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

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Summary

Intensive researches on modified-release hydrocortisone compounds developed in the last decade have paved the way for obtaining near-physiological glucocorticoid replacement in the adrenal insufficient patient. The dual-release Duocort (Plenadren) allows a unique morning intake and closely mimics the circadian rhythm of cortisol secretion, except for the progressive nocturnal increase and the morning cortisol peak observed in healthy subjects. Duocort treatment during a 6-month period was associated with favorable changes in weight, blood pressure and glycemic control in patients with diabetes mellitus. Chronocort, a multiparticulate formulation with sustained-release properties replaces endogenous cortisol in a near-physiologic manner and fully restores the end of night cortisol peak. A twice-daily Chronocort regimen was effective in controlling androgen excess in adults with CAH. Recently, the new multiparticulate formulation Infacort was designed for the treatment of adrenal insufficiency during infancy. Long term effectiveness and safety studies are needed until these promising hydrocortisone formulations become routine therapeutic tools in adrenal insufficiency.

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

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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 glucocorticoid doses 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 m^2 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 by 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

Johannsson 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

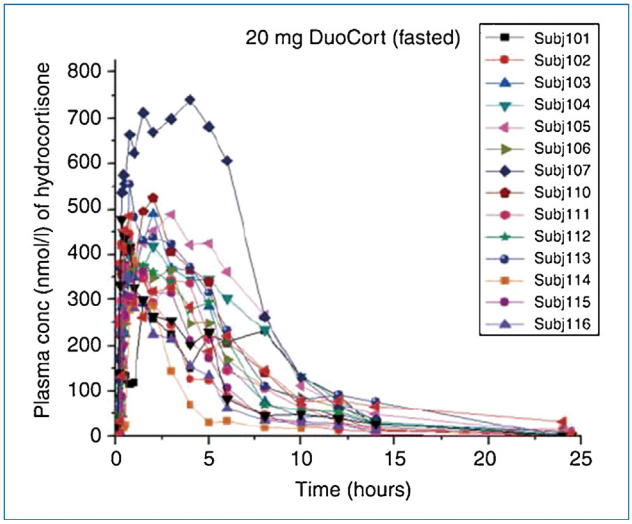

FIGURE 1

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]