Conventional glucocorticoid replacement overtreats adult hypopituitary patients with partial ACTH deficiency

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Summary

BACKGROUND Glucocorticoid therapy is associated with potentially serious side-effects, but there is no information available regarding glucocorticoid requirement in adult hypopituitary patients with partial ACTH deficiency.

SUBJECTS Ten male adult hypopituitary patients with partial ACTH deficiency, baseline plasma cortisol > 200 nmol/l but a peak stimulated cortisol < 500 nmol/l and 10 matched healthy male control volunteers participated.

DESIGN Patients were assigned, in a random order, to a cross-over protocol of treatment for 1 week with full dose hydrocortisone (10 mg twice daily), half-dose hydrocortisone (5 mg twice daily), or no treatment. All patients completed all three of the treatment limbs.

MEASUREMENTS Following each treatment schedule, patients underwent an 11-h cortisol day curve (CDC), and the results were compared with those from the 10 control volunteers on no glucocorticoid treatment.

RESULTS The integrated CDC values were significantly higher in patients taking a full dose of hydrocortisone compared to controls ($P < 0.001$). There was no significant difference in the integrated CDC between patients on half-dose ($P = 0.37$) or no hydrocortisone treatment ($P = 0.13$), compared to control subjects. Peak post-absorption cortisol values were higher in patients receiving full-dose hydrocortisone treatment compared to controls ($P < 0.001$). There was no significant difference in plasma sodium concentration, blood pressure or corticosteroid-binding globulin between patients on any treatment schedule and controls.

CONCLUSION Adult patients with pituitary disease and partial ACTH deficiency have a cortisol secretory pattern comparable to that of healthy controls. Conventional full-dose replacement with 10 mg twice daily of hydrocortisone produces hypercortisolaemia, whereas half-dose produces a CDC that is not statistically different from that of healthy controls. The results suggest that current conventional glucocorticoid replacement overtreats patients with partial ACTH deficiency under normal unstressed physiological conditions.

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Adrenocorticotrophin hormone (ACTH) deficiency is a common manifestation of hypothalamic–pituitary disease, but there is no unified approach to diagnosis or treatment. The gold standard method for the diagnosis of ACTH deficiency is the insulin tolerance test (ITT, Fish *et al*., 1986). Other provocative tests of cortisol secretion, such as the glucagon test (Spathis *et al*., 1974; Rao & Spathis, 1987) and the short ACTH (synachten) test (Stewart *et al*., 1988) are used in some centres. A variety of normal peak cortisol responses to provocative tests have been reported by different units, with normal cut-off concentrations quoted between 500 and 600 nmol/l (Jones *et al*., 1994; Lindholm, 2001).

In addition, there is no clear consensus on the optimum glucocorticoid replacement dose. In the particular case of patients with partial ACTH deficiency, there is no agreement as to whether regular maintenance glucocorticoid therapy is needed at all. Anecdotally, practice varies between full-dose replacement therapy in some centres, to no glucocorticoid treatment other than during intercurrent illness in other units. The lack of agreement on optimum practice is a reflection of the paucity of published data on the adequacy of different glucocorticoid replacement regimens. Prescribing the appropriate dose of glucocorticoid is crucial, as excessive doses are associated with metabolic disturbances, osteoporosis and hypertension resulting in a cushingoid state (Poltz *et al*., 1952). In this paper we report the cortisol day profiles of patients with partial ACTH deficiency treated with full-strength hydrocortisone replacement dose, half-strength hydrocortisone replacement dose, and no glucocorticoid treatment therapy.

Methods

Subjects

Male adult hypopituitary patients with partial ACTH deficiency, defined as a fasting 08·00 h total serum cortisol exceeding 200 nmol/l with a stimulated peak value of less than 500 nmol/l, were identified from the Beaumont Hospital Pituitary Database. ACTH reserves were assessed fewer than 6 months before the start of the study in all patients. Our local practice is to use the ITT as gold standard for the identification of ACTH deficiency, with glucagon stimulation testing (GST) as an alternative when the ITT is contraindicated because of seizure disorders or cardiac disease. A peak cortisol response > 500 nmol/l is defined in our laboratory as normal. Because glucagon stimulation is associated with subnormal cortisol responses in about 8% of healthy subjects (Rao & Spathis, 1987), patients whose ACTH deficiency was defined by abnormal response to GST were only included if they also had both significant GH deficiency (stimulated peak < 3 ng/ml and IGF-1 below age-specified reference range) and gonadotrophin deficiency, in order to exclude those with false negative responses to glucagon.

