EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES

http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 2
26-29
Year: 2016

ADRENAL INSUFFICIENCY: CURRENT THERAPEUTIC REPLACEMENT STRATEGIES. IS THERE ANY EVIDENCE OF IMPROVED CLINICAL OUTCOMES WITH THE USE OF ONCE DAILY LONG ACTING HYDROCORTISONE THERAPY?

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Article Received on 26/11/2015 **Article Revised on 17/12/2015** **Article Accepted on 08/01/2016**

INTRODUCTION

Adrenal insufficiency can be subdivided into three broad categories: (*1*) Chronic primary adrenal insufficiency, also called Addison's disease, in which autoimmune adrenalitis is the most frequent cause (Carey RM 1997). (*2*) Chronic secondary adrenal insufficiency is most frequently caused by hypothalamic-pituitary tumors (*3*) acute adrenal crisis may result from stress in patients with chronic adrenal insufficiency who are not adequately replaced, but it also occurs in patients with acute adrenal hemorrhage or pituitary apoplexy (Yoram Shenker 2001). Chronic replacement therapy with glucocorticoids and, in primary adrenal insufficiency, mineralocorticoids requires careful monitoring. However, current replacement strategies still require optimization as evidenced by recent studies demonstrating significantly impaired subjective health status and increased mortality due to inappropriate GC replacement therapy in patients with primary and secondary adrenal insufficiency (ArltW2009). Further studies have explored the potential of modified delayed-release hydrocortisone to improve the prospects of patients with adrenal insufficiency.

Cortisol secretion: circadian rhythm

Cortisol is an essential stress hormone, has a diurnal rhythm regulated by the central body clock and this rhythm is a metabolic signal for peripheral tissue clocks (So, A.Y.2009). Normal individuals, without disease of the hypothalamo—pituitary— adrenal (HPA) axis, at midnight, have very low or undetectable cortisol levels that build up overnight to peak first thing in the morning. Cortisol levels then decline slowly throughout the day (Debono *et al.* 2009)

Figure1.

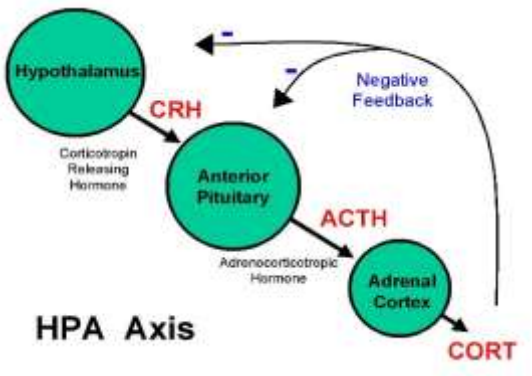

Figure-1 Hypothalamic –pituitary –adrenal axis (HPA Axis) - Adapted from www.biology.ucr.ed

Loss of cortisol rhythmicity, as seen in jetlag or shift workers, results in fatigue, depression and metabolic abnormalities including insulin resistance (Spiegel K.2005).

A general principle in endocrinology is to replace hormones to replicate, as much as possible, physiological concentrations to avoid unfavorable effects (Debono M 2013).

Current therapeutic replacement strategies in patients with AI

Hydrocortisone is the pharmaceutical name of the endogenous active steroid cortisol. Orally administered hydrocortisone is the most commonly used GC for cortisol replacement therapy (Filipsson H 2006).

Physiological daily cortisol production rates vary between 5 and 10 mg/m^2 (Esteban NV 1991) which is equivalent to the oral administration of 15 to 25 mg hydrocortisone to be given 2-3 times/day. Morning dose is higher and is usually 1/2 to 2/3 in the morning. (Arlt W 2009).

The immediate release hydrocortisone has a short half-life(Mah et al 2004)makes it difficult to replicate the physiological cortisol release, therfore, a number of research studies have explored different hydrocortisone regimes to try and identify the best doses and patterns of treatment, respectively(Debono M 2010).

Whether a thrice daily glucocorticoid regimen should be preferred over twice daily administration is not clear because well-designed and appropriately powered studies are lacking. On other hand, Mah et al 2004, concluded that the thrice-daily dosing before food was the preferred

hydrocortisone regime but still was far from replicating physiological cortisol rhythm. **Figure-2**

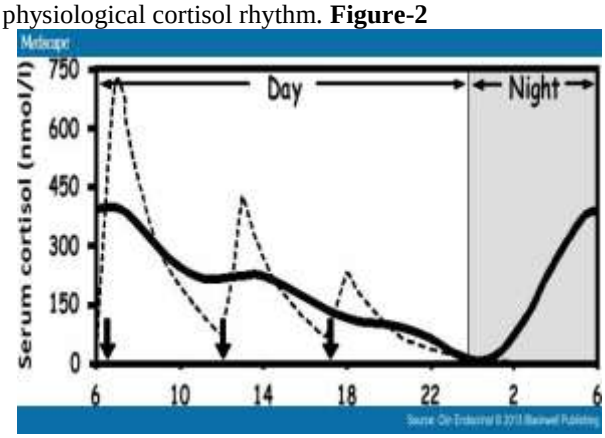

Figure-2 Circadian rhythm of serum cortisol in normal subjects (solid line) and simulated cortisol profile for a patient (broken line) following thrice-daily hydrocortisone administration (10 mg at 06:00 h, 5 mg at 12:00 h and 2·5 mg at 18:00 h (arrows).Adapted from Debono M 2013,J Clin Endocrinol Metab/Medscape.

