GETTING CORTISOL REPLACEMENT OPTIMAL IN ADRENAL INSUFFICIENCY

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INTRODUCTION

Adrenal Insufficiency is the term given to conditions where cortisol production is compromised. Traditionally, the term is broken down into problems with the adrenal glands (primary adrenal insufficiency, e.g. congenital adrenal hyperplasia) or secondary adrenal insufficiency where there is a problem in the production of either corticotropin releasing hormone from the hypothalamus, or adrenocorticotropin (ACTH) hormone from the pituitary gland. In adult practice these are often secondary to the treatment of pituitary tumours. Hypopituitarism falls into the secondary adrenal insufficiency category characterised by deficiencies in other pituitary hormones such as growth hormone and thyroid stimulating hormone.

Cortisol plays a vital role in the body. Almost two thirds of human genes are in some way regulated by cortisol. It is important in the regulation of blood glucose concentrations, modulates how the immune system works and is important for cardiovascular health, particularly in terms of blood pressure and cardiac function. Deficiency of cortisol can lead to life threatening adrenal crises whereas when present in excess, Cushing's syndrome results.

Cortisol is produced by the adrenal glands under the direction of ACTH from the pituitary gland. This production follows a specific pattern with high concentrations measured in the blood first thing in the morning and low, but detectable, concentrations late evening.

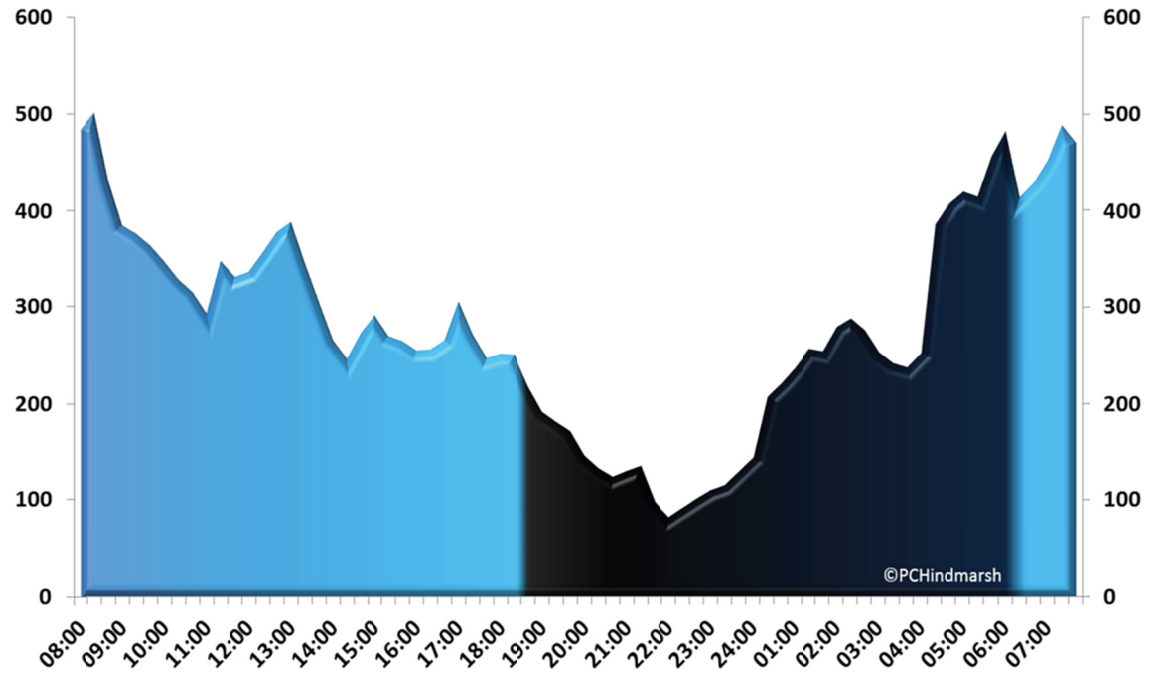

Figure 1. The circadian rhythm of cortisol in the blood stream

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Figure 1 shows an example of this pattern which is known as the circadian rhythm of cortisol. Important points to note are cortisol starts to rise slowly from midnight reaching a peak around 07:00h (7 am). Thereafter, high concentrations are maintained throughout the morning with values then declining until 16:00h (4 pm) when there is naturally a mini burst of cortisol production. Thereafter, a further decline in concentrations take place until the lowest values are reached around 22:00h (10 pm) and 24:00h (midnight).

