Doses and steroids to be used in primary and central hypoadrenalism

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Abstract
Traditionally hydrocortisone has been the first choice for replacement therapy in patients with adrenal insufficiency. Paediatricians have used body surface area adjusted dosing and adult physicians have tended to use fixed doses twice or thrice daily. Cortisol secretion has a distinct circadian rhythm being low at the time sleep onset, rising from between 02.00 h and 04.00 h in the morning to peak just after the time of waking then falling during the day. The pharmacokinetics of immediate release hydrocortisone means that no treatment regimen is capable of simulating the normal circadian rhythm of cortisol. Recent data with hydrocortisone infusions suggests that circadian delivery of hydrocortisone can improve biochemical control of patients with adrenal insufficiency. It is anticipated in the future that modified release formulations of hydrocortisone will provide more optimal replacement therapy.

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1. Introduction
Hydrocortisone is the generic pharmaceutical name for cortisol and is the preferred replacement therapy for these patients [1,10]. Because of the short half-life of immediate release hydrocortisone and the requirement for multiple dosing during the day, some physicians use longer acting steroids such as prednisolone or dexamethasone. However, there is no universal agreement regarding appropriate dose, timing or monitoring of replacement therapy [4]. Over treatment with glucocorticoids may result in the features of Cushing syndrome and under treatment with chronic fatigue and reduced resistance to illness. Paediatricians commonly use dose based on body surface area but traditionally adult physicians have used a fixed dose, which was originally 20 mg hydrocortisone in the morning and 10 mg in the evening. This was based on estimates of cortisol production at 12–15 mg/m² per day. However it is now recognised that these original estimates were too high and the more accurate estimate of cortisol production suggests approximately 6–11 mg/m² per day [5,7]. Thus common treatment regimens in adults generally give hydrocortisone 10–20 mg/m² per day allowing for incomplete bioavailability [10]. There has been a tendency for physicians to move from twice daily dosing to a thrice daily hydrocortisone regimen but usually physicians continue to use a fixed dose in adults [4]. In this manuscript, we discuss the work we have done looking at a thrice daily weight related hydrocortisone dosing regimen and follow-up studies looking at providing circadian delivery of hydrocortisone through intravenous infusions.

2. The physiology of cortisol secretion
Cortisol is secreted in a circadian fashion under the control of pituitary ACTH [6]. Fig. 1 shows very distinct circadian rhythm demonstrated in a large group of health volunteers using modern cortisol assays [3]. It can be seen that cortisol levels are high first thing in the morning, fall during the day, and interestingly in this data it is quite clear there is a small peak before the midday meal and the evening meal. Cortisol levels then fall to very low levels prior to sleeping and don’t start to rise until between 02.00 h and 04.00 h. The circadian rhythm of cortisol is controlled by ACTH released from the pituitary, which is regulated by CRF and ultimately the central clock in the suprachiasmatic nucleus. It has been demonstrated that there is a small peak of cortisol just prior to waking and it has been argued that this is a signal for waking, but generally cortisol peaks within the hour after waking [2]. There is a bidirectional relationship between cortisol circadian rhythm and the sleep wake cycle which is evident in everyday life with sleep deprivation and jet lag. The general goal of endocrine replacement is to try and reproduce the normal physiological rhythm, but clearly this is a challenge within the context of cortisol secretion.
3. Thrice daily weight-related hydrocortisone dosing

We have examined variables that determine hydrocortisone disposition in patients with adrenal insufficiency in order to try and develop practical protocols for individualised prescribing and monitoring of hydrocortisone treatment [8]. We looked at serum cortisol profiles in 20 cortisol insufficient patients given oral hydrocortisone as either fixed or body surface area adjusted dose in a fasted or fed state. We measured endogenous cortisol levels in healthy subjects. Body weight was the most important predictor of hydrocortisone clearance. A fixed dose of 10 mg of hydrocortisone first thing in the morning over exposed patients whereas weight adjusted dosing decreased interpatient variability. Food taken before hydrocortisone delayed its absorption. Serum cortisol measured 4 h after hydrocortisone predicted the cortisol area under curve. Based on these observations we recommended a weight adjusted hydrocortisone dosing, thrice daily before food, monitored with a single serum cortisol measurement using a normogram [8]. This regimen was prospectively examined in 40 cortisol insufficient patients, 85% of whom opted to remain on the thrice daily treatment regimen. However it is quite clear from the data that using immediate release hydrocortisone it is not possible to provide circadian replacement therapy, as these patients have no cortisol release during the night.

4. Circadian hydrocortisone infusions in patients with adrenal insufficiency

As outlined above, conventional hydrocortisone therapy with immediate release hydrocortisone cannot provide physiological replacement therapy as it misses the nighttime rise in cortisol release. We have explored the potential of circadian delivery of hydrocortisone as proof of concept for such therapy using intravenous infusions of hydrocortisone [9]. We investigated whether the circadian intravenous infusion of hydrocortisone could improve control of ACTH and androgen levels. This was done in patients with primary adrenal insufficiency and patients with congenital adrenal hyperplasia (CAH).
studied two healthy subjects, two patients with Addison’s disease, and two patients with CAH. In patients on thrice daily oral hydrocortisone, peak serum cortisol levels were higher than in normal subjects and overnight levels were very low (Fig. 2). Patients had very high plasma ACTH levels before their morning dose of hydrocortisone both at the beginning and at the end of their conventional oral therapy. In the patients with CAH serum 17OH-progesterone was also elevated at the beginning and end of conventional treatment. The overall 24 h mean cortisol levels were similar for conventional oral hydrocortisone and the circadian infusion. At 07.00 h ACTH levels were much higher on conventional treatment than after circadian infusion: Mean ± SEM 311.2 ± 85.4 versus 70.5 ± 45 ng/l, respectively ($P < 0.05$). The same pattern was observed for 17OH-progesterone, which was 550 and 777 nmol/l after conventional treatment and 3 and 64 nmol/l after circadian infusion (Fig. 3). Based on these observations it is clear that the circadian infusion of hydrocortisone can decrease morning ACTH and 17OH-progesterone levels to near normal even in patients with very poor biochemical control of their disease.

5. Conclusion

Current therapy with immediate release hydrocortisone is the most commonly used regimen for replacing patients with primary and secondary adrenal insufficiency. However, no current treatment regimen can provide the physiological rhythm of cortisol release. Infusions with hydrocortisone can simulate cortisol circadian rhythm and evidence from small numbers of patients suggests there is improved biochemical control. Technology is now available to make modified release hydrocortisone and it is anticipated in the future that delayed and sustained formulations of hydrocortisone will be able to provide a more physiological replacement therapy for patients with adrenal insufficiency.

References