We also excluded patients with severe cardiac or respiratory disease, patients with terminal illness and patients on antiepileptic therapy or other medications which interfere with hydrocortisone metabolism. Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) levels. We identified 14 patients who fulfilled the above criteria; 10 agreed to participate in the study. All patients had pituitary tumours. Eight patients had ACTH deficiency defined by ITT (nadir glucose value < 2·2 mmol/l was achieved in each case) and two patients by GST.

All six nonacromegalic patients had GH deficiency; four were treated with recombinant human GH. Eight patients were gonadotrophin-deficient and were on testosterone replacement.

Four patients were on regular maintenance hydrocortisone treatment prior to starting the study. The four patients with acromegaly had a mean GH value on a five-point GH-day curve of less than 2·5 ng/ml, with serum IGF-1 in the normal age-specified reference range. Clinical details of patients are summarized in Table 1.

Ten healthy male control volunteers were studied. All patients and controls gave written informed consent to participate in the study, which was approved by the Beaumont Hospital Medical Research (Ethics) Committee.

Study design

All 10 participating patients were assigned, in a cross-over protocol, to take conventional full-dose oral hydrocortisone, defined as 10 mg twice daily, for 1 week; half-dose of oral hydrocortisone, defined as 5 mg twice daily, for 1 week; and no hydrocortisone treatment for 1 week. The patients sequentially took each treatment in a random order. On the last day of each treatment schedule, the subject was admitted to our clinical research centre for a cortisol day curve (CDC), which was a modification of that described by Trainer & Besser (1995). Patients were admitted at 07·00 h, following a 12-h fast. A heparinized intravenous cannula was inserted in a peripheral vein and clotted blood samples for serum total cortisol measurements were drawn at 08·00, 09·00, 10·00, 11·00, 13·00, 15·00, 17·00, 18·00 and 19·00 h. Hydrocortisone treatment was given at 08·00 and 17·00 h.

Baseline clotted blood samples were withdrawn for measurement of corticosteroid-binding globulin (CBG), free T4, TSH, testosterone, prolactin and IGF-1. A lithium–heparin blood sample was also collected for measurement of plasma sodium on each the three testing days.

Resting pulse rate (PR) and blood pressure (BP) were measured on the morning of each of the three testing days. BP was measured

Table 1 Clinical characteristics of patients

Patient	Age (years)	BMI kg/m^2	Diagnosis	Pituitary surgery	Other hormone deficiencies	Basal cortisol (nmol/l)	Peak stimulated cortisol (nmol/l)	Hormone replacement
1	50	33·2	prolactinoma	No	GH, GT	258	467 (ITT)	T
2	41	25·8	acromegaly	Yes	GT	228	329 (ITT)	T, HC
3	49	27·2	NSA	No	GH, GT	215	344 (GST)	T, rh-GH
4	48	28·7	NSA	Yes	GH, GT	298	495 (ITT)	rh-GH, T
5	60	31	acromegaly	Yes	GT	215	471 (ITT)	T, HC
6	41	31·9	acromegaly	Yes	_	206	446 (ITT)	HC
7	41	38·5	prolactinoma	Yes	GH, GT	385	442 (ITT)	rh-GH, T, HC
8	32	32·5	prolactinoma	No	GH, GT	282	409 (ITT)	T
9	23	24·8	prolactinoma	Yes	GH, GT	294	418 (GST)	rh-GH, T
10	54	37	acromegaly	Yes	GT	358	494 (ITT)	T

Peak cortisol indicates stimulated level after ITT (insulin tolerance test); or GST (glucagon stimulation test). NSA, nonsecretory adenoma; GH, growth hormone; GT, gonadotrophins; T, testosterone; HC, hydrocortisone; rh-GH, recombinant human growth hormone.

with the patient in a supine position using a manual mercury spygmomonometer. BP value was the mean of three measurements 15 min apart. Patients were specifically asked about any symptoms of steroid deficiency.