Note that at no time are concentrations of cortisol zero. There is always some cortisol present even when at the nadir of cortisol production.

The reason for this circadian rhythm is not clear (1) but certainly over night the presence of cortisol is important, especially in children in maintaining normal glucose concentrations and helping to avoid episodes of hypoglycaemia. The circadian rhythm is maintained by a series of clock genes within the hypothalamus and cortisol is probably a mediator of instructions from these central clock genes to the peripheral clock genes present in all tissues, ensuring that the two are synchronised.

The rise of cortisol from midnight varies depending on age. For example, in children, the rise starts at 22:00h whereas in young adults often the rise does not commence until 02:00h (2 am). This then reverts back towards midnight in the older population (2).

One of the important concepts in endocrinology is to replace any missing hormone with a synthetic form of that hormone and replacement should mimic natural production as closely as possible. In this case, cortisol is missing and we are replacing cortisol with the synthetic form, hydrocortisone. If we mimic the circadian rhythm of cortisol in terms of replacement we need to understand the way in which cortisol needs to be administered in order to achieve similar circulating concentrations. The way hydrocortisone is metabolised by individuals varies. There is variation in the absorption pattern and how hydrocortisone is metabolised through the liver and kidneys (3).

This is important because it implies that no one size fits all in terms of dosing and dose timing.

INDIVIDUALISED DOSING

In paediatrics, dosing is calculated on body size whereas in adults more standardised dosing tends to be the norm. For many years dosing schedules for paediatrics and adults has differed in that paediatric practice, particularly for the management of congenital adrenal hyperplasia, has focused on mimicking as closely as possible the circadian rhythm.

In adult practice it has always been advised to give the last dose of hydrocortisone no later than 18:00h (6 pm). The reasoning behind this decision is not clear.

It certainly cannot be because 'there is no cortisol production overnight' because that is simply not the case as circadian studies reveal (2). This is highlighted in the high prevalence of hyperpigmentation in people with Addison's disease who take their last dose no later than 18:00h (6 pm). This does not occur in hypopituitarism due to the lack of ACTH production.

Dosing in the period of time from when the person wakes up until 18:00h (6 pm) means that the total daily dose of hydrocortisone is spread over a very short period of time, namely 12 – 15 hours and would leave the individual without cortisol for 9 to 12 hours each day (38 – 50% of the 24 hour period).

This is in contrast to the way that the adrenal glands go about generating cortisol concentrations through the 24 hour period to generate the circadian rhythm. Figure 2 (4) shows the distribution of adrenal activity required through four arbitrary time blocks to produce the cortisol concentrations in the circadian rhythm.

