

Assessment of corticosteroid replacement therapy in adults with adrenal insufficiency

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The dose of replacement therapy for hypoadrenalism has nearly always been chosen empirically in the past. Most adults have received hydrocortisone 20–30 mg daily, divided into two doses, or equivalent amounts of cortisone acetate, prednisolone or dexamethasone. Subsequent adjustment has been based on simple, predominantly clinical, criteria: well-being, weight, blood pressure and measurement of plasma electrolytes. The dose of 20–30 mg hydrocortisone daily was chosen because it had been shown to be equivalent to classical estimates of the daily secretion rate of cortisol.¹ However, it has recently been suggested that such estimates of cortisol secretion may have been too high,² and several groups have argued that conventional doses of corticosteroid replacement therapy may also be excessive.^{3–5} They have drawn attention to the potential risks of chronic overtreatment, and in particular to the increased risk of osteoporosis. For these reasons, it is now argued that simple criteria are not sufficient for judging the adequacy or otherwise of replacement therapy, and that some form of additional biochemical surveillance may be required. The purpose of this review is to examine the potential risks of misjudging the optimal dose, and to evaluate the various biochemical measures which could form the basis of monitoring.

RISKS OF INADEQUATE REPLACEMENT THERAPY

While current attention is fixed mainly on the risks of using excessive doses of glucocorticoid

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replacement therapy, the risks of *under-treatment* are more immediately life-threatening and must not be forgotten. If the maintenance dose of corticosteroid replacement therapy is insufficient, the patient may suffer chronic lassitude and reduced resistance to illness. They may suffer symptomatic postural hypotension, and plasma sodium concentrations may be low or low normal, at 130 to 135 mmol/L. This was not infrequently seen in people stabilized on a standard, non-tailored dose of cortisone acetate – because of its irregular absorption and irregular conversion *in vivo* to cortisol – but this preparation is not now in common use in the majority of countries. Symptoms of hypoadrenalism are usually now encountered in the course of management only in those who are attempting to withdraw from immunosuppressant doses of glucocorticoids and in whom the hypothalamic–pituitary–adrenal axis has been suppressed. Children on glucocorticoid replacement therapy, however, remain at risk of nocturnal hypoglycaemia (with or without grand mal fits) if they become hypoadrenal during sleep, and this may be more common than is generally recognized.

However, it must not be forgotten that both children and adults are at risk of hypoadrenal crisis at times of stress from intercurrent illness or accident, particularly if they are unable to absorb their replacement therapy because of gastrointestinal upset. It is possible that this potentially life-threatening complication of glucocorticoid dependence is under-recognized because of under-reporting. In the last 10 years, two people from Nottingham [one post-adrenalectomy for Cushing's disease, and one with idiopathic adrenocorticotrophic hormone (ACTH) deficiency] have died in apparent hypoadrenal crisis in this way, while on holiday. It is conceivable that chronic, borderline under-replacement may predispose individuals to such fatal crises. If so, then improved means of monitoring may help to pre-empt them.

THE RISKS OF EXCESSIVE REPLACEMENT THERAPY

The clinical effects of using doses of glucocorticoids which are in excess of those needed to replace adrenocortical deficiency are well-recognized: weight gain, high blood pressure, hyperglycaemia, suppression of growth rate in childhood, easy bruising and osteoporosis. Perhaps the most insidious of these, and one which was relatively unrecognized until the advent of bone mineral density (BMD) scanning, is osteoporosis.³⁻⁵ However, recent attention has also been paid to the potential effects of glucocorticoid replacement therapy on cardiovascular risk⁶ and raised intraocular pressure.⁷

Risk of osteoporosis in people treated with conventional doses of glucocorticoid replacement therapy

