (<i>High scores indicate better QoL</i>)*							
Physical functioning	79.8 (19.3)	98.6 (2.9)	0.0001	79.8 (19.3)	80.8 (20.31)	0.69	0.05 (−0.34, 0.44)
Role physical	60 (39.5)	100 (0)	<0.0001	60 (39.5)	76 (36.1)	0.003	0.42 (0.03, 0.81)
Bodily pain	76 (24.8)	85.4 (13)	0.13	76 (24.8)	72.6 (27.5)	0.23	−0.13 (−0.76, 0.51)
General health	55.6 (20.9)	88.2 (11.8)	<0.0001	55.6 (20.9)	57.2 (21.9)	0.39	0.07 (−0.56, 0.71)
Vitality	34.2 (17)	57.3 (9.7)	<0.0001	34.2 (17)	41.6 (19.9)	0.001	0.4 (−0.25, 1.03)
Social functioning	75.8 (24.4)	96.5 (8.4)	0.0008	75.8 (24.4)	80 (23.6)	0.16	0.17 (−0.47, 0.81)
Role emotional	70 (37.65)	92.6 (18.3)	0.018	70 (37.7)	81.3 (31.7)	0.048	0.32 (−0.32, 0.96)
Mental health	73.8 (17.34)	87.3 (9.9)	0.003	73.8 (17.3)	77.2 (19.3)	0.032	0.19 (−0.46, 0.82)
Nottingham Health Profile (<i>Low scores indicate better QoL</i>)							
Energy level	36.3 (38.9)	2.2 (9.2)	<0.001	36.3 (38.9)	25.3 (36.2)	0.028	0.29 (−0.35, 0.93)
Pain	13.0 (24.6)	1.1 (4.8)	0.04	13.0 (24.6)	13.4 (26.7)	0.49	0 (−0.64, 0.633)
Emotional reaction	15.9 (22)	4.2 (15.3)	0.04	15.9 (22)	12.3 (20.6)	0.059	0.17 (−0.47, 0.8)
Sleep	19.3 (25)	6.6 (18.5)	0.03	19.3 (25)	17.3 (25.7)	0.38	0.08 (−0.56, 0.71)
Social isolation	11.2 (24.5)	0 (0)	0.06	11.2 (24.5)	13.1 (27.7)	0.31	0.07 (−0.71, 0.56)
Physical abilities	8.2 (13.2)	0.2 (3.5)	0.03	8.2 (13.2)	8.0 (13.4)	0.67	0.01 (−0.62, 0.65)
AddiQoL (<i>High scores indicate better QoL</i>)							
Fatigue	30.9 (8.3)	43.2 (3)	<0.0001	30.9 (8.3)	34.1 (7.8)	0.001	0.37 (−0.28, 1.01)
Symptoms	40.5 (10)	50.8 (2.4)	<0.0001	40.5 (10)	43.7 (7.7)	0.0006	0.35 (−0.29, 0.99)
Emotions	35 (6.9)	42.4 (3.9)	<0.0001	35 (6.9)	37.0 (6.7)	0.016	0.29 (−0.35, 0.93)
Miscellaneous (sleep, sexuality, and impact of intercurrent disease, six items)	18.2 (5.0)	25.5 (2.5)	<0.0001	18.2 (5.0)	19.9 (5.1)	0.019*	0.33 (−0.31, 0.97)

Significance $P < 0.05$. *Marked out of 100; §Represents patients with AI at baseline.

AI, adrenal insufficiency; DR-HC, dual-release hydrocortisone.