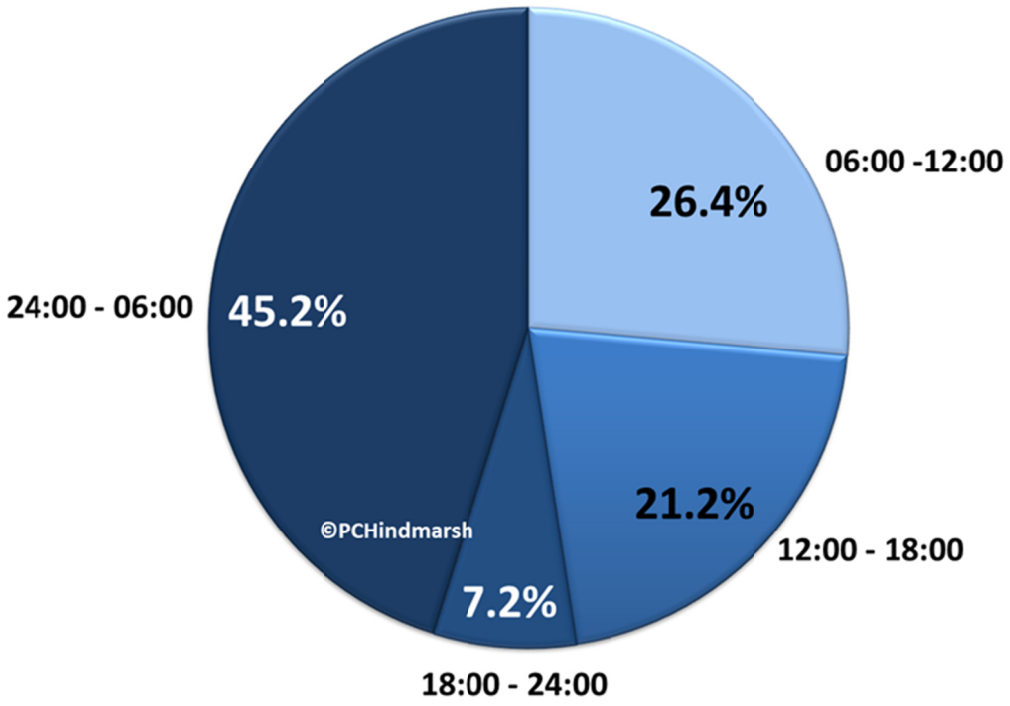

Figure 2. Estimated amount of cortisol needed to be generated in four time blocks by the adrenal glands as a proportion of total daily production to produce circadian cortisol concentrations

This helps us to understand why distribution of hydrocortisone dosing is important. The figure gives a guide to how the total daily cortisol production is distributed and not a statement of actual dosing times.

Any dosing schedule needs to be checked carefully. For cortisol this means frequent blood sampling throughout the 24 hour period to ensure that the profile obtained does not have periods where there is excess cortisol present (over treatment) or periods of under treatment (where the cortisol falls too low).

It is important to know the total daily coverage so that dosing frequency to gain optimal distribution can be adjusted.

When considering individualised dosing we need to know how the individual absorbs hydrocortisone and how it is metabolised by the body. These studies are undertaken using classical pharmacology where absorption profiles of cortisol can be created (5) (Figure 3).

