Therapeutic innovations in endocrine diseases – Part 2: Modified-release glucocorticoid compounds: What good do they provide to the adrenal insufficient patient?

Yves Reznik

CHU Côte-de-Nacre, université de Caen, service d’endocrinologie et maladies métaboliques, 14033 Caen cedex, France

reznik-y@chu-caen.fr

Introduction

Patients with primary adrenal insufficiency (PAI) exhibit an altered quality of life [1], reduced bone mineral density [2,3], altered glucose and lipid metabolism, and finally a two-fold mortality increase compared to the general population [4–6]. Patients with central hypopituitarism also have double the standardized mortality rate [7,8]. Whether the current glucocorticoid compounds used for replacement therapy are involved in morbidity and mortality of the adrenal insufficient patient is an issue still debated. Such increase may relate to glucocorticoid over-replacement possibly driving the increased rate of cardiovascular and infectious diseases recorded in large series of patients [6]. Moreover the adrenal insufficient patient has lost the normal circadian rhythm of cortisol which influences sleep quality, and frequently complains of early morning fatigue and
impaired quality of life (QoL) [1,9-11]. In contrast, insufficient glucocorticoid exposure may precipitate acute adrenal crisis when the patient is exposed to stress or concurrent acute illnesses. In the recent years, adrenal crisis still represent a common source of morbidity and mortality in adrenal insufficient patients with an annual risk as high as 8–10% [12,13]. High-maintenance glucocorticoids are associated with non-physiologic plasma cortisol concentrations [14] and recent guidelines have recommended to reduce daily hydrocortisone dose to 15–25 mg per day corresponding to the 5–10 mg per m² of body surface area cortisol production rate previously determined in humans [15,16]. Despite such adjustment of hydrocortisone daily dose, most patients remain over-replaced with the current hydrocortisone compound and are exposed to the peaks and troughs of its pharmacokinetic profile [14,17]. These findings have highlighted the need for developing new compounds exhibiting pharmacokinetic and pharmacodynamic profiles which get closer to the physiological circadian cortisol secretion. In this brief review, we will overview the characteristics and clinical impact of modified-release hydrocortisone oral formulations which actually are available or in development.

Current hydrocortisone compound

Hydrocortisone is the pharmaceutical name of the endogenous steroid « cortisol ». It is the most widely used glucocorticoid compound utilized for hormone replacement in the adrenal insufficient patient. The pharmacokinetic properties of hydrocortisone include an oral administration of 20 mg for its complete absorption with a mean 96% bioavailability, a Cmax of 305 ng/mL (823 nmol/L) and a Tmax of 1,2 h. The recommended hydrocortisone replacement regimen includes a morning intake of half daily dose and 1 (or 2) intake(s) at mid-day (and mid-afternoon) [15]. The short plasma half-life of hydrocortisone explains the very low cortisol levels measured at the end afternoon on a twice-daily regimen. A thrice-daily regimen offers plasma diurnal cortisol levels which better mimics the physiological circadian variations of endogenous cortisol secretion. The high variability of the maximum cortisol concentration can be reduced when using a weight-adjusted dosing [18]. Whatever the daily regimen, waking cortisol plasma concentrations are uniformly undetectable, contrasting with the morning peak of endogenous cortisol observed in healthy subjects. In view with the limitations of the conventional hydrocortisone compound including the peaks and troughs of cortisol plasma concentrations during daytime and the undetectable concentrations at night and at waking, there was a need for developing new hydrocortisone compounds with pharmacokinetic characteristics allowing a more physiological diurnal and nocturnal cortisol profile. In 2015, three compounds have been developed in Sweden and in the United Kingdom, which pharmacological properties and clinical utilization are reviewed in this article.

A hydrocortisone compound designed to allow a once morning daily intake

Johansson et al. from Gothenburg, Sweden have developed Duocort (Plenadren®), a hydrocortisone formulation with combined immediate and extended-release design to allow a unique morning intake. The formulation consists of one extended-release core surrounded by an immediate release coating, allowing the immediate release part to be delivered and rapidly absorbed due to its high intestinal permeability. The inner remaining part is released at a slower rate in the small and large intestine. The pharmaceutical compound exists in 5 mg and 20 mg tablets. The pharmacokinetics of Duocort tablets were determined in healthy adults whose endogenous cortisol secretion was blocked by betamethasone [19]. When Duocort was administered in the fasting state, the maximum concentrations (Cmax) were 188 nmol/L and 403 nmol/L for the 5 mg and 20 mg dose respectively, and the mean time to reach Cmax (Tmax) was 40–50 min for the two doses. A plasma cortisol raise was obtained within 20 min (> 200 nmol/L) with a peak occurring 50 min after 20 mg oral intake and thereafter plasma cortisol concentrations remaining above 200 nmol/L for about 6 hrs (figure 1). The terminal half-lives of 5 mg and 20 mg hydrocortisone formulations calculated from the interval 5–24 h were 2.80 and 3.90 hours respectively, and all plasma concentrations measured 18–24 hours after hydrocortisone intake remained below 50 nmol/L. In the fed state, the time to reach a concentration of 200 nmol/L was delayed by 28 min based on LC-MS/MS assay. Food intake did not prevent hydrocortisone absorption but rather