Zelissen and colleagues³ reported a glucocorticoid dose-related reduction in BMD in men, but not women, with Addison's disease. However, Florkowski and colleagues⁴ found the reverse: reduced BMD in Addisonian women, but not in men. In a third study Peacey *et al.*⁵ found no evidence of osteoporosis in (an admittedly small number of) patients with Addison's disease. This group did find, however, that there was a dose-dependent reduction in BMD in 20 patients with *secondary* hypoadrenalism. Such an effect in patients with hypothalamic and pituitary disease raises the question of the relative contribution to osteoporosis risk made by associated hypogonadism, growth hormone (GH) deficiency, use of excessive doses of thyroxine replacement and, most important of all, earlier glucocorticoid exposure in patients whose initial problem was Cushing's disease. The evidence for a significant adverse effect on fracture risk in people treated with conventional doses of glucocorticoids remains, therefore, rather weak and the results of further studies would be welcome. Although Peacey *et al.*⁵ demonstrated encouraging short-term changes in serum osteocalcin in response to glucocorticoid dose adjustment, it should be remembered that this may reflect a direct pharmacological effect of glucocorticoids on osteocalcin secretion.

JUDGING THE DOSE OF REPLACEMENT THERAPY

There are three main difficulties encountered in choosing the optimal dose. The first is that it is simply not possible to emulate the natural,

highly complex, circadian rhythm of plasma cortisol, even with twice or thrice daily regimens.^{8,9} One inescapable problem is the timing of the morning peak. Since the natural peak starts with the onset of rapid eye movement sleep in the early hours,¹⁰ it can only ever be copied if the morning dose of hydrocortisone is taken at 0300 or 0400 h. The peak which follows a dose of hydrocortisone on waking is several hours too late.

The second difficulty is that the aim of treatment may not always be simply that of correcting glucocorticoid deficiency: an additional requirement may be the suppression of nocturnal ACTH secretion. This would be the case in, for example, congenital adrenal hyperplasia (CAH) or the management of polycystic ovary syndrome (PCO) with glucocorticoids. Since the suppression of nocturnal ACTH secretion in such circumstances can usually be achieved only by inducing abnormally high circulating glucocorticoid levels in the middle of the night, it is very much easier to err on the side of over-, rather than under-treatment.

The third difficulty relates to the use of biochemical measures to adjust therapy. Serum and urinary cortisol measurement can be used only in those who are receiving treatment with either cortisone acetate or hydrocortisone. In those receiving prednisolone or dexamethasone there is no alternative to the use of conventional simple, primarily clinical assessments. The same is true of fludrocortisone – a predominantly, but not exclusively, mineralocorticoid preparation – which is often used in conjunction with glucocorticoids in primary adrenal disease.

MEASURES OF CORTICOSTEROID ACTIVITY IN PATIENTS ON REPLACEMENT THERAPY

There are various measures that can be used, but not all of them are appropriate in all circumstances.

0900 h (casual) cortisol concentration

Measurement of the cortisol concentration in a single sample gives little idea of the range of concentrations through 24 h. Its only place in the assessment of hypoadrenalism is in those who have been treated for disease of the hypothalamic-pituitary-adrenal (HPA) axis and in whom an attempt is being made to withdraw replacement therapy. An 0900 h cortisol concentration of < 100 nmol/L is strongly suggestive

of inadequate endogenous reserve, while one of >600 nmol/L strongly suggests that the reserve is normal.

24-h urine free cortisol

In the normal person, and in the person with untreated Cushing's syndrome, urine free cortisol (UFC) excretion reflects the cortisol secretion rate. The same is true of patients with Cushing's syndrome whose cortisol secretion is restrained by the use of metyrapone,¹¹ but the question to be answered is whether UFC can necessarily be used to judge whether or not a dose of exogenous glucocorticoid replacement therapy is optimal.