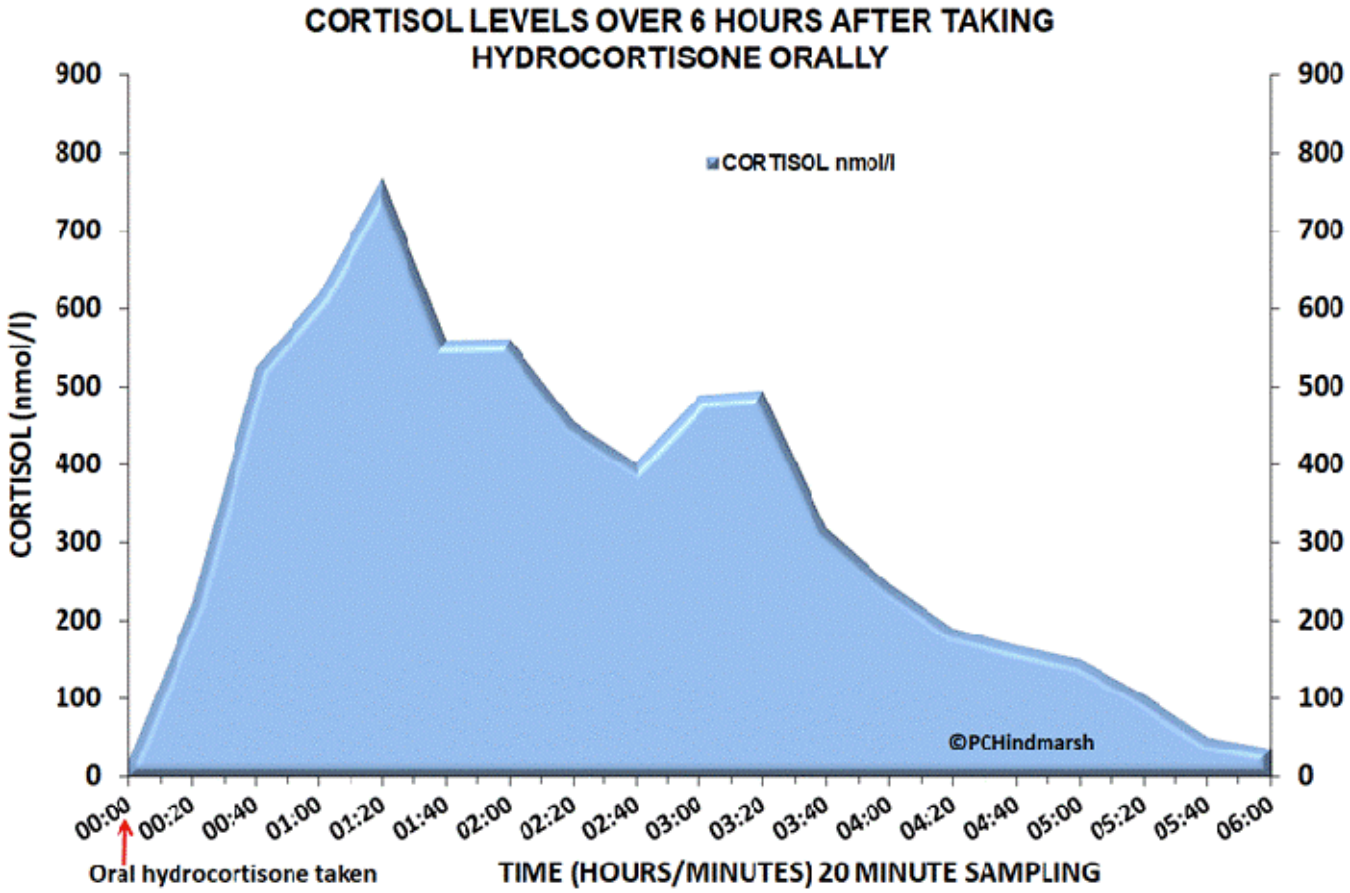

Figure 3. Plasma cortisol concentrations following oral hydrocortisone

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There will be individuals who absorb quickly and those who absorb slowly and this is important in determining in part, the dosing frequency. The clearance of hydrocortisone from circulation is best estimated following an intravenous bolus injection of hydrocortisone, followed by frequent sampling. From these cortisol measurements the half-life of cortisol can be derived along with the volume of distribution and clearance (6).

Figure 4 shows the variation in half-life in 50 individuals (3).

There is wide variation in half-life from 40 minutes to 225.3 minutes (average is approximately 80 minutes). When we put this together with the absorption characteristics, we have a number of potential options of individuals who absorb quickly and clear quickly, who will need a very frequent dosing regimen through to those who absorb slowly and clear slowly, for whom perhaps a twice daily regimen would be sufficient.