All-cause mortality is increased in patients with hypopituitarism when compared with age- and sex-matched controls (31), and this is predominantly due to cardiovascular disease (CVD) (32, 33, 34). Cardiovascular risk factors are highly prevalent in adult patients with hypopituitarism (35). A recent systematic review and meta-analysis of all available large-scale blood pressure-lowering randomised trials (36), revealed that a 10 mmHg reduction in SBP reduced the risk of cardiovascular disease events by 20%, coronary heart disease by 17%, stroke by 27%, heart failure by 28% and all-cause mortality by 13%. Additionally, they observed that proportional reductions were seen in trials that included patients with lower baseline systolic blood pressure (<130 mmHg) and major cardiovascular events were reduced in high-risk patients with baseline comorbidities (36). Therefore, a mean SBP reduction of 6.9 mmHg in our patients with SAI (even with baseline SBP <130 mmHg) is significant and may translate to a risk reduction in cardiovascular events.

In comparison to the study by Johannsson *et al.* (8), we did not observe a significant reduction in BP in

patients with PAI. However, our study included a smaller number of patients with PAI and therefore was potentially underpowered to appreciate a significant difference. Also, our patients with PAI were receiving a lower median daily HC dose of 20 mg (s.d. 15–20 mg) at study entry, compared to the study by Johannsson *et al.*, where approx. 88% of patients were receiving a daily HC dose of ≥ 25 mg, with 19% receiving 40 mg of HC daily. In patients who receive higher doses of hydrocortisone, there is a potential for cortisol to inappropriately activate the mineralocorticoid receptor (MR) (37). From a clinical perspective, a non-statistical reduction in BP in patients with PAI may be a reassuring observation. Patients with PAI have concurrent mineralocorticoid deficiency, making them vulnerable to fluctuations in salt and water balance and therefore blood pressure homeostasis.

We observed a significant reduction in the mean total WBC count (and in particular a reduction in neutrophil count) post 12 weeks of DR-HC. This is a potential further beneficial effect of DR-HC as several epidemiological studies have shown a positive correlation between WBC count and risk of cardiovascular disease both in healthy

Figure 4

Quality of life standard deviation scores (Z scores) calculated using age- and gender-matched control data for the SF36 (A), NHP (B) and AddiQoL (C) questionnaires between Visit 1 (on conventional hydrocortisone) and Visit 2 (post 12 weeks of dual-release hydrocortisone) in the entire cohort. QoL – the quality of life, SF36 – short form 36 QoL questionnaire, NHP – Nottingham health profile questionnaire, Z scores – standard deviation scores calculated using age- and gender-matched control data. Data expressed in mean (S.E.M.) unless otherwise stated. P value > 0.05 , * P value < 0.05 , ** P value < 0.01 , *** P value < 0.001 . NHP: positive Z score denotes worse QoL compared to healthy controls. SF36 and AddiQoL: negative Z score denotes worse QoL compared to healthy control.

subjects and in patients with established CVD (38, 39, 40, 41). Studies have shown that the higher risk for CVD associated with increased total WBC count seemed to be accounted for by the increased neutrophil count (42, 43).

We also observed a small but significant reduction in the mean concentration of the liver enzyme, ALT. Serum ALT has been shown in cross-sectional studies to be associated with the presence of fatty liver on ultrasonography and with liver fat content as measured by MRI spectroscopy (44). Additionally, serum ALT has been proposed as a biomarker for non-alcoholic fatty liver disease (NAFLD) (45). Recent data by Guarnotta who showed an improvement in the hepatic steatosis index post 12 months of DR-HC treatment, however, this study focused on patients with secondary AI only (17). There is a paucity of data investigating NAFLD in patients with primary adrenal insufficiency hence the observed reduction post-DR-HC in our study population, including both PAI and SAI, is interesting and requires further investigation.

We have confirmed, with a more comprehensive set of assessments, the previously reported improvement in QoL associated with DR-HC therapy (8, 10, 14, 15, 46). Our study group reported significant improvements in energy, physical roles, emotional roles, vitality and mental health. Patients with PAI reported significant improvements in all domains of the AddiQoL. These self-reported improvements in QoL challenge the argument that the observed reductions in BP, body weight, and BMI may be explained by simply reducing total daily cortisol exposure and potentially rendering the patient hypo adrenal, as numerous studies have shown that insufficient glucocorticoid replacement results in a reported deterioration in QoL (47).