Patients and their next of kin were counselled and given written information regarding symptoms of glucocorticoid deficiency and instructed to contact the study co-ordinator promptly if they developed any of these symptoms or became unwell. Patients had a 24-h access by telephone to the study co-ordinator.

Ten healthy male controls also had 11-h CDCs. This was done only once, on no hydrocortisone treatment. Baseline blood samples, PR and BP were measured using a similar protocol to the patients.

Analytical methods

Serum total cortisol was measured using fluoroimmunoassay (FIA), AutoDELFIA (Perkin Elmer, Turku, Finland) with intra-assay coefficients of variation (CV) of 3·6%, 2·7% and 3% and an interassay CV of 1·6%, 1·1% and 1·5%, at serum cortisol concentrations of 210, 517 and 781 nmol/l, respectively. Samples from each individual were assayed in a single batch in each case.

Serum CBG was measured using radioimmunoassay (Bio-Source UK Ltd, Nivelles, Belgium). The interassay CV is 6·0% and 4·9% at CBG concentrations of 24·2 and 112·4 mg/l, respectively. The intra-assay CV is 7·7%, 3·8% and 3·3% at CBG concentrations of 33·1, 62·2 and 109·4 mg/l, respectively.

Serum total testosterone, FT4, TSH and prolactin were measured using FIA, AutoDELFIA (PerkinElmer, Turku, Finland), IGF-1 was measured using HCl-extraction radioimmunoassay (Nicholas Institute Diagnostics, San Juan Capistrano, CA, USA). Plasma sodium was measured by ion-selective electrode (Olympus 2700, Tokyo, Japan).

Statistical methods

Analysis of variance (ANOVA) models were used to compare serum cortisol results of patients on full-dose, half-dose and no hydrocortisone treatments, and controls at various time periods and also to compare peak and trough cortisol values between patients and controls. Multiple comparison tests using a Bonferroni correction factor was used to determine if results reached significance at the 5% level. The Student's *t*-test was used to compare body mass index (BMI), PR, BP, plasma sodium and CBG levels between patients and control groups. *P*-values less than 0·05 were taken as significant. Stata (version 8, Stata Inc., College Station, TX, USA) was used for the statistical analysis.

Results

Patients and control subjects were matched for age, BMI and CBG values (Table 2).

Figure 1 shows the mean CDCs of the patients and controls. The integrated CDC of the patients on no treatment (*P* = 0·13) and half-treatment (*P* = 0·37) were not significantly different to the integrated CDC of the controls. The cortisol profile of patients on no treatment closely resembled that of healthy controls (Fig. 1). The integrated CDC was significantly higher when patients took full treatment compared to controls (*P* < 0·001).

Peak postabsorption serum cortisol was significantly higher in patients on full treatment compared to controls (*P* < 0·001) but there was nonsignificant difference in peak cortisol between patients on half-treatment (*P* = 0·087) or patients on no treatment (*P* = 0·37), compared to controls. Trough cortisol values were not significantly different in patients on any of the treatment schedules, when compared to controls (Table 3).

All 10 patients remained well throughout the duration of the study. Pulse rate, systolic BP and diastolic BP were similar on all treatment schedules, and did not differ between patients and the controls (Table 3). All patients and controls had serum IGF-1, thyroid function, testosterone and prolactin values in the normal reference ranges.

Discussion

This the first study to examine the serum cortisol profiles of male adult hypopituitary patients with partial ACTH deficiency both on and off glucocorticoid treatment. It has previously been suggested that a basal posthypophysectomy cortisol level of greater than 250–270 nmol/l is safe, based on the assumption that this level predicts a normal cortisol response to provocative stimuli (Auchus *et al.*, 1997; Courtney *et al.*, 2000). Our data, which were collected in patients with baseline serum cortisol of > 200 nmol/l,

Table 2 Baseline characteristics of patients and controls

	Patients, *n* = 10	Controls, *n* = 10	*P*-value
Age (years)	43·9 ± 10·8	38·9 ± 12·2	0·34
BMI (kg/m[2)])	31·1 ± 4·5	30·8 ± 4·3	0·88
CBG (mg/l)	41·7 ± 7·1	44·9 ± 4·6	0·25
Baseline cortisol	273·9 ± 61·8	357·3 ± 84·4	0·021
Peak stimulated cortisol	432·9 ± 58·9		