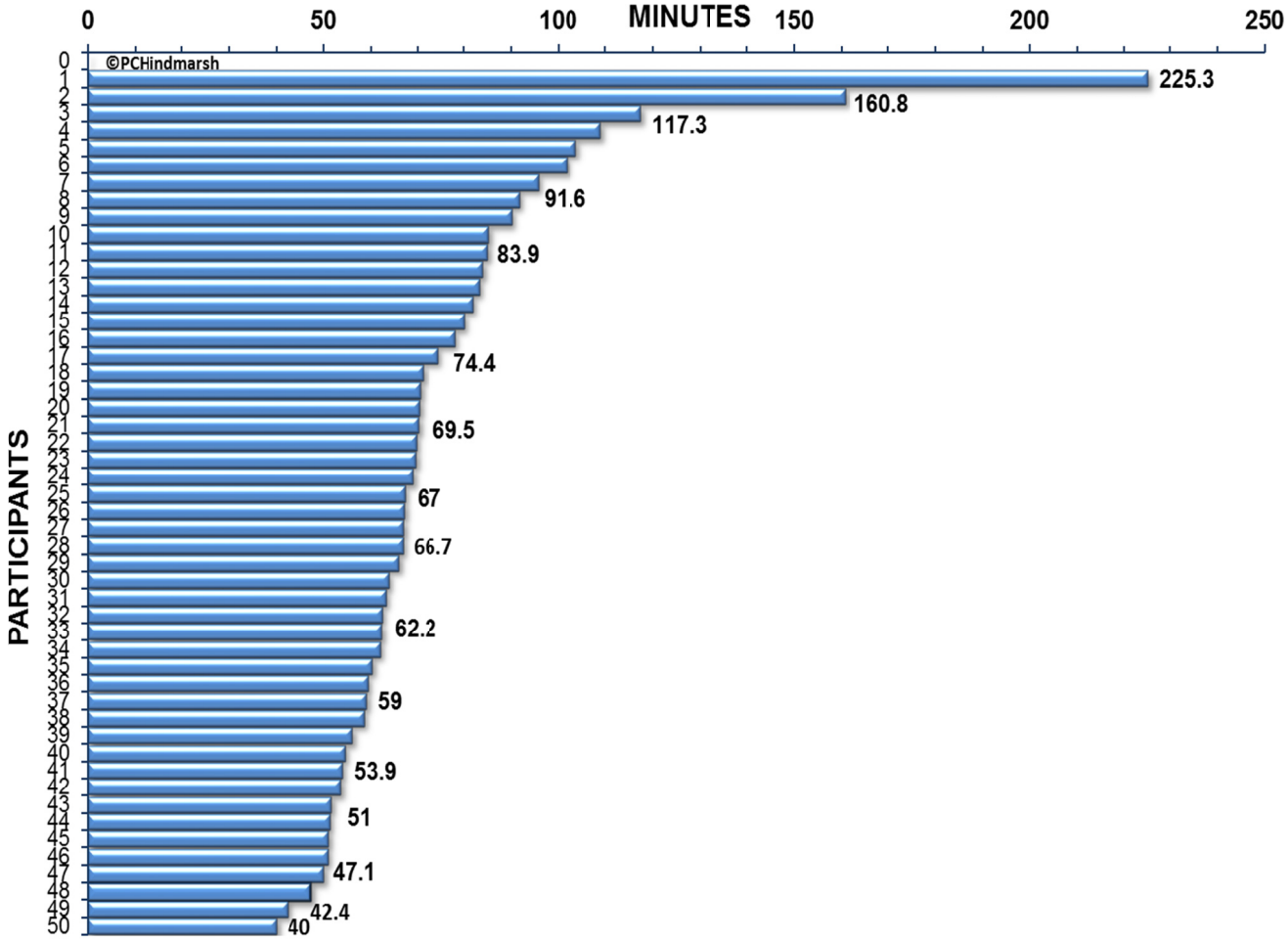

Figure 4. Range of half-lives in individuals following an intravenous bolus of 30mg hydrocortisone

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Getting the timing of doses correct is extremely important as is understanding the absorption and clearance of hydrocortisone. This is because of the phenomenon of stacking which can take place if the timing of the dosing is out of phase with the known pharmacology of the drug in the individual.

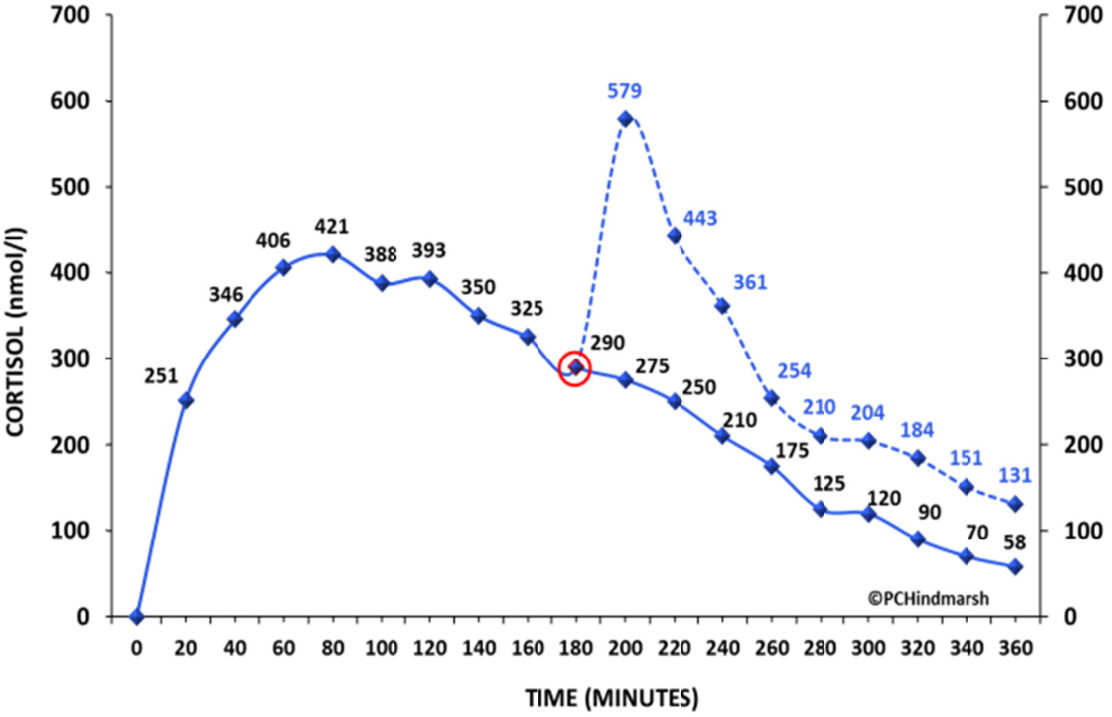

Figure 5. Hydrocortisone stacking. A dose of hydrocortisone is given at time zero and a further lower dose given 180 minutes later. The second dose stacks on top of the previous dose (red circle) giving a higher cortisol concentration than expected

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Figure 5 illustrates what happens if a dose of hydrocortisone is given too soon. Although the dose might be expected to produce a certain peak, if it is taken before there is adequate clearance of the previous dose then a much higher than expected concentration of cortisol will ensue. This is called 'over stacking'. Profiles allow us to evaluate the best time to stack a dose to ensure levels do not fall too low, this is known as 'useful stacking.'