Various factors govern the amount of cortisol that will appear unchanged in the urine. These include: the sum of the amount secreted and the amount absorbed; the concentration of cortisol binding globulin (CBG); and the rates of 11-dehydrogenation (to cortisone), hepatic conjugation and conversion to other cortisol breakdown products. There is considerable individual variation in all of these, and each can also be modified by coincident disease and its treatment. Sex hormone replacement therapy will modify the excretion of UFC through changes in CBG concentration, while GH treatment of hypopituitarism has also been shown to affect the metabolism of cortisol and the proportion which is excreted unchanged. Having said that, it is worth noting that the results of different studies do not agree on the way in which plasma and urinary cortisol (and 11-hydroxy-metabolites) are affected: whether decreased^{12,13} or increased.¹⁴

While it is known that the UFC excretion rate is relatively constant within any one individual on corticosteroid therapy,¹⁵ there is considerable variation between individuals who are taking a particular dose, and little relationship overall between hydrocortisone dose and UFC excretion rate.¹⁶ If anything, UFC appears to correlate most closely with the height of the peak achieved after an oral dose,⁵ and it is thought that relatively high peaks of cortisol in serum may temporarily saturate CBG, as well as pathways for conjugation and dehydrogenation, and hence may result in the preferential excretion of unchanged cortisol. Thus, it would seem that although there is a close association in any one person between UFC and mean and peak cortisol values determined from multiple sampling for serum cortisol through the day,^{5,16} the test is of little value on its own in the routine

assessment of the dose of corticosteroid replacement therapy.

It is known that people whose doses of replacement therapy are so low that they are clinically hypoadrenal (as judged by increased pigmentation and postural hypotension for example) will have levels of UFC which are overtly low.¹⁵ The converse is also likely to be true: that those who take so much treatment that they are Cushingoid will also have a high urinary cortisol excretion rate. But it is far from clear that the urine assay can be used to determine adequacy of treatment in those without such clear clinical signs.

Nevertheless, measurement of UFC has a place in the assessment of some individuals who might be judged to be at especial risk of, say, osteoporosis. Thus, a high UFC result in such a person should lead the clinician to question the possibility that both mean and peak serum concentrations are too high, and to consider the wisdom of both reducing the total daily dose and splitting it into three or more fractions. Further detail may be provided in such cases by measuring the profile of serum cortisol through the day.

Cortisol day curves

The use of day curves has long been recommended,¹⁷ but on minimal objective evidence. In particular, there was no standard with which the profiles should be compared. However, Howlett recently analysed the results of a large retrospective series, suggesting sensible, albeit arbitrary, targets.¹⁶ Thus, he argued, patients who take their morning dose when they get up (and not after the first sample of the day curve) should have a concentration at 0900 h of 100–700 nmol/L, while those samples taken at 1230 and 1730 h should be above 50 nmol/L ('and ideally above 100 nmol/L'). In this way, the day curve can establish that the profile contains neither inappropriate peaks nor prolonged troughs. Not surprisingly, he found that this was more often achieved in those patients whose treatment was split into three doses through the day. The size of the peak after the morning dose varied enormously, however, with little relationship to the amount which had been taken.

Peacey and colleagues used different criteria to evaluate replacement therapy in their prospective study of 32 patients.⁵ Thus, the morning dose was given after the first sample at 0900 h, and sampling continued every 90 min for 12 h. They gave no criteria for the 0900 h result, but aimed for morning and evening peaks of less

than 650 and 250 nmol/L, respectively, with no troughs below 200 nmol/L between 1500 and 1800 h. They also aimed for a mean cortisol concentration of 150–300 nmol/L in six samples (including, presumably, the first, low, one). Using these criteria they found 24/32 (88%) of their patients required a dose reduction or other change in treatment.

These studies have clearly demonstrated that conventional practice needs adjustment: the total daily dose used has tended to be too high, and people might derive 'better' (with the word being arbitrarily defined) profiles when they take smaller doses of hydrocortisone, more often. Thus, they have taught us that the usual maintenance dose of hydrocortisone therapy should be between 15 and 20 mg total each day, split into at least three doses. In this way, the risk of osteoporosis should be lessened as a result of routine practice, particularly in those who are at especial risk – those who have had Cushing's syndrome and those who are deficient in GH and/or sex steroids. In such people, there may be an indication for using cortisol day curves as the basis for making further adjustments to therapy. If so, the protocol should be that adopted by Howlett.¹⁶ Whether or not such day curves need to be performed on a routine basis is, however, debatable. Clinicians who elect to perform them should also understand that method-dependent bias may vary from one laboratory to another, and that target cortisol concentrations should be adjusted accordingly.