Results presented as mean ± SD. BMI, body mass index; CBG, corticosteroid-binding globulin.
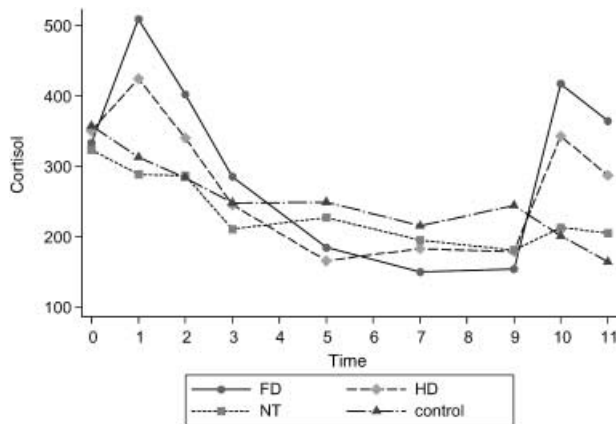
Fig. 1 Cortisol day curves for patients and controls. Time expressed in hours and serum cortisol expressed in nmol/l. FD, full treatment (10 mg twice daily); HD, half-dose (hydrocotisone 5 mg twice daily); NT, no hydrocortisone treatment.

show that the daytime cortisol profile, without treatment, is comparable to that of healthy subjects. We used this basal cortisol level for recruitment purposes, based on our (unpublished) observation that patients with pituitary disease who have a basal serum cortisol > 200 nmol/l, and who are not receiving glucocorticoid replacement, do not present with symptoms or signs of cortisol deficiency under unstressed conditions.

Historically, the glucocorticoid replacement dose for patients with adrenal insufficiency was 30 mg of oral hydrocortisone daily, given in divided doses (Besser & Jeffcoate, 1976). However, the daily cortisol production rate was subsequently shown to be $5 \cdot 7 \, \text{mg/m}^2/\text{day}$ (Estaban *et al.*, 1991), prompting a reappraisal of the optimum glucocorticoid replacement doses and a reduction in the mean recommended dose of hydrocortisone replacement to 20 mg daily (Peacey *et al.*, 1997). Our data show that, in patients with partial ACTH deficiency, 20 mg of hydrocortisone, given in divided doses of 10 mg twice daily, produces two supraphysiological peaks in serum cortisol concentration,

and an integrated CDC statistically higher than that of healthy controls. We have also shown that low-dose hydrocortisone therapy produces a cortisol profile similar to that of healthy controls. Our results suggest that current conventional hydrocortisone replacement doses are supraphysiological for patients with partial ACTH deficiency, and a further appraisal of optimal glucocorticoid replacement doses is indicated.

In this study, we used twice daily hydrocortisone, which reflects our clinical practice. This is the most common regimen used in clinical practice, though some authors have advocated dividing hydrocortisone into three doses (Groves *et al.*, 1988; Howlett, 1997; Peacey *et al.*, 1997). This last regimen produces higher trough serum cortisol concentrations (Groves *et al.*, 1988; Howlett, 1997), and lower peak concentrations (Howlett, 1997). Although we have not studied the CDCs on the trice daily regimen, our data suggest that, for patients with partial ACTH deficiency, twice-daily low-dose hydrocortisone is sufficient to mimic normal cortisol day profiles, such that more frequent dosage regimens are not needed. Indeed, our data show that even without hydrocortisone replacement, the trough serum cortisol concentrations are similar to physiological troughs in healthy controls, suggesting that in partial ACTH deficiency, routine glucocorticoid replacement may not be necessary under unstressed conditions.