Understanding these pharmacology principles allows us to achieve the correct dosing schedule for individuals receiving hydrocortisone replacement. As with any replacement therapy, it is important to check what is delivered. Unfortunately, because of the circadian rhythm of cortisol and the need for frequent administration of hydrocortisone, it is not possible to have a single blood measure which can be taken at any particular time of the day to give an indication of adequacy of replacement, unlike thyroxine replacement therapy where concentrations in the blood are more constant.

With cortisol more frequent sampling is required. This requires 24 hour profiles, measuring cortisol to determine whether the individual is either under or over exposed to hydrocortisone and whether changes to the dose and/or frequency of administration are going to be required.

Although it is popular to undertake day curves, these do not provide the full story with respect to adequacy of replacement therapy (Figure 6).

Figure 6 illustrates this particular point where the actual 24 hour cortisol profile is depicted on the right compared to that obtained with the cortisol day curve on the left. The cortisol peak concentration at 13:00 (1 pm) is very high which could be misinterpreted as requiring a reduction in the early morning dose. The fact that it arises as can be seen in the 24 hour profile, is as a result of dosing at midday and stacking on top of the previous dose.

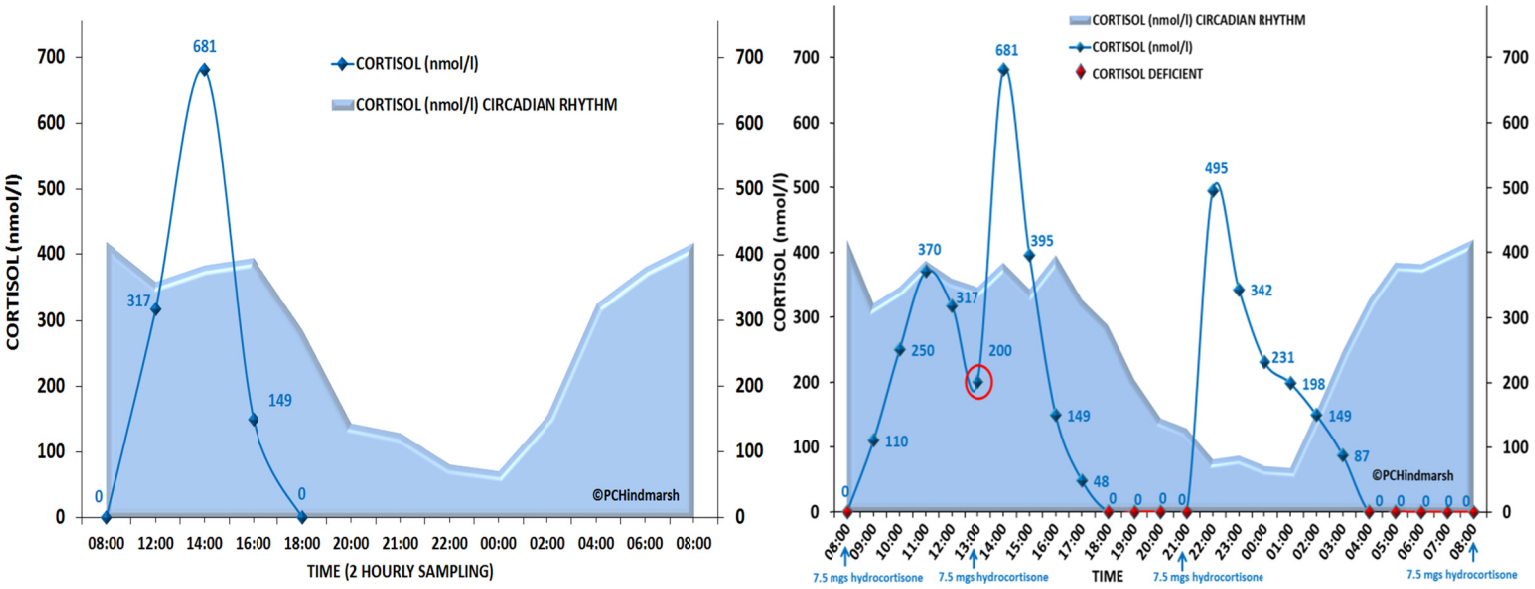

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Figure 6. Cortisol Day curves. The panel on the left shows a day curve constructed with 4 hourly samples. The panel on the right shows what is actually happening with more frequent sampling. It would be easy to think the 681 nmol/l level is from the morning dose whereas it results from stacking the lunchtime dose on the tail of the morning dose (red circle). The correct change to medication is to give the lunchtime dose later and perhaps at a lower dose rather than change the morning dose.

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SIDE EFFECTS

One of the arguments for giving the last dose of hydrocortisone or any glucocorticoid at 18:00h (6 pm) are individuals have difficulty getting off to sleep. Where this has been tested in carefully controlled sleep studies (7, 8), there is no evidence to suggest that hydrocortisone has any effect on time to onset of sleep or sleep quality.

From a series of questionnaires in 226 individuals, the proportion of individuals who have difficulties in getting off to sleep, who dosed at 6 pm, was no different to those who complain of having difficulties getting off to sleep when the dosing was much later in the evening.

Several stated they slept better when taking a late dose. Indeed, in congenital adrenal hyperplasia in paediatric practice there are no problems reported of individuals having difficulty with sleep onset or sleep duration when the dose is given at a much later time (midnight or 01:00 (1 am)).

