Is physiological glucocorticoid replacement important in children?

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ABSTRACT

Cortisol has a distinct circadian rhythm with low concentrations at night, rising in the early hours of the morning, peaking on waking and declining over the day to low concentrations in the evening. Loss of this circadian rhythm, as seen in jetlag and shift work, is associated with fatigue in the short term and diabetes and obesity in the medium to long term. Patients with adrenal insufficiency on current glucocorticoid replacement with hydrocortisone have unphysiological cortisol concentrations being low on waking and high after each dose of hydrocortisone. Patients with adrenal insufficiency complain of fatigue, a poor quality of life and there is evidence of poor health outcomes including obesity potentially related to glucocorticoid replacement. New technologies are being developed that deliver more physiological glucocorticoid replacement including hydrocortisone by subcutaneous pump, Plenadren, a once-daily modified-release hydrocortisone and Chronocort, a delayed and sustained absorption hydrocortisone formulation that replicates the overnight profile of cortisol. In this review, we summarise the evidence regarding physiological glucocorticoid replacement with a focus on relevance to paediatrics.

INTRODUCTION

Glucocorticoids are essential stress hormones that regulate metabolic, cardiovascular and immunological homeostasis. Cortisol, synthesised in the adrenal cortex, is the main glucocorticoid in humans and deficiency may result in death from an adrenal crisis. Glucocorticoids, and specifically hydrocortisone (cortisol), have been used for the treatment of primary and secondary adrenal insufficiency since the 1950s,[1] and were rapidly shown to improve prognosis.[2] Glucocorticoid replacement therapy has changed little since its first use, although there is a better understanding of the hypothalamic-pituitary-adrenal (HPA) axis and the importance of preserving the cortisol circadian rhythm for health. Recent evidence suggests that patients with adrenal insufficiency have poor health outcomes potentially related to long-term excess glucocorticoid therapy.[3 4] This has led to the development of new treatment regimens and drug formulations that attempt to provide more physiological cortisol replacement.

CIRCADIAN RHYTHMS AND THE HPA AXIS

The HPA axis is a classical endocrine feedback loop; hypothalamic corticotropin-releasing hormone and arginine vasopressin stimulate pituitary release of adrenocorticotrophic hormone (ACTH), which in turn stimulates cortisol secretion, cortisol then completes the loop through negative feedback at both the hypothalamus and pituitary. The HPA axis begins to function from week 6 of fetal life but is quiescent throughout most of gestation.[5] Close to term, a rise in corticosteroid concentrations is thought to support adaption to parturition and it is possible that maternal or fetal stress, through increasing glucocorticoid production, may trigger preterm birth.[6] The HPA axis is immature at birth, although the elements of the circadian system are present and even preterm infants will respond to light and dark triggers.[7] The development of the neonatal and childhood cortisol circadian rhythms has been variously reported (table 1). During the first weeks of life there is no evident circadian rhythm, however, within 2 months from delivery the HPA axis demonstrates a recognisable rhythm with a cortisol peak in the early morning and nadir at midnight and this resembles the adult circadian rhythm by 9 months of age.[8] Once established, the cortisol circadian rhythm is similar through childhood and into adult life with minimal reported differences with age and puberty. The HPA axis circadian rhythm is regulated by the central pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN rhythm has an approximate period of 24.2 hours, such that it requires a daily resetting via the light/dark photoperiod to maintain a 24-hour rhythm.[9] In adults, serum cortisol concentration has a nadir at midnight, rises from around 02:00–04:00 hours, peaks shortly after waking, declines over the day and is quiescent (though still with detectable cortisol concentrations) from around 18:00–02:00 hours.[10] Interestingly, there is an ACTH rise shortly before waking that may be a trigger for waking and there is some day-to-day higher central control of this, such that people expecting to wake later in the day have their cortisol peak correspondingly delayed.[11] The HPA axis also displays an ultradian rhythm with glucocorticoid pulses occurring approximately every hour and a quarter.[12] A number of factors may influence the cortisol circadian rhythm and the cortisol rhythm itself regulates metabolism and human behaviour (figure 1). Most tissues in the body possess clock genes that are synchronised by the central pacemaker in SCN,[13] and there is evidence that the circadian rhythm of glucocorticoids can act as a secondary messenger from the central pacemaker to peripheral clock genes.[14] Changes in basal concentrations of steroids and disruption of the rhythm are caused by stress such as infection, and raised basal cortisol concentrations with loss of the circadian variability are linked to psychiatric illnesses including post-traumatic stress disorder and depression.[15 16]