In addition, weight-related dosing, commonly used in children, appears to generate a smoother pharmacokinetic profile and decrease interpatient variability, but data demonstrating superiority of such a regimen are lacking (Mah et al 2004). Some countries do not have access to hydrocortisone and therefore have to resort to long-acting synthetic glucocorticoids. However, prednisolone and dexamethasone have considerably longer biological half-lives, likely resulting in unfavorably high night-time glucocorticoid activity with potentially detrimental effects on insulin sensitivity and bone mineral density (Jodar E 2003).

The major limitation of current GC replacement strategies, is not fully able the mimic the cortisol rhythm and patients still have an increased morbidity and mortality despite replacement (Arlt W 2009).

Patients with primary adrenal insufficiency require mineralocorticoid replacement, which usually consists of fludrocortisone 0.05-0.2 mg/day. Measurements of blood pressure, serum sodium plus potassium, and renin activity should be checked regularly for monitoring dose replacement (Oelkers W 1992).

Monitoring Glucocorticoids therapy

As no objective method or biomarker for monitoring treatment in patients with adrenal insufficiency has been demonstrated, many endocrinologists have adopted careful attention to signs symptoms potentially suggestive of glucocorticoids over or under treatment, as a means of deciding when to change doses (Debone M 2013). **Table -1.**

Table-1 Clinical assessment of glucocorticoids replacement therapy (Arlt W 2006)

Inadequate GC Replacement	Excessive GC Replacement
-Malaise	-Cushingoid features
-Postural hypotension	-Glucose intolerance
-Diarrhea	-Hypertension & cardiovascular diseases
-Abdominal pain	-Neuropsychiatric illness such as depression
-Weight loss	-Protein catabolism
-Poor response to stress and illness	-Osteoporosis
-Electrolytes abnormalities	

Measurement of plasma ACTH and/or random serum cortisol cannot used as criteria for GCS dose adjustment Feek CM 1981). Similarly, measurements of urinary free cortisol excretion provide no benefit in dose adjustment (Howlett TA 1997).

Timed serum cortisol measurements and serum cortisol day curves can be of some value in selected patients, *e.g.* in case of suspected noncompliance or malabsorption; to monitor replacement therapy (Peacey SR 1997).

Long-acting hydrocortisone formulations: Areas for future researches

There is an unmet clinical need for more convenient, and likely more compliance, and more physiological preparations of hydrocortisone (Debone M 2013). Modified release hydrocortosine (dual release DR-HC) preparations have been investigated in many trails as a more practical and effective solution for patients with adrenal insufficiency.

Plenadren is a recently licensed modified-release formulation of hydrocortisone. It has an immediate-release coating combined with an extended-release core; can be taken as once-daily morning dose, provides cortisol concentrations which are closer to the normal cortisol rhythm (Johannsson, G.et al 2009, 2012).

Chronocort is another modified release HC formulation. Pharmacokinetic modelling of Chronocort® suggested that giving a 20-mg dose at 23:00 h and a 10-mg dose at 07:00 h could replicate the normal physiological cortisol rhythm (Debono M. 2009). Further studies are now required to demonstrate efficacy in patients.

Nilsson AG et al 2014, have concluded the safety of DR-HC in patients with primary AI and demonstrates that such treatment is well tolerated during 24 consecutive

months of therapy. In a study by Quinkler M et al2015, showed that modified release hydrocortisone decrease BMI and HbA1c compared to conventional HC therapy. In addition, it seems to stabilize health related-quality of life over time.

Ongoing DREAM study is a randomized, controlled, open, three-armed, multi-center study designed to compare the effects of dual-release hydrocortisone preparations (Plenadren) versus conventional glucocorticoid therapy on anthropometric parameters, metabolic syndrome, infectious, immunological profile, cardiovascular system, bone mass and quality of life in patients affected by primary or secondary adrenal insufficiency. It is currently conducted by Andrea M. Isidori, at University of Roma La Sapienza, and estimated study completion date in June 2016 (ClinicalTrials.gov).

CONCLUSION

There's an interindividual variation in cortisol sensitivity and concentrations, therefore, the total daily hydrocortisone dose should not be based on cortisol production rate alone .It is not possible with current formulations of hydrocortisone to fully replicate the normal circadian rhythm of cortisol, although new sustained release HC formulations may provide a closer fit. We currently use a weight-related thrice-daily dosing regimen. In the absence of objective parameters and biomarkers for monitoring replacement therapy, clinical symptoms and, when required, cortisol day curves can be helpful.

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