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Management and treatment options for patients with poorly controlled congenital adrenal hyperplasia

Opciones de manejo y tratamiento para pacientes con hiperplasia suprarrenal congénita mal controlada

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Summary

Patients with 21-hydroxylase deficiency congenital adrenal hyperplasia (21OHD-CAH) have poor health outcomes, including increased mortality, short stature, impaired fertility, and increased cardiovascular risk factors such as obesity. This primarily relates to the inadequacy of standard glucocorticoid replacement therapy for controlling CAH, and the use of glucocorticoid doses that often exceed those recommended for adrenal replacement. There has been a lack of paediatric dose-appropriate hydrocortisone formulations, and standard glucocorticoid replacement cannot control the overnight rise in ACTH that drives the excess adrenal androgens. To address this, there are therapies in development and approved that target controlling the overnight excess rise in ACTH. Corticotrophin Releasing Factor type 1 receptor (CRF_1) antagonists, have been trialled in patients with poorly controlled CAH, and have reduced ACTH and androgen biomarkers in these patients. Improvements in glucocorticoid replacement include Alkindi taste-masked hydrocortisone granules in capsules for opening, which provide age-appropriate dose titration for the growing child; and Efmody Modified Release Hydrocortisone Hard Capsules (MRHC) which replace the diurnal rhythm of cortisol and improve the control of CAH.

Keywords: Congenital adrenal hyperplasia, 21-hydroxylase deficiency, adrenal insufficiency, hydrocortisone, glucocorticoid, CRF antagonist.

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Resumen

Los pacientes con hiperplasia suprarrenal congénita (HSC) por deficiencia de 21-hidroxilasa (21OHD) presentan malos resultados en materia de salud, como una mayor mortalidad, baja estatura, problemas de fertilidad y un aumento de los factores de riesgo cardiovascular, como la obesidad. Esto se relaciona principalmente con la inadecuación de la terapia estándar sustitutiva de glucocorticoides para controlar la HSC y el uso de dosis de glucocorticoides que suelen superar las recomendadas para la sustitución suprarrenal. No ha habido suficientes formulaciones pediátricas de hidrocortisona adecuadas a la dosis, y la sustitución estándar de glucocorticoides no puede controlar el aumento de hormona adrenocorticotropa (ACTH) durante la noche, que favorece el exceso de andrógenos suprarrenales. Para solucionarlo existen tratamientos en desarrollo y aprobados cuyo objetivo es controlar el aumento excesivo de ACTH durante la noche. Los antagonistas del receptor del factor liberador de corticotropina de tipo 1 se han probado en pacientes con HSC mal controlada y han reducido los biomarcadores de ACTH y andrógenos en estos pacientes. Las mejoras en la sustitución de glucocorticoides son, entre otras, los gránulos de hidrocortisona Alkindi de sabor enmascarado en cápsulas que se abren, que ofrecen un ajuste de la dosis adecuado a la edad del niño en crecimiento, y las cápsulas duras de hidrocortisona de liberación modificada Efmody, que sustituyen el ritmo diurno del cortisol y mejoran el control de la HSC.

Palabras clave: antagonista del CRF, deficiencia de 21-hidroxilasa, glucocorticoide, hidrocortisona, hiperplasia suprarrenal congénita, insuficiencia suprarrenal.

Background

Patients with 21OHD-CAH have two major problems: adrenal insufficiency and androgen excess. Adrenal insufficiency causes life-threatening adrenal crises[1-3], while androgen excess causes atypical genitalia in 46,XX neonates, promotes abnormal growth, and in adulthood, virilization of women and infertility in both sexes[4]. The treatment aims to replace cortisol, but supraphysiological doses of glucocorticoid are typically needed to lower ACTH and adrenal androgens, which chronically exposes patients to excess glucocorticoid treatment, resulting in poor outcomes including short stature, obesity, hypertension, osteoporosis and an adverse metabolic profile[1-3,5-7]. Patients with CAH have mortality rates up to 5 times higher than those of the healthy population[8,9], with adrenal crisis the leading cause of death[9]. The majority of the poor health outcomes in patients with CAH result from the inability to precisely titrate currently available glucocorticoid preparations in order to both adequately replace the deficiency, and sufficiently attenuate the overnight rise in ACTH that drives adrenal-derived androgen excess. Researchers have targeted different levels of the hypothalamic-pituitary-adrenal axis, ranging from suppressing ACTH release from the pituitary to improving hydrocortisone replacement, in order to address the poor health outcomes.