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Table 1 Previous publications on cortisol concentrations and circadian rhythm in neonates infants and children[36 69–82]

Study	Age range	Number of subjects	24 hours profile	Notes	Study findings	Study conclusions
Neonatal studies						
Price *et al*[69]	Neonates	8 term	Yes: 4 samples	Salivary sampling longitudinal study term till 24 weeks age	Variable cortisol pattern until average of 12 weeks	Circadian rhythm established in first few months of life
Hindmarsh *et al*[70]	Neonates and adults	10 term 10 preterm 10 adults	Yes: 930 and 1530 samples	Venous sampling	Morning cortisol was significantly higher than afternoon in all groups	Diurnal rhythm seen in neonates aged 3–4 days
Jonetz-Mentzel and Wiedemann[71]	Neonates–18 years	687 healthy children	No: one sample 08:00–10:00 hours	Venous	Cortisol in neonates aged 5 days lower than other age groups	Low cortisol in neonates aged 5 days reflects lack of circadian rhythm
Santiago *et al*[72]	Neonates	9 term	Yes	Three salivary samples per day collected on weeks 2, 4, 8, 12, 16, 20, 24	Circadian rhythm appeared at median 8 weeks No relationship to sleeping through the night	Circadian rhythm in cortisol appears earlier than previously expected and as early as 2 weeks in some babies
Iwata *et al*[73]	Neonates	27 term	Yes	Eight salivary samples over a 24-hour period	Non-circadian rhythm Acrophase of cortisol secretion linked to birth time in infants <5 days of age	Initial HPA axis activity entrained to birth time rather than day/night periodicity
Stroud *et al*[74]	Neonates	100 term	No	Longitudinal salivary testing in cohort with/without maternal smoking for 1 month	Cortisol higher in maternal smoking neonates	Maternal smoking alters HPA axis in neonates: epigenetic alteration of glucocorticoid receptor postulated
Studies in older children						
Lashansky *et al*[75]	2 months–17 years	102 term	No: Synacthen test	Cross-sectional Synacthen-stimulated levels	Standard Synacthen test demonstrated rapid cortisol response	Cortisol response highest in infants and postpubertal
de Weerth *et al*[76]	2–5 months	14 term	Yes	5×salivary monthly	Circadian patterns depended significantly on analysis	Circadian rhythm can be seen from 2 months onwards
Wallace *et al*[77]	Median age 11 years	14 healthy	Yes	Serum samples every 20 min for 24 hours	Clear circadian rhythm demonstrated for cortisol and ACTH No relationship to puberty or sex	Normal circadian rhythm is seen in children with similar levels of cortisol secretion to adults
Ghizzoni *et al*[78]	6–11 years	8 healthy 8 NCCAH	Yes	Comparison of cortisol and TSH curves	24-hour cortisol AUC not different but NCCAH had lower nocturnal cortisol and higher nocturnal TSH	TSH and cortisol inversely correlated. Blunted overnight cortisol rise in NCCAH leads to higher TSH
Knutsson *et al*[79]	2–18 years	235 healthy children	Yes	Venous cross-sectional with longitudinal n=28	No differences between males or females or age groups or pubertal status in circadian rhythm and cortisol	Circadian rhythm and absolute cortisol does not vary through childhood or puberty
DeVile *et al*[80]	3–20 years	50 SAI	Yes	Venous	Patients had a non-physiological mid-morning nadir	Thrice-daily hydrocortisone did not adequately replicate the circadian rhythm of cortisol in patients
Hermida *et al*[81]	Prepubertal children	135 children: 14 GHD 36 SS 57 VSS 28 NS	Yes	Serum cortisol and GH analysis	Similar circadian rhythm for cortisol secretion seen in all groups	The relationship between GH and cortisol secretion is unclear, and GH-deficient children can have entirely normal cortisol secretion patterns
Peters *et al*[36]	5–9 years and adults	29 SS 80 adults	Yes	Serum cortisol profiles Deconvolution analysis	Circadian pattern similar in adults and children with earlier nadir and slightly higher peaks in children Mean 24-hour cortisol secretion Adults 6.3 mg/m^2/day Children 8.0 mg/m^2/day Non-significant difference	Morning cortisol is a fair reflection of adrenal sufficiency in adults and children, but care must be taken when assessing nadir in children (ie, for Cushing's disease)
Shirtcliff *et al*[82]	9–15 years	306 children followed longitudinally	Yes: 3 samples	Salivary cortisol followed longitudinally	Stable intra-individual circadian rhythm Sex differences seen at puberty	Circadian rhythm is strongly individual and stable across pubertal development

