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Modified-Release Hydrocortisone: Is It Time to Change Clinical Practice?

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The appreciation of the unacceptable outcomes of patients with adrenal insufficiency has brought new developments in glucocorticoid replacement therapy. Efforts have moved beyond simple dose adjustments of the traditional immediate-release hydrocortisone to new formulations of hydrocortisone aimed at mimicking the circadian pattern of physiological glucocorticoid release. The present report has briefly summarized the evidence base behind recent studies that have reported benefits using modified-release preparations and set this in context for today's clinical practice.

Freeform/Key Words: cortisol, modified-release, adrenal insufficiency, outcomes

It was 1950 when Kendall, Reichstein, and Hench shared the Novel Prize in Physiology or Medicine for their discoveries relating to the "hormones of the adrenal cortex, their structure, and biological effects." In what has remained an illustrative exemplar for modern day translational medicine, the isolation and purification of cortisone and the demonstration of its anti-inflammatory properties in patients with rheumatoid arthritis was seminal in driving a glucocorticoid anti-inflammatory industry. The immense and long-lasting impact on the outcomes of patients with acute and chronic inflammatory disease is clear for all to see. This also enabled the introduction of adrenal replacement therapy; thus, Addison disease was no longer a fatal disease. However, unlike the "inflammation industry," almost 70 years later, the vast majority of endocrinologists are still using the same glucocorticoid therapy—hydrocortisone, given in divided doses across the day—based on the original Nobel laureates discovery.

However, 70 years on, all is not well. We now know that our patients with adrenal insufficiency (AI), whether primary in its original or secondary to hypothalamic-pituitary disease, have unacceptable outcomes with a poor quality of life [1, 2], multiple morbidities [3], and an unacceptable increase in mortality [4, 5] only partly attributable to adrenal crises. Underlying infection and cardiovascular disease are root causes with an evidence-based link to total daily glucocorticoid intake, with higher replacement doses conferring the greatest risk [5]. In the absence of any robust tissue biomarkers that might indicate glucocorticoid sufficiency (with the possible exception of ACTH, 17-OH progesterone, and androstenedione for patients with congenital adrenal hyperplasia) and the realization that the earlier measures of normal daily cortisol secretion were an overestimate, many endocrinologists have, accordingly, reduced the mean daily doses of hydrocortisone given to patients with AI. Patients with primary AI, on average, will receive higher daily doses than those with

Abbreviation: AI, adrenal insufficiency; DREAM, Dual Release Hydrocortisone vs Conventional Glucocorticoid Replacement in Hypocortisolism.

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secondary AI, probably because of the confounding effect of GH deficiency on 11β-hydroxysteroid dehydrogenase type 1 activity and reduced cortisol clearance.

Undoubtedly, the daily dose matters (at least for mortality and quality of life), but what about the mode of replacement? Most patients with AI receive daily immediate-release hydrocortisone; because of its short half-life (~60 minutes), this will be usually split into two or three doses, resulting in a profile that bears little resemblance to the normal circadian pattern of cortisol secretion [6]. The importance of the normal cortisol circadian rhythmicity in setting endogenous clock genes is a key factor across metabolic, stress, and infection control [7]. Jet lag is perhaps the best example of what happens when the clock is not entrained to the external light–dark cycle and a newly imposed sleep–wake cycle requires several days to adapt. The cortisol rhythm remains locked to the clock. An additional layer of complexity exists that is beyond the scope of the present report, because it relates to the so-called ultradian secretion—cortisol pulsatility patterns within a circadian secretion, which can also affect stress, sleep patterns, and metabolic outcomes. However, this has yet to be fully evaluated.