Inadequate GC replacement therapy is suspected to be a major cause of reduced QoL in AI, although evidence has been lacking (48, 49). Immediate release HC given in twice/thrice daily doses is associated with considerable variability in cortisol concentrations, with a substantial proportion of patients being undertreated and overtreated during the same 24-h period (13). DR-HC avoids these multiple daily peaks and troughs in cortisol levels, which may translate to the observed improvement in QoL for these patients.

Transition to once-daily, dual-release hydrocortisone appeared to be safe, with no significant adverse events. Minor adverse events were recorded and perhaps, given the non-blinded nature of the study, patients may have increased awareness of associated signs and symptoms than to a real change in cortisol exposure. We did observe an increase in fasting triglycerides, which has been seen

Figure 5

Quality of life scores in patients with PAI ($n = 21$) and SAI ($n = 30$) at baseline, on conventional immediate release hydrocortisone (Visit 1) and post 12 weeks of dual-release hydrocortisone (Visit 2). Data expressed in mean (s.e.m.) unless otherwise stated, significance P value < 0.05 . PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; NHP, Nottingham Health Profile; SF-36, Short Form 36; AddiQoL, Addison's Disease-specific Quality of Life questionnaire. SF-36 and AddiQoL: High scores indicate better QoL, NHP: Low scores indicate better QoL for NHP.

in the previous trials (8, 15), and which merits further investigation.

Our study has some limitations. First, patients were not blinded to the treatment (for safety purposes) which could influence subjective parameters such as the QoL questionnaires. Secondly, patients who took part in the study may have been a more motivated patient cohort as they agreed to take part in the study. However, we feel our paper also has strengths including the inclusion of patients with primary and secondary adrenal insufficiency, which allowed comparison of the effect of DR-HC. The relatively lower dose of hydrocortisone used in our cohort compared to previous studies. All our patients were receiving hydrocortisone before a switch to DR-HC in comparison to previous studies which have had patients

who have switched from other glucocorticoids (such as prednisolone or cortisone acetate) and was, therefore, a more homogenous group of patients for comparison.

Conclusion

In patients with adrenal insufficiency, with adverse cardiovascular profiles and impaired quality of life, replacement therapy with DR-HC, which more closely resembles the normal endogenous circadian cortisol rhythm than immediate-release HC, offers measurable benefits with a reduction in blood pressure, weight and BMI compared with conventional HC treatment. Patients with SAI demonstrated a greater reduction in blood pressure

compared to patients with PAI post-DR-HC treatment, which has important implications, as this cohort have excess cardiovascular mortality. Additionally, DR-HC confers significant improvements in QoL compared to immediate-release HC, particularly in patients with primary adrenal insufficiency, which was also reflected in the patient preference for DR-HC in this study. This study highlights the potential difference in the benefits of DR-HC between patients with primary and secondary adrenal insufficiency and the need for a personalized approach to the management of patients with adrenal insufficiency receiving hydrocortisone therapy (50).

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-20-0642>.

Declaration of interest

R D is funded by the Irish Research Council, The Meath Foundation and The Irish Endocrine Society. M S has received funding for this Investigator-Initiated Study from Shire (IE). The other authors have nothing to disclose.

Funding

The Irish Research Council, The Meath Foundation, Irish Endocrine Society, Shire Ltd. The funders of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Acknowledgements

The authors would like to thank all the study participants who kindly volunteered to participate in this study. The authors would also like to thank the staff of the RCSI Clinical Research Facility, Dublin, Ireland, and Dr Iona Galloway, Dr Maria Tomkins and Dr Liam O Murchadha, Department of Endocrinology, Beaumont Hospital, Dr Conor Woods, Department of Endocrinology, Naas General Hospital, Ireland and Professor Jeremy Tomlinson, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, UK, for their assistance during the study.

