ADRENAL FUNCTION

Novel formulation of hydrocortisone shows promise

A modified-release formulation of hydrocortisone that aims to mimic the normal pattern of cortisol secretion could provide a novel option for the medical management of patients with congenital adrenal hyperplasia (CAH), say the authors of a report published in *Clinical Endocrinology*.

Glucocorticoid therapy for CAH can be a challenge: a fine balance must be maintained between adequate control of the androgen excess that results from 21-hydroxylase deficiency and the adverse effects associated with overtreatment. In healthy individuals, production of cortisol displays a distinct circadian rhythm: levels reach a nadir at around midnight and peak early in the morning. Glucocorticoid formulations that replicate this profile might, therefore, overcome the shortcomings of traditional glucocorticoid therapy.

In response to this need, a novel oral formulation of hydrocortisone has been developed that allows delayed and sustained release of the drug. Chronocort® (Phoqus Pharmaceuticals, West Malling, UK) has already undergone phase I testing in healthy volunteers. The results of these studies demonstrated that administration of Chronocort® after dexamethasone-induced suppression of endogenous cortisol production results in a physiological profile of cortisol secretion. Verma and colleagues have now evaluated Chronocort® in patients with CAH.

The researchers enrolled 14 patients (mean age 26.8 years) in this phase II, open-label, crossover study of Chronocort® versus a conventional, immediate-release, oral hydrocortisone preparation. After screening, participants switched from their usual glucocorticoid regimen to thrice-daily conventional hydrocortisone (10 mg at 0800 h, 5 mg at 1500 h and 15 mg at 2200 h) for 1 week, followed by once-daily Chronocort® (30 mg at 2200 h) for 4 weeks. Steady state, 24 h sampling of the serum levels of cortisol, 17-hydroxyprogesterone, androstenedione and adrenocorticotrophic hormone was performed to assess the pharmacokinetic and pharmacodynamic profiles of Chronocort®.

As expected, conventional hydrocortisone therapy resulted in three peaks of cortisol; by contrast, Verma *et al.* found only a single peak (at ~0600 h) after administration of Chronocort®. Morning levels of 17-hydroxyprogesterone were lower after treatment with Chronocort® than after conventional hydrocortisone therapy, which indicated improved control of adrenal androgen production. However, afternoon levels of 17-hydroxyprogesterone, androstenedione and adrenocorticotrophic hormone were elevated during treatment with Chronocort®. The researchers conclude that a single dose of Chronocort® might not be sufficient to provide full cortisol coverage.

The next step will be to perform additional studies of increased duration

that allow twice-daily administration of Chronocort® and dose adjustments as and when required. In the meantime, Verma and colleagues' preliminary work provides proof of the principle that a physiological profile of cortisol can be achieved and lays the foundation for a new strategy in the treatment of patients with CAH.

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Original article Verma, S. *et al.* A pharmacokinetic and pharmacodynamic study of delayed- and extended-release hydrocortisone (Chronocort™) versus conventional hydrocortisone (Cortef™) in the treatment of congenital adrenal hyperplasia. *Clin. Endocrinol. (Oxf.)* doi:10.1111/j.1365-2265.2009.03636.x