These findings are particularly important because there is increasing evidence that even minor over-replacement with glucocorticoids may have detrimental side-effects. Patients with primary or secondary adrenal insufficiency taking a mean hydrocortisone dose of $29 \cdot 5$ mg daily were shown to have a 19% rise in serum osteocalcin concentrations after a hydrocortisone dose reduction to $20 \cdot 8$ mg daily (Peacey *et al.*, 1997); the authors concluded that even mildly excessive doses of corticosteroids could have adverse effects on bone formation with possible long-term implications for the development of osteoporosis. Patients with adrenal insufficiency receiving 15 or 20 mg of hydrocortisone, or $0 \cdot 1$ mg/15 kg body weight of dexamethasone, have low serum ionized calcium levels without compensatory rise in PTH levels (Suliman *et al.*, 2003); the authors suggested that this finding is

Table 3 Peak and trough cortisol values during the cortisol day curves, and clinical parameters of patients and controls

	Patients				
	FD	HD	NT	Controls	*P*-value
Peak cortisol (nmol/l)	$508 \cdot 6 \pm 86$	$424 \cdot 3 \pm 93 \cdot 9$	$323 \pm 74 \cdot 2$	$357 \cdot 3 \pm 84 \cdot 5$	$< 0 \cdot 001$
Trough cortisol (nmol/l)	$149 \cdot 8 \pm 49 \cdot 1$	$165 \cdot 6 \pm 71 \cdot 7$	$180 \cdot 5 \pm 64 \cdot 1$	$164 \cdot 4 \pm 35 \cdot 1$	$0 \cdot 69$
Pulse rate(beats/minutes)	$68 \cdot 2 \pm 3 \cdot 4$	$66 \cdot 6 \pm 3 \cdot 1$	$67 \cdot 9 \pm 2 \cdot 4$	$66 \cdot 9 \pm 2 \cdot 7$	$0 \cdot 46$
Systolic BP (mmHg)	$129.5 \pm 12 \cdot 4$	$134 \cdot 3 \pm 14 \cdot 5$	$131 \cdot 1 \pm 9 \cdot 6$	$131 \cdot 1 \pm 10 \cdot 5$	$0 \cdot 84$
Diastolic BP (mmHg)	$83 \cdot 4 \pm 8 \cdot 7$	$83 \cdot 7 \pm 10 \cdot 7$	$79 \cdot 1 \pm 11 \cdot 6$	$83 \cdot 9 \pm 8 \cdot 3$	$0 \cdot 66$
Plasma sodium (mmol/l)	$140 \cdot 5 \pm 1 \cdot 7$	$140 \cdot 2 \pm 1 \cdot 7$	$141 \cdot 2 \pm 2 \cdot 2$	$139 \cdot 2 \pm 1 \cdot 5$	$0 \cdot 11$

Results are expressed as mean ± SD. FD, full dose (hydrocortisone 10 mg twice daily); HD, half-dose (hydrocortisone 5mg twice daily); NT, no hydrocortisone treatment.

consistent with evidence of suppression of the bone remodelling cycle. Male hypoadrenal patients treated with standard glucocorticoid replacement have also been shown to have reduced bone mineral density (BMD; Zelissen *et al.*, 1994). The potential risk for osteoporosis is particularly important in patients with hypopituitarism, who may also be deficient in GH and sex steroids, which augment any tendency to reduced BMD. For protection against the development of osteoporosis in hypopituitary patients it is important therefore not to prescribe supra-optimal glucocorticoid replacement doses.

Excess glucocorticoid therapy may also have disadvantageous metabolic consequences. Hypopituitary patients on glucocorticoid replacement showed reduced insulin sensitivity and diminished glucose tolerance on the mornings when hydrocortisone was given, compared to the mornings without hydrocortisone (Al-Shoumer *et al.*, 1995). As their data indicated a decrease in insulin sensitivity with standard hydrocortisone doses, the authors recommended a reappraisal of optimum corticosteroid regimens. McConnell *et al.* (2001) showed that a cohort of hypopituitary patients treated with a mean daily dose of hydrocortisone of 20 mg had a lower prevalence of impaired glucose tolerance and diabetes than that reported in hypopituitary patients prescribed higher mean daily doses of glucocorticoids (Beshyah *et al.*, 1994). They speculated that the lower prevalence of abnormal glucose tolerance in their cohort may have reflected the lower glucocorticoid replacement doses. There is also evidence that glucocorticoid treatment is associated with a dose-related increase in the frequency of cardiovascular disease (Wei *et al.*, 2003), with no safe dose threshold below which there is no excess risk. Recent epidemiological data suggest that there is increased vascular mortality in hypopituitary patients, which may be partly related to excess glucocorticoid supplementations (Tomlinson *et al.*, 2001).