ACTH, adrenocorticotrophic hormone; AUC, area under the curve; GHD, growth hormone deficiency; HPA, hypothalamic-pituitary-adrenal; NCCAH, non-classical congenital adrenal hyperplasia; NS, normal stature; SAI, secondary adrenal insufficiency; SS, idiopathic short stature; TSH, thyroid-stimulating hormone; VSS, very short stature <−3SDS.

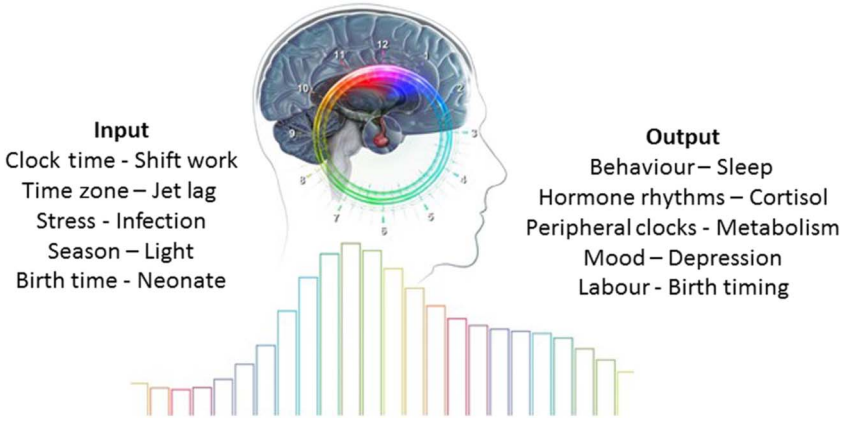

Figure 1 Central clock input and output in relation to circadian rhythms.

THE IMPACT OF DISRUPTING CIRCADIAN RHYTHMS ON HEALTH

In jet lag and shift work, the diurnal activity of the individual is shifted in time. In young men travelling across a 7-hour time zone shift, it took up to 11 days for peak cortisol secretion values to reset and 21 days to reset the nocturnal cortisol nadir. These changes in HPA activity were accompanied by sleeplessness and nausea.[17] Switching the sleep/awake patterns, as in shift work, has more long-term consequences and is associated with an increased incidence of obesity and diabetes mellitus.[18] Shifting the sleep cycle by 12 hours results in insulin resistance.[19] Population studies have shown increased risk of coronary events and cerebrovascular disease in shift workers, and a potential link to cancer.[20] There is a growing body of work showing an association between sleep disturbance, lack of sleep and an adverse metabolic profile.[21] In young adults subjected to restricted sleep patterns, those placed on a simulated shift work pattern not aligned to the normal day/night pattern showed a reduction in insulin sensitivity and rise in high sensitivity C-reactive protein (a marker of cardiovascular risk), which was more marked in those with sleep restriction and misalignment than sleep restriction alone.[22] Work in pregnant women has shown that even when pre-pregnancy body mass index is controlled for, women with gestational diabetes mellitus have worse sleep patterns and a higher tendency to obstructive sleep apnoea than those without.[23] Short-term disruption in sleep results in a 20% overall increase in cortisol secretion, and a damping of the cortisol circadian rhythm.[24] Cortisol is a key regulator of glucose metabolism with elevated concentrations resulting in reduced insulin sensitivity.[25] Thus, the evidence points to loss of the cortisol circadian rhythm being associated with an increased incidence of obesity, diabetes mellitus and an increase in biomarkers of cardiovascular risk.