![Figure 1: Individual and mean plasma concentration-time profile for hydrocortisone, in healthy subjects, after a single oral administration of 20 mg Duocort in the fasted state. From Johanssohn et al. [19]](image-url)
increased its bioavailability. This new formulation allows an effective morning plasma concentration within 20 min after the oral intake of a 20 mg tablet, and provides a cortisol free interval during night, therefore avoiding dose accumulation. The morning peak (about 600 nmol/L) together with afternoon levels (above 100 nmol/L) mimics the normal diurnal cortisol profile of healthy subjects. Duocort provides rapid gastrointestinal absorption, a high bioavailability and a variability of maximum cortisol concentrations equal to that of conventional immediate release formulations [19]. In order to assess if a unique morning intake of 30 mg dual-release hydrocortisone should provide a more circadian-based plasma cortisol profile than the same thrice-daily dose of conventional immediate release hydrocortisone (10 mg at 8 h, 12 h and 16 h), a pharmacokinetic study was performed during a 12-week cross-over study in 64 adults with PAI [20].

The mean total cortisol area under curve (AUC) of the 24 h period after the first hydrocortisone intake was 19.4% lower with DUCORT than with conventional hydrocortisone. The cortisol AUC of the 10-24 h period was even 58% lower with Duocort than with the conventional hydrocortisone. One cortisol peak was observed with Duocort during the 24 h period instead of 3 peaks with the conventional hydrocortisone, while the terminal half-life of cortisol was 4.6 hrs with Duocort and 1.8 h with conventional hydrocortisone.

What is the clinical impact of the dual-release compound when compared to the immediate release hydrocortisone? In the same trial including 64 PAI patients, different end-points were compared to the immediate release hydrocortisone: weight decreased by 11 patients with concomitant diabetes mellitus, mean HbA1c decreased by 0.6% with Duocort compared to conventional hydrocortisone. Adverse events (AE) were scarce, 6 serious AE occurred with Duocort (2 gastroenteritis and 2 adrenal crisis) and 2 with conventional hydrocortisone (2 gastroenteritis). This pilot study provides the evidence of more physiological cortisol concentrations and better metabolic profile with Duocort including lower weight, blood pressure, cholesterol and glycaemia in the diabetic patients [20].

Whether Duocort is safe on a once daily regimen was recently assessed in a 6-month and another 18-month study-period including the 64 patients with PAI previously mentioned [20]. Patients received 20–40 mg Duocort in an open-label study where the main outcomes were AE and intercurrent illnesses [21]. During the randomized 3-month period, patients had 1.5 intercurrent illness event with Duocort vs 1.0 with conventional hydrocortisone (NS). During the 18-month extension period with Duocort, the mean number of intercurrent illness episodes per patient remained stable. No relationship was observed between the lower cortisol exposure (AUC 0–24 h) with Duocort and the incidence of AEs. The authors concluded that Duocort was well tolerated during a period of 24 consecutive months with Duocort therapy and that adherence to the compound was strong [21].

A hydrocortisone compound designed to restore a physiological cortisol peak at waking

Ross et al. from Sheffield, United Kingdom have developed a modified-release (MR) hydrocortisone compound (Phoqus Lab, UK) consisting of a tablet with an insoluble barrier coat protecting all but the upper face of the tablet. The unprotected face exposes a layer that slowly erodes in the small intestine, therefore providing the sustained-release properties of the compound. Two different dose units of 5 and 15 mg were available. The MR hydrocortisone pharmacokinetics was determined in 32 healthy patients whose endogenous cortisol secretion was blocked by dexamethasone [22]. In comparison with 10 mg of the conventional immediate release (IR) hydrocortisone, 15 mg MR hydrocortisone exhibited a similar Cmax (16.6 ± 1.4 vs 18.4 ± 0.7 µg/dL) corresponding to the 15.5 µg/dL (range 11.7-20.6) physiological cortisol peak from healthy subjects. The Tmax was largely delayed with MR in comparison with IR (7.41 ± 0.57 vs 1.8 ± 0.2 h), with a Cmax occurring at 06:00 am after an intake of 15 mg MR at 10:00 pm the day before (figure 2). The peak concentration and cortisol exposure increased with incremental MR doses and the time delay between drug administration and the maintenance of a cortisol concentration higher than 3.5 µg/dL was prolonged (5.19 ± 0.43 with MR vs 0.5 ± 0.08 h with IR). A 30 mg MR dosing provided the best cortisol exposure over 24 hrs (88% cortisol AUC of healthy subjects). Nevertheless MR bioavailability was below 75% that of IR.