References

- Arlt W & Allolio B. Adrenal insufficiency. *Lancet* 2003 **361** 1881–1893. ([https://doi.org/10.1016/S0140-6736\(03\)13492-7](https://doi.org/10.1016/S0140-6736(03)13492-7))
- Bensing S, Brandt L, Tabaroj F, Sjöberg O, Nilsson B, Ekblom A, Blomqvist P & Kampe O. Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency. *Clinical Endocrinology* 2008 **69** 697–704. (<https://doi.org/10.1111/j.1365-2265.2008.03340.x>)
- Erichsen MM, Lovas K, Fougner KJ, Svartberg J, Hauge ER, Bollerslev J, Berg JP, Mella B & Husebye ES. Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death. *European Journal of Endocrinology* 2009 **160** 233–237. (<https://doi.org/10.1530/EJE-08-0550>)
- Bergthorsdottir R, Leonsson-Zachrisson M, Oden A & Johannsson G. Premature mortality in patients with Addison's disease: a population-based study. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 4849–4853. (<https://doi.org/10.1210/jc.2006-0076>)
- Skov J, Sundstrom A, Ludvigsson JF, Kampe O & Bensing S. Sex-specific risk of cardiovascular disease in autoimmune Addison disease—a population-based cohort study. *Journal of Clinical Endocrinology and Metabolism* 2019 **104** 2031–2040. (<https://doi.org/10.1210/jc.2018-02298>)
- Aulinas A & Webb SM. Health-related quality of life in primary and secondary adrenal insufficiency. *Expert Review of Pharmacoeconomics and Outcomes Research* 2014 **14** 873–888. (<https://doi.org/10.1586/14737167.2014.963559>)
- Filipsson H, Monson JP, Koltowska-Haggstrom M, Mattsson A & Johannsson G. The impact of glucocorticoid replacement regimens on metabolic outcome and comorbidity in hypopituitary patients. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3954–3961. (<https://doi.org/10.1210/jc.2006-0524>)
- Johannsson G, Nilsson AG, Bergthorsdottir R, Burman P, Dahlqvist P, Ekman B, Engstrom BE, Olsson T, Ragnarsson O, Ryberg M *et al.* Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 473–481. (<https://doi.org/10.1210/jc.2011-1926>)
- Johannsson G, Skrtic S, Lennernas H, Quinkler M & Stewart PM. Improving outcomes in patients with adrenal insufficiency: a review of current and future treatments. *Current Medical Research and Opinion* 2014 **30** 1833–1847. (<https://doi.org/10.1185/03007995.2014.925865>)
- Isidori AM, Venneri MA, Graziadio C, Simeoli C, Fiore D, Hasenmajer V, Sbardella E, Gianfrilli D, Pozza C, Pasqualetti P *et al.* Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial. *Lancet: Diabetes and Endocrinology* 2018 **6** 173–185. ([https://doi.org/10.1016/S2213-8587\(17\)30398-4](https://doi.org/10.1016/S2213-8587(17)30398-4))
- Isidori AM, Hasenmajer V & Venneri MA. Once-daily, modified-release hydrocortisone in patients with adrenal insufficiency – authors' reply. *Lancet: Diabetes and Endocrinology* 2018 **6** 270–271. ([https://doi.org/10.1016/S2213-8587\(18\)30040-8](https://doi.org/10.1016/S2213-8587(18)30040-8))
- Khoo B. Once-daily, modified-release hydrocortisone in patients with adrenal insufficiency. *Lancet: Diabetes and Endocrinology* 2018 **6** 269. ([https://doi.org/10.1016/S2213-8587\(18\)30044-5](https://doi.org/10.1016/S2213-8587(18)30044-5))
- Behan LA, Rogers B, Hannon MJ, O'Kelly P, Tormey W, Smith D, Thompson CJ & Agha A. Optimizing glucocorticoid replacement therapy in severely adrenocorticotropin-deficient hypopituitary male patients. *Clinical Endocrinology* 2011 **75** 505–513. (<https://doi.org/10.1111/j.1365-2265.2011.04074.x>)
- Quinkler M, Miodini Nilsen R, Zopf K, Venz M & Oksnes M. Modified-release hydrocortisone decreases BMI and HbA1c in patients with primary and secondary adrenal insufficiency. *European Journal of Endocrinology* 2015 **172** 619–626. (<https://doi.org/10.1530/EJE-14-1114>)
- Mongioi LM, Condorelli RA, La Vignera S & Calogero AE. Dual-release hydrocortisone treatment: glycometabolic profile and health-related quality of life. *Endocrine Connections* 2018 **7** 211–219. (<https://doi.org/10.1530/EC-17-0368>)
- Guarnotta V, Di Stefano C, Santoro A, Ciresi A, Coppola A & Giordano C. Dual-release hydrocortisone vs conventional glucocorticoids in adrenal insufficiency. *Endocrine Connections* 2019 **8** 853–862. (<https://doi.org/10.1530/EC-19-0176>)
- Guarnotta V, Mineo MI, Radellini S, Pizzolanti G & Giordano C. Dual-release hydrocortisone improves hepatic steatosis in patients with secondary adrenal insufficiency: a real-life study. *Therapeutic Advances in Endocrinology and Metabolism* 2019 **10** 2042018819871169. (<https://doi.org/10.1177/2042018819871169>)
- Ceccato F, Selmin E, Sabbadin C, Dalla Costa M, Antonelli G, Plebani M, Barbot M, Betterle C, Boscaro M & Scaroni C. Improved