ADRENAL INSUFFICIENCY

Adrenal insufficiency is classified into primary, secondary and tertiary, where primary is failure of the adrenal gland, secondary failure of the pituitary and tertiary hypothalamic dysfunction resulting in adrenal suppression commonly through chronic exposure to glucocorticoids.[26] The most common cause for primary adrenal insufficiency in Western world adults is autoimmune Addison's disease, but the causes in children differ, with congenital adrenal hyperplasia (CAH) being the most important cause in preschool children and autoimmune Addison's disease appearing in adolescence.[27] The goals of treatment for adrenal insufficiency are to replace physiological cortisol concentrations.[28] In CAH, there is the additional need to suppress excess adrenal androgen production, which is a consequence of the excess ACTH drive.[29] Mutations in the *CYP21A2* gene encoding the enzyme 21-hydroxylase account for 95% of CAH cases.[30 31] In 21-hydroxylase deficiency, failure in cortisol synthesis results in reduced cortisol feedback and consequently increased pituitary ACTH release, which in turn promotes overproduction of 17-hydroxyprogesterone, progesterone and adrenal androgens. Replacement of cortisol switches off the excess ACTH drive from the pituitary and reduces the overproduction of adrenal androgens. The importance of replacing the circadian rhythm of cortisol is most evident in CAH, where the early morning increase in ACTH causes excess androgens on waking, and current treatment regimens fail to fully control androgens in the majority of paediatric and adult patients.[32 33]

CURRENT GLUCOCORTICOID THERAPY IN CHILDREN

The dosage of hydrocortisone used for adrenal replacement has reduced over time.[34] There has also been a move from twice-daily dosing to thrice-daily dosing with some evidence of benefit.[35] More complex regimes with four times per day dosing, or dosing with reversed circadian pattern or strict 8 hourly dosing patterns are recommended by some paediatricians, but to date there has been no definitive evidence of superiority of any of these regimens and none of these regimens has replaced the physiological profile of cortisol in children or adults.[36] Paediatric therapy for adrenal insufficiency in Europe was surveyed in 2014 through the European Society of Paediatric Endocrinologists.[37] Although the survey response was small (67 respondents), participants represented 16 countries, and the vast majority of prescribers were using generic hydrocortisone either as crushed/dispersed tablets or as specially manufactured (ie, unlicensed) formulations. Manipulation of the doses was necessary as the standard tablet for hydrocortisone is 10 mg, which is too large a dose for the majority of children. Most paediatricians were prescribing hydrocortisone three times per day. In older children and adults, prednisolone or dexamethasone was used by some, but these are avoided in childhood because of their more potent effect on growth. Treatment with hydrocortisone results in cortisol profiles that are unphysiological, despite many different regimens being used. Children treated with hydrocortisone experience several spikes in cortisol concentrations over the day, often to supraphysiological concentrations, followed by prolonged periods of hypocortisolaemia between doses.[38] Some regimens leave children and adults with low concentrations of cortisol over the evening, and with most current regimens cortisol concentrations fall to undetectable levels overnight, and do not rise again until the first dose of hydrocortisone has been absorbed.