Corticotrophin releasing factor (CRF) receptor antagonists

The primary regulator of ACTH synthesis and release is Corticotrophin Releasing Factor (CRF), which is released from the hypothalamus and acts directly on the pituitary CRF type 1 receptor (CRF1)[10]. Small molecule CRF1 receptor antagonists have been synthesized and tested in patients with CAH[11], and two orally active, selective, non-steroidal CRF1 receptor antagonists are in development as therapies for CAH: Crinecerfont (Neurocrine Biosciences, Inc, USA) and Tildacerfont (Spruce Biosciences, USA). Both have been shown to lower ACTH, 17-hydroxyprogesterone (17OHP) and androstenedione (A4) in patients with CAH[12,13].

Optimized hydrocortisone dosing in children

Until 2018, the lowest available licenced preparations of hydrocortisone were 10 mg tablets in Europe. This dose is not appropriate for treating neonates, infants and young children with adrenal insufficiency, who require a daily dose of 10-15 mg/m^2 with single doses as low as 0.5 mg[14]. Crushed hydrocortisone tablets suspended in water are often used in some countries[15], although accurate dosing is impossible as hydrocortisone does not dissolve well in water and may adhere to plastic material when applied with syringes[16,17]. Another common practice is to compound hydrocortisone. However, in a German study up to 25% of compounded batches did not fulfil the acceptance criteria of the European Pharmacopeia[18]. In Europe, the UK and the US, Alkindi® hydrocortisone granules (Diurnal Europe B.V., The Netherlands) are now licensed for children with AI from birth to 18 years of age (birth to 17 years in US), and are available in low doses of 0.5, 1, 2 and 5 mg (Figure 1). They were developed to address the age group-specific needs of neonates, infants and young children[19,20]. As part of the development programme, a single-dose clinical trial was undertaken in neonates, infants and children under 6 years with AI, of whom the majority had CAH[21]. The children were then invited to participate in a prospective follow-up study of continued treatment with hydrocortisone granules[22]. Seventeen children with CAH aged from birth to 6 years had their hydrocortisone medication changed from pharmacy-compounded capsules to hydrocortisone granules. The patients were followed up prospectively for 2 years. The median daily hydrocortisone dose varied by age group, and declined between entry and the end of study: 9.9-12.0 to 8.6-10.2 mg/m^2/d, respectively. There were

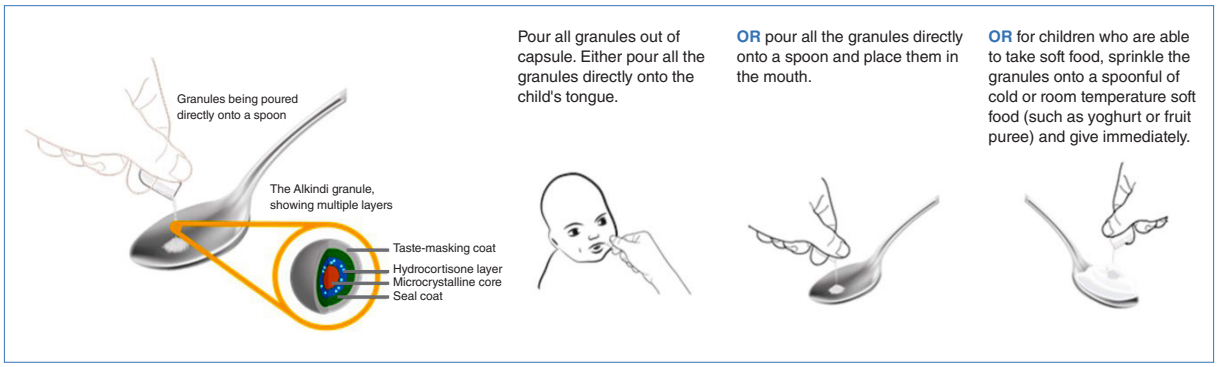

Figure 1. Hydrocortisone granules in capsules for opening, EMA- & FDA-approved for AI in children (Alkindi). Reproduced with permission from Diurnal.

no trends for accelerated or reduced growth. No adrenal crises were observed despite 193 treatment-emergent adverse events, which were mainly common childhood illnesses. This first prospective study of glucocorticoid treatment in children with AI and CAH demonstrated that accurate dosing and monitoring from birth results in hydrocortisone doses at the lower end of the recommended dose range, and normal growth without increased occurrence of adrenal crises.