Clinical Study	R Dineen and others	Benefits of dual-release hydrocortisone in adrenal insufficiency	184:2	264
----------------	---------------------	--	-------	-----

- salivary cortisol rhythm with dual-release hydrocortisone. *Endocrine Connections* 2018 **7** 965–974. (<https://doi.org/10.1530/EC-18-0257>)
- 19 Frara S, Chiloiro S, Porcelli T, Giampietro A, Mazziotti G, De Marinis L & Giustina A. Bone safety of dual-release hydrocortisone in patients with hypopituitarism. *Endocrine* 2018 **60** 528–531. (<https://doi.org/10.1007/s12020-017-1512-1>)
 - 20 Boffa RJ, Constanti M, Floyd CN, Wierzbicki AS & Guideline Committee. Hypertension in adults: summary of updated NICE guidance. *BMJ* 2019 **367** l5310. (<https://doi.org/10.1136/bmj.l5310>)
 - 21 Brazier JE, Harper R, Jones NM, O’Cathain A, Thomas KJ, Usherwood T & Westlake L. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992 **305** 160–164. (<https://doi.org/10.1136/bmj.305.6846.160>)
 - 22 Oksnes M, Bensing S, Hulting AL, Kampe O, Hackemann A, Meyer G, Badenhop K, Betterle C, Parolo A, Giordano R *et al.* Quality of life in European patients with Addison’s disease: validity of the disease-specific questionnaire AddiQoL. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 568–576. (<https://doi.org/10.1210/jc.2011-1901>)
 - 23 Hunt SM, McKenna SP, McEwen J, Backett EM, Williams J & Papp E. A quantitative approach to perceived health status: a validation study. *Journal of Epidemiology and Community Health* 1980 **34** 281–286. (<https://doi.org/10.1136/jech.34.4.281>)
 - 24 Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA *et al.* Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 364–389. (<https://doi.org/10.1210/jc.2015-1710>)
 - 25 Schoff C, Mayr B, Maison N, Beuschlein F, Meyer G, Badenhop K, Kienitz T & Quinkler M. Daily adjustment of glucocorticoids by patients with adrenal insufficiency. *Clinical Endocrinology* 2019 **91** 256–262. (<https://doi.org/10.1111/cen.14004>)
 - 26 Johannsson G, Lennernas H, Marelli C, Rockich K & Skrtic S. Achieving a physiological cortisol profile with once-daily dual-release hydrocortisone: a pharmacokinetic study. *European Journal of Endocrinology* 2016 **175** 85–93. (<https://doi.org/10.1530/EJE-15-1212>)
 - 27 Johannsson G, Bergthorsdottir R, Nilsson AG, Lennernas H, Hedner T & Skrtic S. Improving glucocorticoid replacement therapy using a novel modified-release hydrocortisone tablet: a pharmacokinetic study. *European Journal of Endocrinology* 2009 **161** 119–130. (<https://doi.org/10.1530/EJE-09-0170>)
 - 28 Dunne FP, Elliot P, Gammage MD, Stallard T, Ryan T, Sheppard MC & Stewart PM. Cardiovascular function and glucocorticoid replacement in patients with hypopituitarism. *Clinical Endocrinology* 1995 **43** 623–629. (<https://doi.org/10.1111/j.1365-2265.1995.tb02928.x>)
 - 29 Danilowicz K, Bruno OD, Manavella M, Gomez RM & Barkan A. Correction of cortisol overreplacement ameliorates morbidities in patients with hypopituitarism: a pilot study. *Pituitary* 2008 **11** 279–285. (<https://doi.org/10.1007/s11102-008-0126-2>)
 - 30 Peacey SR, Guo CY, Robinson AM, Price A, Giles MA, Eastell R & Weetman AP. Glucocorticoid replacement therapy: are patients over treated and does it matter? *Clinical Endocrinology* 1997 **46** 255–261. (<https://doi.org/10.1046/j.1365-2265.1997.780907.x>)
 - 31 Sherlock M, Ayuk J, Tomlinson JW, Toogood AA, Aragon-Alonso A, Sheppard MC, Bates AS & Stewart PM. Mortality in patients with pituitary disease. *Endocrine Reviews* 2010 **31** 301–342. (<https://doi.org/10.1210/er.2009-0033>)
 - 32 Bates AS, Van’t Hoff W, Jones PJ & Clayton RN. The effect of hypopituitarism on life expectancy. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 1169–1172. (<https://doi.org/10.1210/jcem.81.3.8772595>)