HEALTH OUTCOMES IN CAH AND ADRENAL INSUFFICIENCY

The most common cause of adrenal insufficiency in childhood is CAH, so it is in this population that we have most knowledge of health outcomes in children treated with glucocorticoid replacement therapies. CAH is a complex condition, and even with optimal treatment androgen concentrations are seldom normal, and so it can be difficult to distinguish the adverse effects of glucocorticoid treatment from those of the disease itself. In general, paediatric patients tolerate the cortisol profile achieved from hydrocortisone therapy well in the short term, but there is increasing evidence for poor health outcomes in the long term.[32 33] In adult patients with acquired adrenal insufficiency, quality of life may be poor and an increased prevalence of psychological morbidity is also reported. Both outcomes have been related to hydrocortisone doses.[39 40] In paediatric patients with CAH, quality of life is reported to be reduced, with boys and girls equally affected suggesting that this is not simply related to either androgen excess in girls or associated disorders of sex development.[41] The reasons for poor quality of life are likely to be multifactorial, but it is possible that abnormal glucocorticoid profiles may contribute to this adverse outcome. Working memory performance is lower in children with CAH than in unaffected relatives, leading to speculation that the abnormal cortisol profile in childhood may adversely affect cognitive development.[42] Children with CAH have an increased prevalence of obesity, insulin resistance, elevated leptin concentrations, dyslipidaemia and impaired glucose metabolism.[43–46] It is likely that this is due, in part, to the supraphysiological doses of glucocorticoid that are often required to achieve satisfactory ACTH suppression in childhood. Pharmacogenetic studies suggest that variability in glucocorticoid sensitivity and metabolism may also affect hydrocortisone requirements and metabolic outcomes.[47–49] Adults with CAH remain shorter than the normal population and short stature in patients with CAH is associated with hypertension, suggesting that treatment in childhood impacts on long-term health in adult life.[50]

NEW GLUCOCORTICOID REPLACEMENT TECHNOLOGIES

Subcutaneous infusions of insulin have been used in diabetes for many years and have potential advantages over discrete injections.[51] Several researchers have tried similar technology to infuse hydrocortisone over a 24-hour period in patients with adrenal insufficiency. In open-label studies or case reviews, there have been subjective improvements in quality of life and reductions in hospital admissions.[52] The only blinded randomised controlled trial showed no preference between infusion and oral hydrocortisone in patients with Addison's disease with pre-existing good quality of life.[53] In children with CAH, subcutaneous hydrocortisone infusions have been used to improve androgen control during puberty, when altered hydrocortisone pharmacokinetics and poor adherence make treatment particularly challenging.[54] Subcutaneous infusion therapy in adolescent CAH males resulted in improved androgen profiles, but the potential long-term benefits on cardiovascular risk factors, quality of life, learning and psychological well-being have yet to be examined.[55 56] The lack of large trials and case series is due in part to the cost and complexity of switching a patient to an infusion. A pump costs in the order of £2000,[57] and the patients and family need intensive training to be able to re-site cannulae every 3 days, manage sick day rules through temporary basal rates and deal with potential pump failure or blockage.[53] With these hurdles, and without advantages that pumps in diabetes seem to offer, it seems likely that pumps will remain a specialised option in adrenal insufficiency for patients with very specific needs. Advances in the diabetes field in transdermal infusion mechanisms and smaller pumps may in time make this technology more accessible.[58]

Plenadren (Bailiwick of Jersey) is a modified-release hydrocortisone with an outer coating layer that provides an immediate release of the drug and an extended-release core. Plenadren provides a more extended serum profile of cortisol compared with immediate-release hydrocortisone. In adults, the licensed regimen of a single morning dose of Plenadren gives similar cortisol exposure to a thrice-daily regime of immediate-release hydrocortisone, although Plenadren tends to provide higher concentrations of cortisol in the late morning and lower in the late evening than a conventional regime and overall has approximately 20% less bioavailability (figure 2).[59–61] The expectation is that a once-daily Plenadren regime will improve adherence and quality of life, although this remains to be demonstrated in blinded trials. Open-label studies with Plenadren have shown an improvement in quality of life and reduction in central adiposity in adult patients with adrenal insufficiency, and these changes have been sustained at 12 months of treatment with improvements in lipid profile.[62] Plenadren is not licensed for use in children. A small case series of children with Addison's disease and secondary adrenal insufficiency, in whom manipulation of hydrocortisone doses and frequency of dosing failed to achieve satisfactory cortisol replacement, has suggested that Plenadren may have a place in paediatric practice. However, two to three Plenadren doses a day were required to maintain acceptable cortisol concentrations during waking hours.[63] For the treatment of CAH, Plenadren is unlikely to control excess androgens as the overnight rise in cortisol is not replicated, and nocturnal dosing of Plenadren would expose patients to high levels of during the quiescent period of the cortisol circadian rhythm.