In terms of circadian change, compelling data have highlighted the risks of peaks and troughs in cortisol levels across the day and, in particular, the deleterious effects of late afternoon cortisol exposure. Glucose intolerance, abdominal obesity, coronary atherosclerosis, insomnia, and disturbed sleep patterns have all been linked to elevated evening levels of cortisol [5, 8]. In attempting to mimic the normal circadian rhythm, two novel preparations and one existing product have come to the fore. Plenadren® (developed by Duocort, Viropharma, and then Shire Pharmaceuticals) is a combination of immediate- and delayed-release hydrocortisone authorized for use in the European Union and given once daily on awakening. Although this fails to reproduce the normal early morning rise in cortisol levels (4:00 to 8:00 AM)—as, of course, does immediate-release hydrocortisone—pharmacokinetic studies have shown a close match with the physiological profile of cortisol across most of the waking period. The original randomized clinical trial [9] (n = 64; 12 weeks' duration), which compared this modified-release preparation with immediate-release hydrocortisone, demonstrated weight reduction and improvement in glucose tolerance, blood pressure, and quality of life scores for patients receiving the new preparation. A more recent single-blinded randomized trial [the Dual Release Hydrocortisone vs Conventional Glucocorticoid Replacement in Hypocortisolism (DREAM) study (10)] compared 43 subjects receiving regular hydrocortisone replacement with 46 patients who were switched to the same dose of modified-release hydrocortisone. After 24 weeks, a 4-kg difference in weight was found between the groups, with a weight loss of 2.1 kg in the modified-release treated group and a 1.9-kg weight gain in the conventionally treated group. Additional longer term (2 to 5 years) safety and retrospective surveillance studies have demonstrated no increase in adverse events or, importantly, in adrenal crises with the novel preparation and have endorsed longer term beneficial effects, especially for quality of life and glucose tolerance. It is important to note that although the daily doses were the same in the two groups in these two trials, the pharmacodynamic properties of once-daily modified-release hydrocortisone meant that, on average, 20% less bioavailable hydrocortisone was available in patients receiving this treatment. Whether this accounts for the beneficial effects is unknown; however, it is worth emphasizing that earlier studies evaluating simply a reduction in the daily cumulative doses of immediate-release hydrocortisone failed to demonstrate any benefit on metabolic traits or blood pressure.

The DREAM study also provided an important link between the circadian cortisol rhythm, clock genes, and innate immunity. Reduced natural T-cell killer function in patients with AI taking hydrocortisone had been proposed to explain the excess morbidity and mortality from infection. Compared with the controls, the patients with AI in the DREAM study had more classic monocytes ($CD14^+CD16^-$) and a reduction in $CD16^+$ natural killer cells. It is the recognition of IgG-opsonized cells through the CD16 receptor that enables natural killer cell activation of antibody-dependent cytotoxicity and adaptive immunity. Depletion of $CD16^+$ cells in AI might explain the chronic proinflammatory state similar to that reported in severe obesity. In patients switching to modified-release hydrocortisone, the monocyte phenotype was partially restored, and the $CD16^+$ natural killer cell count was increased. It is interesting to

postulate that amelioration of this "low-grade inflammatory state" might underpin some of the beneficial changes in quality of life scores. In a subsequent analysis of expression of glucocorticoid circadian clock genes in peripheral mononuclear cells [11], many were found to be altered in patients with AI, with values returning to normal in patients switched to modified-release hydrocortisone.

Chronocort® is another modified-release hydrocortisone preparation under development from Diurnal—a novel academia–industry partnership founded by Richard Ross (University of Sheffield). This is given twice daily, on retiring to bed and on awakening, and has been shown to reproduce the normal circadian cortisol levels. The main focus has been on patients with AI secondary to congenital adrenal hyperplasia; however, the drug is yet to be licensed. A phase II trial has demonstrated superior suppression of morning levels of 17-OH progesterone (and, by inference, overnight androgen secretion) in patients with congenital adrenal hyperplasia [12]. The results of a phase III trial are awaited.

Some investigators have exploited the pharmacokinetics of an established synthetic glucocorticoid, prednisolone. With a longer half-life of 5 to 6 hours, once-daily prednisolone in doses of 3 to 5 mg/d has been proposed as an alternative to immediate-release hydrocortisone but might require the additional burden of a prednisolone assay for monitoring. A clinical trial to compare the two regimens has been registered on ClinicalTrials.gov [13].

On the back of these advances, is it time to change practice? The answer to this question is one of scale—certainly, "no" for all patients with AI, but possibly a "yes" for some. Larger outcome-based trials are required that account for the altered bioavailability of modified-release hydrocortisone before we can definitively ascribe a benefit compared with current practice. Even if confirmed, we will need to scrutinize the health economics of making a switch. In the United Kingdom, in what has been an unacceptable escalation in the cost of many generic drugs, the price of immediate-release hydrocortisone has fluctuated dramatically as imported supplies have replaced major pharmaceutical company production. However, this will need to be assessed against the annual cost of Plenadren® of ~£3000 (£8/20-mg tablet). The main objective must be to ensure that patients with AI are treated with the lowest daily effective dose of glucocorticoid, to aggressively treat comorbidities, and to prevent intercurrent infection and adrenal crises. In the United Kingdom alone, ~50 patients are known to die each year with a death certification diagnosis of adrenal crisis (the actual number is likely to be much higher). Innovations such as new European Emergency cards, emergency hydrocortisone kits, endorsement of hydrocortisone supplementation during intercurrent illness ("sick day rules"), and enhanced education across patients and healthcare workers alike are all required to address this unacceptable outcome [14, 15]. In the interim, however, modified-release hydrocortisone, where available, is an alternative for our patients with AI, who, despite the above, continue to have very poor quality of life and those at greatest risk of the metabolic consequences of immediate-release hydrocortisone.

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