Tetracosactrin, hypoglycaemia stress and corticotrophin-releasing hormone (CRH) tests

The hypoglycaemia stress test has been the gold standard test for adequacy of HPA function for over 30 years. However, clinicians are increasingly hesitant about its routine use, particularly in children. Although not rigidly logical, the tetracosactrin test has therefore been widely adopted as a substitute, and it has been shown that the cortisol response to tetracosactrin (Synacthen; Alliance Pharmaceuticals Ltd, Chippenham, UK) is a reliable marker of ACTH reserve in the majority of instances.¹⁸ Nevertheless, this approach remains the subject of controversy¹⁹ and Clark *et al.* have recently demonstrated the considerable dependence of serum cortisol results on both laboratory method and on the gender of the subject.²⁰ Moreover, the short tetracosactrin test cannot be used in this way in those who have recently undergone pituitary surgery (or recent apoplexy)

since the degree of adrenocortical reserve will reflect prior ACTH activity, rather than that which is current. It is also of little value in determining the effective reserve of the HPA axis in those attempting to withdraw from long-term treatment with anti-inflammatory doses of glucocorticoids. In such patients there is a case for considering the use of the CRH test. Thus, Schlaghecke and colleagues²¹ showed very close correlation between the results of CRH stimulation and insulin-induced hypoglycaemia in 61 patients who had been treated with exogenous glucocorticoids.

17 α -hydroxyprogesterone

Plasma concentrations of 17 α -hydroxyprogesterone (17OHP) are elevated in people with congenital adrenal hyperplasia from either 11- or 21-hydroxylase deficiency. When elevated, it is an indication that ACTH secretion is not adequately suppressed (particularly through the night), but it is not a marker of effective circulating glucocorticoid concentrations. Hence, attempts to suppress 17OHP (or testosterone in adult women) into the reference range are likely to result in over-treatment: ACTH can only be well suppressed by the administration of doses which result in glucocorticoid levels remaining elevated through the early hours of the morning, when ACTH starts to rise.

Measurements of ACTH and plasma renin activity

ACTH measurements are not widely used in documenting the adequacy of treatment of primary adrenocortical disease. The hormone is released in pulses, particularly in the early hours of the morning, and measurement of isolated samples is of limited value. If concentrations are suppressed below the low limit of the reference range, the patient is probably receiving excessive doses of corticosteroid. Assays of plasma renin activity have been found to be of similarly limited value in titrating replacement doses of mineralocorticoid.²²

Non-biochemical markers

Overall well-being is probably the single criterion which is most used by clinicians, with complaints of non-specific malaise triggering a trial of higher doses in many cases. While reasonable, this approach must be balanced by a conscious search for other markers of possible over-treatment, since non-specific malaise is so prevalent in the general population. Such a marker is the assessment of osteoporosis risk by

determination of BMD, and it should now be considered at some stage in the majority – especially in those whose corticosteroid dependence is the result of treatment of pre-existing Cushing's syndrome, because this group will be at greatest risk. Blood pressure and plasma electrolyte measurement should also be undertaken in all patients from time to time – although they are relatively insensitive markers of overdosage.

MONITORING THE DOSE OF GLUCOCORTICOID REPLACEMENT THERAPY IN DIFFERENT DISORDERS

As mentioned above, biochemical measures have to be tailored to, and interpreted in the light of, clinical circumstances. There is no sensitive measure by which to judge either the dose of mineralocorticoid replacement therapy with fludrocortisone, or of the synthetic glucocorticoids, prednisolone and dexamethasone.

Addison's disease (primary, non-iatrogenic adrenocortical failure)

Well-being is the most useful marker of adequacy of replacement therapy in most adults. Weight and plasma electrolytes are also used. UFC excretion has little place in routine practice (and none in those patients being treated with either prednisolone or dexamethasone) and ACTH assay is of little value. A cortisol day curve should be considered, though, in those in whom there is a suspicion of overtreatment, and to ensure that the minimum dose is being used in those known to be at particular risk of osteoporosis.