Chronocort is a product under development by Diurnal (UK). The product is a modified-release hydrocortisone, but differs from Plenadren in having a delayed and sustained absorption profile rather than an immediate- and sustained-release profile.[64] Chronocort aims to replace physiological cortisol concentrations by dosing at morning and night such that the nighttime dose provides release of hydrocortisone in the early hours of the morning providing a prewaking rise in cortisol levels. A phase II open-label study of Chronocort in 16 adults with CAH showed that a twice-daily regimen of Chronocort provided a similar cortisol rhythm and early morning peak to physiological cortisol concentrations in healthy volunteers (figure 2).[65] Six months usage of Chronocort resulted in lower 24-hour, morning and afternoon 17-hydroxyprogesterone and androstenedione androgens compared with conventional therapy. Whether these short-term effects can be sustained and what effect on overall health status this has in patients is the subject of an ongoing phase III study for Chronocort.

CONCLUSIONS

The circadian rhythm of cortisol is important for health in humans, and there is evidence of deleterious effect when this rhythm is disrupted. Many of the symptoms that patients with adrenal insufficiency complain of such as fatigue, sleep disturbance and poor concentration are seen when the cortisol circadian rhythm is disrupted in jetlag. It is therefore a reasonable hypothesis that replacing cortisol in a circadian manner should be superior to current therapy. This should be no less true in a paediatric than adult population and the sleep cycle may be