 - 33 Bulow B, Hagmar L, Mikoczy Z, Nordstrom CH & Erfurth EM. Increased cerebrovascular mortality in patients with hypopituitarism. *Clinical Endocrinology* 1997 **46** 75–81. (<https://doi.org/10.1046/j.1365-2265.1997.d01-1749.x>)
 - 34 Rosen T & Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990 **336** 285–288. ([https://doi.org/10.1016/0140-6736\(90\)91812-o](https://doi.org/10.1016/0140-6736(90)91812-o))
 - 35 Deepak D, Furlong NJ, Wilding JP & MacFarlane IA. Cardiovascular disease, hypertension, dyslipidaemia and obesity in patients with hypothalamic-pituitary disease. *Postgraduate Medical Journal* 2007 **83** 277–280. (<https://doi.org/10.1136/pgmj.2006.052241>)
 - 36 Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A & Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016 **387** 957–967. ([https://doi.org/10.1016/S0140-6736\(15\)01225-8](https://doi.org/10.1016/S0140-6736(15)01225-8))
 - 37 Stewart PM & Edwards CR. The cortisol-cortisone shuttle and hypertension. *Journal of Steroid Biochemistry and Molecular Biology* 1991 **40** 501–509. ([https://doi.org/10.1016/0960-0760\(91\)90269-b](https://doi.org/10.1016/0960-0760(91)90269-b))
 - 38 Margolis KL, Manson JE, Greenland P, Rodabough RJ, Bray PF, Safford M, Grimm RH, Jr, Howard BV, Assaf AR, Prentice R *et al.* Leukocyte count as a predictor of cardiovascular events and mortality in postmenopausal women: the Women’s Health Initiative Observational Study. *Archives of Internal Medicine* 2005 **165** 500–508. (<https://doi.org/10.1001/archinte.165.5.500>)
 - 39 Zalokar JB, Richard JL & Claude JR. Leukocyte count, smoking, and myocardial infarction. *New England Journal of Medicine* 1981 **304** 465–468. (<https://doi.org/10.1056/NEJM198102193040806>)
 - 40 Danesh J, Collins R, Appleby P & Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA* 1998 **279** 1477–1482. (<https://doi.org/10.1001/jama.279.18.1477>)
 - 41 Sabatine MS, Morrow DA, Cannon CP, Murphy SA, Demopoulos LA, DiBattiste PM, McCabe CH, Braunwald E & Gibson CM. Relationship between baseline white blood cell count and degree of coronary artery disease and mortality in patients with acute coronary syndromes: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction 18 trial) substudy. *Journal of the American College of Cardiology* 2002 **40** 1761–1768. ([https://doi.org/10.1016/s0735-1097\(02\)02484-1](https://doi.org/10.1016/s0735-1097(02)02484-1))
 - 42 Rana JS, Boekholdt SM, Ridker PM, Jukema JW, Luben R, Bingham SA, Day NE, Wareham NJ, Kastelein JJ & Khaw KT. Differential leukocyte count and the risk of future coronary artery disease in healthy men and women: the EPIC-Norfolk Prospective Population Study. *Journal of Internal Medicine* 2007 **262** 678–689. (<https://doi.org/10.1111/j.1365-2796.2007.01864.x>)
 - 43 Wheeler JG, Mussolino ME, Gillum RF & Danesh J. Associations between differential leucocyte count and incident coronary heart disease: 1764 incident cases from seven prospective studies of 30,374 individuals. *European Heart Journal* 2004 **25** 1287–1292. (<https://doi.org/10.1016/j.ehj.2004.05.002>)
 - 44 Westerbacka J, Corner A, Tiikkainen M, Tamminen M, Vehkavaara S, Hakkinen AM, Fredriksson J & Yki-Jarvinen H. Women and men have similar amounts of liver and intra-abdominal fat, despite more subcutaneous fat in women: implications for sex differences in markers of cardiovascular risk. *Diabetologia* 2004 **47** 1360–1369. (<https://doi.org/10.1007/s00125-004-1460-1>)
 - 45 Kim WR, Flamm SL, Di Bisceglie AM, Bodenheimer HC & Public Policy Committee of the American Association for the Study of Liver Disease. Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. *Hepatology* 2008 **47** 1363–1370. (<https://doi.org/10.1002/hep.22109>)
 - 46 Giordano R, Guaraldi F, Marinazzo E, Fumarola F, Rampino A, Berardelli R, Karamouzis I, Lucchiarini M, Manetta T, Mengozzi G *et al.* Improvement of anthropometric and metabolic parameters, and

