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EDITORIAL

Improving glucocorticoid replacement in patients with adrenal insufficiency

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The outcome among patients with adrenal insufficiency (AI) is not as excellent as was previously thought [1]. Recent studies have observed increased mortality both in patients with primary and secondary AI that are explained by both cardiovascular and infectious diseases, suggesting that both the maintenance dose and the rescue therapy during an intercurrent illness are inadequate [2].

The aim of glucocorticoid replacement is to obtain physiological cortisol exposure, both in terms of the dose and the time exposure profile in order to mimic the normal diurnal variation in serum cortisol. Also during increased need, such as during physical and mental stress, e.g., during an infection, the dose needs to be increased. Based on small studies on cortisol production rate in the resting state, it is clear that a dose above 20 mg per day is too high for most patients. Therefore, several attempts have been done to reduce the overall cortisol exposure during the replacement therapy. Three previous open prospective studies have reduced the dose of conventional hydrocortisone (HC) replacement by 30–50 % (approximately 30 to 20–15 mg of HC per day) and found an increase in bone formation markers and a small reduction in body weight, but with no impact on blood pressure or glucose metabolism [3–5]. In addition, one open study which randomised patients to two different regimens of glucocorticoid replacement using doses between 15 and 30 mg of HC per day was unable to show an impact of dose on QoL [6].

Based on the pharmacokinetic properties of conventional oral immediate-release HC formulations, it is impossible to achieve a physiological serum cortisol profile as there is a rapid increase in serum cortisol after an oral administration and a rapid decrease reaching low unphysiological troughs in between each dose [7, 8]. The early morning rise in serum cortisol before awakening will not be mimicked using conventional HC.

Giordano and colleagues in this issue of the Journal have reported data from a clinical intervention study using a newly developed drug, a dual-release oral HC (DR-HC) formulation for glucocorticoid replacement. It has an outer layer of immediate-release HC allowing a peak serum cortisol concentration in the morning after an oral administration in the fasting state, and an inner core with modified-release HC that mimics the serum cortisol profile throughout the day and evening [9]. In the pivotal trial comparing DR-HC with three times daily conventional hydrocortisone tablets (TID) in a 2 × 3-month randomised cross-over trial in patients with Addison's disease, it was shown that the cortisol exposure was higher during the first 4 h after the intake of the DR-HC, whereas the exposure was markedly reduced thereafter due to the absence of the second and third cortisol peaks after TID [10]. The total 24-h exposure was on average 20 % lower with the DR-HC compared with the same daily dose of HC administered as TID due to the serum cortisol peaks associated with TID, but also due to the non-proportional dose–exposure relationship of HC [11]. The switch from TID to DR-HC also resulted in a reduction in body weight, systolic and diastolic blood pressure and HbA1c [10]. In 11 patients with concomitant diabetes mellitus (DM), a reduction in HbA1c was observed with DR-HC compared with TID. After the

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pivotal trial, patients entered a long-term prospective open-labelled safety trial that could show safe outcome with the use of the DR-HC [12]. The long-term safety data are reassuring and of great values as there was an indication of increased reporting of mild adverse events after the switch from conventional TID to DR-HC [10]. Careful analysis of the association between the pharmacokinetic profile and adverse event reporting suggested that this initial increase in number of adverse events was related to increased awareness among the patients during the therapeutic change and not due to the change in cortisol exposure or time exposure profile [12].

Giordano et al. performed a prospective open-labelled 12-month trial in 19 patients with Addison's disease [13]. The aim of the trial was to study the impact of DR-HC treatment on anthropometric, metabolic, and hormonal profile, as well as health-related quality of life in comparison with baseline when using conventional replacement therapy. The strength of the trial is that it involved the homogenous patient population including only patients with autoimmune aetiology, a fixed dose of 20 mg of hydrocortisone per day (either BID or TID) and a stable replacement therapy for at least 3 months before entering the trial. Seventeen patients had autoimmune polyendocrine syndrome including three patients with type 1 DM, 1 with type 2 DM and six patients with chronic atrophic gastritis. Patients were switched from 20 mg of HC per day, either as BID or TID, to 20 mg of the DR-HC as a once daily dose in the morning in the fasting state.

The main clinical outcome from the 12-month trial of DR-HC was a reduction in waist circumference from a median level of 82–78 cm without a significant simultaneous change in body weight, which is a novel observation not previously reported for any other glucocorticoid replacement regimen. Other major observations were a reduction in total- and low-density lipoprotein-cholesterol, HbA1c and an improvement in QoL measured using the disease-specific AddiQoL questionnaire. Again, the reduction in total- and LDL-cholesterol is a new finding as this was not seen during the pivotal trial [10].

Due to the observed mean reduction in HbA1c, the authors report in more detail on the four patients with DM. The HbA1c in these patients was reduced from a median of 60 (range 55–74) on conventional therapy to 47 (range 55–61) mmol/mol on the DR-HC. Also, the insulin requirement was reduced in the three patients with type 1 DM.

Another interesting aspect of the trial reported by Giordano et al. is the involvement of six patients with atrophic gastritis. These patients have vitamin B12 deficiency and an elevated pH in the stomach. The frequency of atrophic gastritis among patients with autoimmune Addison's disease is approximately 10 %. It is therefore important that the dissolution of hydrocortisone in the stomach is not affected by pH as this may influence the bioavailability and the intended serum cortisol profile. The pH in the gastrointestinal tract does not affect the solubility and bioavailability of hydrocortisone per se [14], but the other content of the tablet may. A subgroup analysis of these patients would have been interesting.

The study did not perform 24 h pharmacokinetic profiling, but analysed serum cortisol for 4 h after the morning administration. The important and interesting findings from these profiles are that the 4 h cortisol area under the curve (AUC) was similar with conventional therapy compared with DR-HC and that the AUC at 1 month and after 12 months of DR-HC was similar. This strongly supports the previous observation [10] that no dose accumulation occurs with long-term treatment, an important safety aspects of this new modifier release drug. The study has limitations such as the 4 h sampling that gives limited information on the overall pharmacokinetic properties of the DR-HC and there is no comparative treatment to compare the beneficial metabolic outcome of the DR-HC treatment.

The study of Giordano et al. highlights the importance of the cortisol time exposure profile for the metabolic outcome of patients with AI and glucocorticoid replacement therapy. Their data are further supported by another recent open prospective study showing that a switch from conventional HC to DR-HC reduced body weight and HbA1c [15]. Both studies are limited by their open design and all studies so far are limited by the fact that a switch from conventional HC replacement therapy to DR-HC results in a lower 24-h exposure that may be as large as 20 % if the switch occurs from a TID regimen. Future studies and the clinical experience among skilled clinicians will show the place of this new glucocorticoid replacement regimen.

Compliance with ethical standards

Conflict of interest GJ has received lecture fees and been a consultant of Viropharma and Shire.

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