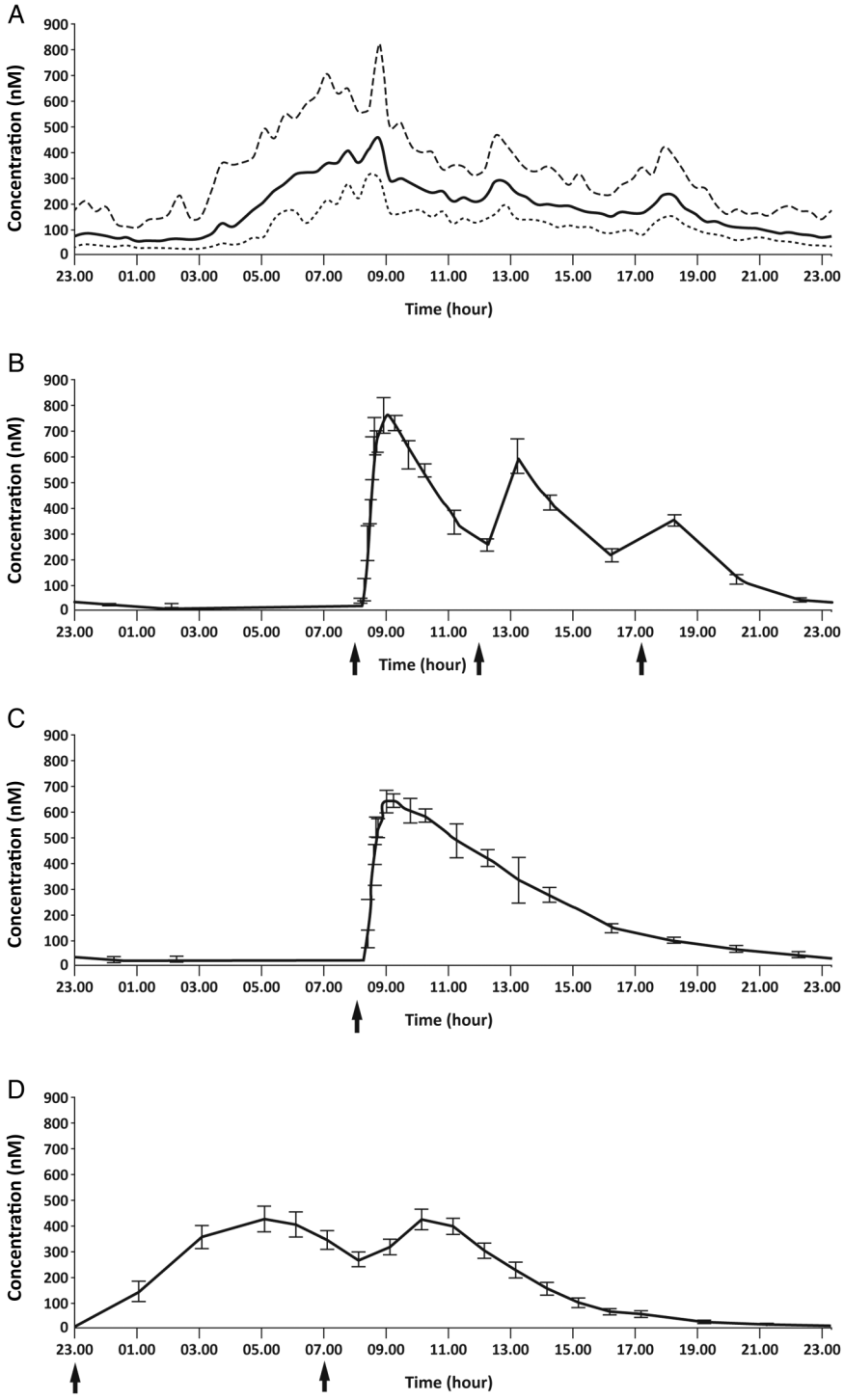

Figure 2 (A) Cortisol concentrations measured by LC-MS/MS in healthy volunteers (mean, 10th and 90th centile).[64] (B) Cortisol concentrations measured by immunoassay on three times daily immediate-release hydrocortisone 20–40 mg in adrenal insufficiency patents (mean and 95% CI).[61] (C) Cortisol concentrations measured by immunoassay on once-daily Plenadren 20–40 mg in patients with adrenal insufficiency (mean and 95% CI).[61] (D) Cortisol concentrations measured by LC-MS/MS on twice daily Chronocort with 20 mg at 23:00 hours and 10 mg at 07:00 hours in patients with congenital adrenal hyperplasia (mean and sem).[65] Arrows on x-axis represent timing of dosing. LC-MS/MS, liquid chromatography-mass spectroscopy/ mass spectroscopy.

more important in a developing individual than adult.[66] Improvements in biochemical, auxological and quality-of-life measures were reported in a 12-month study of patients with Addison's disease treated with Plenadren.[55] In the only double-blind study of hydrocortisone infusion, there was no clear impact on patients' well-being despite this treatment offering the benefit of a physiological early morning rise in cortisol and a smoother cortisol profile; however, this was a small group of patients with good baseline quality of life and the study may have been underpowered to detect a change. In CAH, there is a need for circadian therapy to suppress the overnight ACTH drive and reduce androgen production. This is demonstrated by case studies of hydrocortisone infusions in CAH and a phase II study of Chronocort. Future studies will need to demonstrate clinical benefit associated with improved biochemical control of CAH. Cortisol and cortisone concentrations in saliva and cortisol concentrations in dried blood spots are reported to be robust measures of blood cortisol concentrations,[67] and are particularly attractive for the study of new hydrocortisone formulations in children.[68] However, the relationship between cortisol profiles and medium-term and long-term health outcomes is likely to be complex. It is important to note that the majority of data regarding physiological glucocorticoid replacement is from adult patients and there is a need for further studies in paediatrics to better understand the needs of paediatric patients with adrenal insufficiency.

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