Post-adrenalectomy

The same criteria apply as for Addison's disease, although the risk of osteoporosis should be acknowledged to be particularly high in those who have had treatment for Cushing's syndrome.

ACTH deficiency (disease of the hypothalamus or pituitary)

Such people are not normally treated with fludrocortisone, but their glucocorticoid therapy should be judged as for primary adrenocortical deficiency (see above).

'Medical adrenalectomy' (use of metyrapone or other agents in the medical management of Cushing's syndrome)

Reversible inhibition of corticosteroid synthesis (with metyrapone, aminoglutethimide, mitotane or ketoconazole) is widely used in the management of Cushing's syndrome. The aim is to adjust the dose until mean circulating cortisol concentrations are reduced, ideally towards the normal range. The effectiveness of therapy can be monitored by the use of day curves, with just three or four samples being taken over a period of hours.¹¹ It has also been shown that the UFC correlates reliably with cortisol secretion rate in this group.¹¹

Classical congenital adrenal hyperplasia

The person with classical congenital adrenal hyperplasia^{23,24} is dependent on glucocorticoid replacement therapy for normal survival. Children with 11- or 21-hydroxylase deficiency are best monitored by assessment of well-being, growth and pubertal development. 17OHP and testosterone can be measured but may prove unsuppressible except by doses of glucocorticoid which are excessive by other criteria. Cortisol day curves can be used, but obviously only in those children being treated with hydrocortisone. The criteria for interpretation of results are the same as those for adults.

The monitoring of adults with 11- or 21-hydroxylase deficiency is primarily clinical, assessing weight, well-being, menstruation/ovulation, severity of acne, blood pressure and measurements of plasma electrolytes. 17OHP and testosterone are used as additional markers, with a greater tendency than in childhood to suppress them into the reference range in order to promote, in particular, normal ovarian function. It is thought that the risk of osteoporosis from overtreatment is relatively small because of the opposing effect of hyperandrogenaemia, but use of day curves and of BMD scanning has not been widely practised hitherto. Adult males tend to default from follow-up in specialist endocrine clinics, presumably because they are symptom-free and because attendance is not usually associated with any obvious changes in their treatment. This means that they tend not to be regularly monitored.

Non-classical congenital adrenal hyperplasia

Those with non-classical disease have, by circumstance, sufficient production of endogenous

glucocorticoids to enable them to survive childhood, and they present in adult life with varying degrees of virilism, hirsutism and acne.²³ For obvious reasons, the condition is more likely to be recognized in women than in men. The diagnosis depends on the criteria which are used to define it, but most would agree that an elevated baseline 17OHP concentration on two occasions should be sufficient. A tetracosactrin (short Synacthen) test should be undertaken, not so much to document an exaggerated rise of 17OHP, which may occur, as to exclude a subnormal cortisol response.

Treatment of this group is the same as that for any other cause of hyperandrogenism, and the use of glucocorticoid replacement therapy is restricted to those who are shown to be glucocorticoid-deficient. The only exception to this is the woman contemplating pregnancy, in whom the use of glucocorticoid may be considered to promote ovulation. If pregnancy follows, transplacental transfer of administered glucocorticoids may help reduce the disfigurement of any affected female foetus. If such treatment is contemplated, it is likely to be with dexamethasone and hence can be monitored only indirectly.

SUMMARY

Recent work has taught us that our conventional approach to corticosteroid replacement therapy requires review. Specifically, the doses of hydrocortisone we have used are probably too high for the majority, and should ideally be administered in three or more doses through the day. Nevertheless, there is not much hard evidence that excessive glucocorticoid replacement *per se* will lead to adverse effects such as osteoporosis, even though it may exacerbate any tendency in those who are predisposed to it for other reasons. As such, there is no compelling need for using determinations of either UFC excretion or of the serum cortisol profile in the routine management of patients on replacement therapy. Nevertheless, such measures may be considered in those thought to be at particular risk of osteoporosis, and in whom it is felt that special effort should be made to ensure that they are receiving the minimum dose possible. In such circumstances, a cortisol day curve is likely to be of more value than measurement of UFC.

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