A phase 2 pharmacokinetic and pharmacodynamic study was performed in 14 patients with congenital adrenal hyperplasia (CAH) comparing in a cross-over design 30 mg MR hydrocortisone administered at 10:00 pm with the conventional IR hydrocortisone administered in a thrice-daily regimen [23]. On MR, ACTH levels were low overnight but rose during daytime while cortisol remained low/undetectable. 17-OH progesterone and androstenedione exhibited the same pattern than ACTH. During the night and morning periods, androgen levels were low and similar with both MR and IR but rose with MR during the afternoon and the evening. These data suggested that once daily dosing of MR hydrocortisone did not fully control the hypothalamic-pituitary-adrenal (HPA) axis in CAH patients. Subsequently, a novel MR hydrocortisone formulation Chronocort was developed by the same group using a scalable
technology (Diurnal Ltd), consisting in a multiparticulate formulation composed of an inert microcrystalline core coated with a drug layer, then further coated with polymeric layers that modify the drug release, the enteric coat having a pH trigger of 6.8 which allows small bowel dissolution. A phase 1 study was performed in 16 healthy male subjects whose HPA axis was suppressed by dexamethasone [24]. Different formulations were tested in order to provide an acceptable bioavailability in humans, and the suppression of the sustained-release coat and maintenance of the only delayed release enteric coat allowed a 90% bioavailability relative to hydrocortisone. The DIURF-006 formulation administered at 11:00 pm (20 mg) and 07:00 am (10 mg) provided an overnight cortisol rise with a Cmax of 24 μg/dL similar to that observed in healthy subjects, a median Tmax of 8.5 h after the first dose (figure 3) and a physiological cortisol AUC (DIURF-006: 5610 vs 4706 nmol/L.h in healthy subjects).

A 6-month phase 2 study was performed in 16 adult females with classic CAH in an open-label non-randomized design [25]. Chronocort was initiated at 10 mg (07:00 am) and 20 mg (11:00 pm) and dose titration was performed based on clinical symptoms and 17-OH progesterone and androstenedione hormone levels. The main pharmacokinetic characteristics of Chronocort at 48 h in CAH patients were very similar to those determined in the phase 1 study for Chronocort in healthy subjects and to the normal circadian rhythm of endogenous cortisol: 24 h cortisol AUC were 175±1.3, 203±42 and 171±41 μg/dL.h, Cmax were 21.4±4.2, 24±4.6 and 21.5±7.4 μg/dL, and Tmax were 0654 h, 0706 h and 0800 h for phase 1 study, phase 2 study and healthy subjects respectively. The 24 h cortisol AUC after 6 month Chronocort was reduced to 141±1.6 μg/dL.h. The biomarkers of disease control were improved after 6 months with Chronocort compared to IR: ACTH levels were reduced throughout the day, the percent of time points with elevated androgen levels were reduced from 33% to 12% while the percent of suppressed androgen levels increased from 46% to 69%. Androstenedione and 17-OH progesterone 24 h AUC also decreased significantly after 6-month Chronocort treatment. No significant change in QoL was measured and no serious adverse event was observed.
The same authors have developed Infacort, another multiparticle formulation devoted to children treatment, with an external taste masking coat, hydrocortisone applied to inert microcrystalline core granules coated with a binding layer. Appropriate doses for children of 0.5, 1, 2, 5 and 10 mg Infacort are available, and 10 mg Infacort was proved to be bioequivalent to 10 mg IR hydrocortisone in a phase 1 study [26]. The formulation will help optimize hydrocortisone dosing in neonates and children with adrenal insufficiency.

**Conclusion and perspective**

Intensive research on MR hydrocortisone compounds in the last decade has paved the way for obtaining a near-physiological glucocorticoid replacement in the PAI patient. The dual-release Duocort (Plenadren) mimics the diurnal rhythm of cortisol secretion but does not allow the progressive nocturnal rise and morning cortisol peak. Duocort has a favorable metabolic impact and may be chosen for patients with high cardiovascular risk like those with diabetes mellitus. Chronocort is a new formulation with sustained-release properties allowing a near-physiologic cortisol profile and a physiological cortisol peak at morning. This formulation may be appropriate for controlling androgen excess in adults with CAH. The multiparticulate formulation Infacort is promising for the treatment of adrenal insufficiency during infancy. Long-term studies are mandatory for demonstrating the effectiveness and safety of these hydrocortisone formulations.

**Disclosure of interest:** experimenter for Viropharma

**References**


[16] Cramer JM, Loo K, De Bruin R. The daily cortisol rhythm: its importance for demonstrating the effectiveness and safety of these hydrocortisone formulations.

[17] Duocort (Plenadren) mimics the diurnal rhythm of cortisol glucocorticoid replacement in the PAI patient. The dual-release formulation Infacort is promising for the treatment of adrenal insufficiency during infancy. Long-term studies are mandatory for demonstrating the effectiveness and safety of these hydrocortisone formulations.

[18] References