Giving the last dose at 6pm also leaves the individual without cortisol overnight.

Even dosing at midnight will not last through to the morning which is why **we always add an extra double morning dose at 4am (more@4) during illness**. This is in addition to the doubling of the normal doses taken. This is critically important as this is the time where there is an increase in mortality and morbidity.

Listed in Tables 1 and 2 are the side effects which occur from over or under treatment with hydrocortisone. The cause of all the problems individuals suffer is largely associated with the modality of hydrocortisone or glucocorticoid replacement.

Table 1. Complications of high dose glucocorticoid therapy

Short-Term Therapy	**Long-Term Therapy**
Gastritis	Gastric ulcers
Growth arrest	Short stature
Increase in Appetite	Weight gain
Hypercalciuria	Osteoporosis, fractures
Glycosuria	Slipped epiphyses
Immune suppression	Ischemic bone necrosis
Masked symptoms of infection,	Poor wound healing
esp. fever and inflammation	Catabolism
Toxic psychoses	Cataracts
Headaches	Bruising (capillary fragility)
Hypertension (high blood pressure)	Adrenal/pituitary suppression
	Toxic psychosis
	Striae - Stretch Marks

Table 2. Complications of inadequate glucocorticoid therapy

Short-Term Therapy	Long-Term Therapy
Reduced Appetite	Weight loss
Low blood glucose	Muscle weakness
Tiredness	Hypotension (low blood pressure)
Collapse	Impaired fertility
Headaches	Adrenal Rests
	Skin pigmentation from high ACTH levels

When hydrocortisone has been administered using pump therapy (including hypopituitarism) there has been a dramatic improvement not only in biochemical parameters, but also in quality of life (9). Similarly, there are reports from patients when they have switched to a circadian dosing schedule with oral hydrocortisone, they have felt much better.

Achieving the circadian rhythm with pump therapy has been enormously effective in individuals with a fast clearance, but the pump method is only as good as the information programmed in it. This needs to be calculated using a series of formulae but it can be applied to any individual with adrenal insufficiency (10) and can be helpful in those with severe gastritis as it bypasses the gut.

The most important component of avoiding side effects is knowing the cortisol levels achieved by the hydrocortisone replacement. This is best achieved by undertaking hourly blood sampling, ensuring samples are taken pre-dose, over a full 24 hours to assess cortisol distribution, clearance and stacking.

Another important point to consider is hydrocortisone metabolises differently at various times of the day (11). Same doses of hydrocortisone are cleared more slowly at night than during the day. The exact reasons for this are not clear. What it does mean however, although similar doses may be administered morning and evening, the biological effect may differ. This reiterates the importance of understanding what is being delivered and 24 hour profiles are an important component of this.