Clinical Study	R Dineen and others	Benefits of dual-release hydrocortisone in adrenal insufficiency	184:2	265
----------------	---------------------	--	-------	-----

- quality of life following treatment with dual-release hydrocortisone in patients with Addison's disease. *Endocrine* 2016 **51** 360–368. (<https://doi.org/10.1007/s12020-015-0681-z>)
- 47 Hahner S, Loeffler M, Bleicken B, Drechsler C, Milovanovic D, Fassnacht M, Ventz M, Quinkler M & Allolio B. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. *European Journal of Endocrinology* 2010 **162** 597–602. (<https://doi.org/10.1530/EJE-09-0884>)
- 48 Grossman A, Johannsson G, Quinkler M & Zelissen P. Therapy of endocrine disease: perspectives on the management of adrenal insufficiency: clinical insights from across Europe. *European Journal of Endocrinology* 2013 **169** R165–R175. (<https://doi.org/10.1530/EJE-13-0450>)
- 49 Hahner S, Loeffler M, Fassnacht M, Weismann D, Koschker AC, Quinkler M, Decker O, Arlt W & Allolio B. Impaired subjective health status in 256 patients with adrenal insufficiency on standard therapy based on cross-sectional analysis. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 3912–3922. (<https://doi.org/10.1210/jc.2007-0685>)
- 50 Stewart PM. Modified-release hydrocortisone: is it time to change clinical practice? *Journal of the Endocrine Society* 2019 **3** 1150–1153. (<https://doi.org/10.1210/js.2019-00046>)

Received 9 June 2020

Revised version received 22 October 2020

Accepted 16 November 2020