Circadian glucocorticoid therapies

ACTH rises overnight, between around 2:00 am and 04:00 am, to provide the circadian rhythm of cortisol that peaks shortly after waking and falls to its lowest levels in the evening[23]. This rise in ACTH is exaggerated in CAH because of the failure in cortisol negative feedback, as seen in children taking hydrocortisone[24]. The problem is that hydrocortisone has a short plasma half-life, so that even when a dose is taken in the evening, cortisol levels are low before the morning rise in ACTH[25]. Efmody® (development name Chronocort, Diurnal Europe B.V., The Netherlands) is a modified-release formulation of hydrocortisone (MRHC) licensed in Europe and the UK for the treatment of CAH in patients 12 years old and above. MRHC is a multi-particulate formulation of hydrocortisone with a delayed-release coating that allows for delayed and sustained absorption (Figure 2). When taken at bedtime and on waking, MRHC replicates the overnight diurnal rise in cortisol[26]. In a phase 2 switch study of 16 adult patients with 21OHD-CAH, the cortisol profiles were similar to physiologic cortisol secretion, and MRHC at a lower dose than standard treatment improved control of CAH[27]. In the phase 3 MRHC study[28], 122 adult patients with CAH were randomized to continue either standard therapy or switch to MRHC with a dose taken at bedtime and on arising. Standard therapy consisted of a variety of treatment regimens including hydrocortisone, prednisolone, and dexamethasone (both singly and in combination), and 84% of patients were taking standard glucocorticoids after 6:00 pm in a reverse circadian fashion. After 6 months, the patients who had enrolled in the phase 3 and the previous phase 2 studies were invited to enrol in an open-label extension study of MRHC treatment[28]. In the extension study, dose titration was performed by the local investigators as in a "real world" experience. At the end of the phase 3 trial, the patients who received MRHC had superior hormonal control during the morning and early afternoon compared to those receiving standard therapy (Figure 3), and this advantage was sustained during the 18-month follow-up. The trial failed to meet its primary endpoint, because the difference between the two groups in the morning did not translate into a difference over 24 hours at 6 months. The prespecified methods for data analysis obscured the impact of MRHC in the morning and early afternoon. The raw data showed significant improvement of the clinically relevant endpoint of morning biochemical control, with reduced AUC and 17OHP amplitude in patients receiving MRHC. In the follow-on study, the improvement in biochemical control was maintained at 18 months, and an improved disease control was observed despite a reduction in hydrocortisone dose by 33%, to doses typically used for adrenal replacement therapy (15-25 mg/day). MRHC therapy was

Figure 2. Modified Release Hydrocortisone (MRHC) Hard Capsules EMA- & MHRA-approved for children over 12 years old (Efmody).

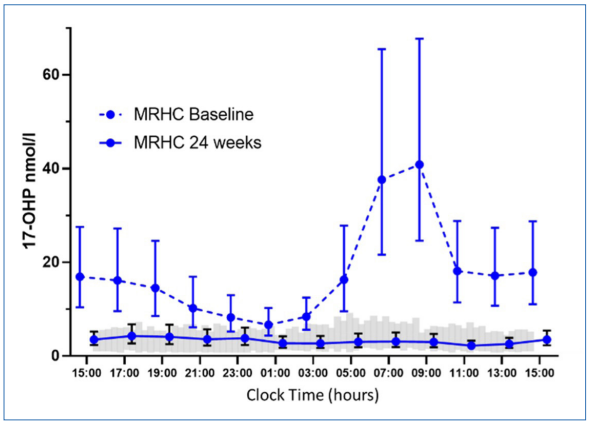

Figure 3. 24-hour profiles of 17-OHP in patients randomized to MRHC before randomization in standard treatment (Baseline) and after 6 months of MHRC, showing that MHRC treatment normalized 17-OHP levels (adapted from reference 28). The grey shaded area is 17-OHP in healthy controls adapted from Ghizzoni et al., Metabolism, Vol 43, No 3 (March), 1994: pp 372-377.

associated with patient-reported clinical benefits, including menses restoration in 8 patients (1 on standard therapy), and 3 patient and 4 partner pregnancies (none on standard therapy). In the phase 3 study, no patients experienced adrenal crises in the MRHC group compared with 3 in the standard group, and in the extension study, there were 4 patients with an adrenal crisis over 18 months, an incidence at the lower end of that reported in cohort studies.

Conclusions

The last ten years have seen advances in our understanding of the pathophysiology of CAH and with it a recognition that our current management is suboptimal. This has led to a variety of different pharmacological approaches for improving the control of CAH. CRF1 receptor antagonists have shown they can reduce androgen biomarkers in patients with poorly controlled CAH, and further studies are planned to test whether they can improve health outcomes. Alkindi provides accurate dosing in children and Efmody MRHC, by replicating the diurnal rhythm of cortisol, can control androgen biomarkers, and patients report restoration of menses and pregnancies.

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