COST EFFECTIVENESS AND BENEFIT

The medications used for glucocorticoid replacement vary in price. Undertaking 24 hour profiles currently with hospital admission is expensive but so too are the days lost to the side effects of over and under replacement therapy. Many patients end up with a poor quality of life. Those costs distributed between the National Health Service, the individual and society, need to be factored into our ongoing understanding of the effectiveness of our therapies.

There is no doubt that individuals on cortisol replacement relay how changing to circadian dosing has improved their quality of life and this needs to be built into assessing interventions such as this.

Given the disease burden associated with adrenal insufficiency (12) a better way of monitoring individuals is warranted. Slow or delayed release preparations will still be subject to the variation in absorption and clearance that standard therapies are subject to. In addition, they may have the additional complication of altered gut transit times and the impact of gut flora (13) which may alter drug delivery.

24 hour profiles (hourly sampling) should be undertaken to ensure the cortisol does not peak too high or fall too low, otherwise on a day to day basis, long term side effects will still occur.

CONCLUSIONS

At this stage we need to ensure that we put into place the endocrine maxim of replacing the missing hormone with a synthetic preparation that closely mimics the normal production of the hormone throughout the 24 hour period. For adrenal insufficiency, this means we need to replace cortisol with the synthetic form of cortisol (hydrocortisone) and to measure the efficacy of our replacement hormone therapy throughout the 24 hour period by plasma cortisol measurements. The therapy should be directed to mimicking the circadian rhythm as closely as possible within the limits of the pharmacology of hydrocortisone. Approaching the problem in this manner should minimise the serious side effect profile of the drug and improve the quality of life of patients.

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REFERENCES

1. Bass J, Takahashi JS. Circadian integration of metabolism and energetics. Science 2010; 330: 1349-54.
2. Van Cauter E, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol J Clin Endocrinol Metab 1996; 81: 2468-2473.
3. Hindmarsh PC, Charmandari E. Variation in Absorption and Half-life of Hydrocortisone Influence Plasma Cortisol Concentrations. Clin Endocrinol (Oxf). 2015; 82: 557-61.
4. Peters CJ, Hill N, Dattani MT, Charmandari E, Matthews DR, Hindmarsh PC. Deconvolution Analysis Of 24h Serum Cortisol Profiles Informs The Amount And Distribution Of Hydrocortsione Replacement Therapy. Clin Endocrinol (Oxf) 2013; 78: 347-51.

5. Charmandari E, Johnston A, Brook CGD, Hindmarsh PC. Bioavailability of oral hydrocortisone in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Endocr 2001; 169: 65-70.
6. Birkett DJ. Pharmacokinetics made easy. Chapters 1-3 pgs 1-25. McGraw-Hill, Sydney, Australia. 1998.
7. García-Borreguero D, Wehr TA, Larrosa O, Granizo JJ, Hardwick D, Chrousos GP, Friedman T. Glucocorticoid replacement is permissive for rapid eye movement sleep and sleep consolidation in patients with adrenal insufficiency. J Clin Endocrinol Metab. 2000; 85: 4201-6.
8. German A, Suraiya S, Tenenbaum-Rakover Y, Koren I, Pillar G, Hochberg Z. Control of childhood congenital adrenal hyperplasia and sleep activity and quality with morning or evening glucocorticoid therapy. J Clin Endocrinol Metab. 2008; 93: 4707-10.
9. Hindmarsh PC. The child with difficult to control Congenital Adrenal Hyperplasia: is there a place for continuous subcutaneous hydrocortisone therapy. Clin Endocrinol (Oxf). 2014; 81: 15-8.
10. Bryan SM, Honour JW, Hindmarsh PC. Management of altered hydrocortisone pharmacokinetics in a boy with congenital adrenal hyperplasia using a continuous subcutaneous hydrocortisone infusion. J Clin Endocrinol Metab. 2009; 94: 3477-3480.
11. Charmandari E, Hindmarsh PC, Johnston A, Brook CGD. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: Alterations in cortisol pharmacokinetics at puberty. J Clin Endocrinol Metab 2001; 86: 2701-8.
12. Gunnarsson C., Ryan MP, Marelli C, Baker ER, Stewart PM, Johannsson G, Biller BMK. Health Care Burden in Patients with Adrenal Insufficiency. J Endocr Soc 2017; 1: 512-523.
13. Honour JW. Historical perspective: Gut dysbiosis and hypertension. Physiol Genomics. 2015; 47: 443-6.