Glucocorticoid therapy is well recognized to cause ocular hypertension and glaucoma (Long, 1977; Garbe *et al.*, 1997), and intraoccular pressure was found to be higher in hypoadrenal patients following 20 mg of morning hydrocortisone when compared to 10 mg (Li Voon Chong *et al.*, 2001). Although intraocular pressures remained within normal limits, the authors concluded that even minor degrees of glucocorticoid excess may have adverse implications for intraocular pressure.

Our patients remained symptomatically well during the short study period. Another study has found no effect on quality of life with the reduction of hydrocortisone dose from 30 mg to 15 mg daily in patients with complete secondary hypocortisolism (Wichers *et al.*, 1999).

Assessment of glucocorticoid replacement in routine clinical practice tends to be arbitrary and based on a synthesis of clinical well being, electrolyte measurement and out-patient blood pressure readings. A simple and highly sensitive biological maker, similar to TSH for thyroxine replacement in primary hypothyroidism, does not exist. Twenty-four-hour urinary free cortisol estimation is occasionally used, but is not a reliable indicator of the optimal hydrocortisone replacement dose (Monson, 1997). By contrast, the CDC (Kehlet *et al.*, 1976; Trainer & Besser, 1995) has been suggested to be an accurate tool for assessing optimal hydrocortisone replacement. However, the accuracy of this method is increased by frequent sampling and we would recognize that physiological peak serum ACTH and cortisol concentrations occur in the early hours of the morning, between 06·00 and 08·00 h (Torpy & Jackson, 2001). Patients with severe ACTH deficiency are particularly vulnerable to symptoms at this time if glucocorticoid replacement is inadequate. However, the basal 08·00 h serum cortisol concentrations in our patients with partial ACTH deficiency, were similar on all three study days, suggesting that the hydrocortisone dosage regimen did not effect the basal morning serum cortisol concentrations. This is probably due to the rapid clearance of hydrocortisone taken on the previous evenings. This suggests that over-replacement with hydrocortisone during the day does not lead to higher morning serum cortisol concentrations, and therefore may not be safer for patients with partial ACTH deficiency.

It could be postulated that supraphysiological serum cortisol peaks suppress endogenous ACTH production, and therefore, slightly excessive glucocorticoid replacement may not lead to significant over-exposure to glucocorticoids. Our data do not support this argument, however, as trough cortisol levels were not significantly lower when patients are treated with full-dose hydrocortisone therapy. This indicates that, despite the short half-life of hydrocortisone, conventional replacement doses do lead to genuine over-exposure to excess glucocorticoids. This observation that trough cortisol was not significantly different from controls, even when patients were on no treatment, is reassuring that lower than conventional doses of glucocorticoid therapy will not expose patients to the risk of hypocortisolaemia. In addition, parameters that reflect corticosteroid action such as plasma sodium and BP remain unchanged, indicating that corticosteroid withdrawal was not causing short-term harm.

This was a short-term study and it would therefore be premature to suggest that it is safe to withhold treatment in patients with partial ACTH deficiency on the basis of our data alone. Some patients with partial ACTH deficiency may progress to severe ACTH deficiency as a result of the recurrence of their underlying pituitary disease or the progressive effects of radiotherapy. Patients who develop intercurrent illness may be particularly susceptible to acute adrenal crises if they are not on maintenance corticosteroids, and may inadvertently omit stress doses of glucocorticoid treatment. In addition, the results of this study cannot be extrapolated to situations of more severe ACTH deficiency, in which the use of full glucocorticoid replacement dosage is justified.

These data should prompt a reappraisal of the appropriate replacement dose of glucocorticoid, particularly with the gathering

evidence that even marginally excessive glucocorticoid doses could be associated with significant morbidity. Patients with partial ACTH deficiency may be better treated with hydrocortisone 5 mg twice daily than full doses, or may not even need glucocorticoid treatment other than during acute illness. Certainly our data suggest that a longer-term prospective trial of lower doses of hydrocortisone therapy, or even no therapy at all, would be justified in hypopituitary patients with partial ACTH deficiency.

Acknowledgements

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