FLUDROCORTISONE THERAPY IN PATIENTS WITH PRIMARY ADRENAL INSUFFICIENCY: ASSOCIATIONS WITH DIFFERENT HYDROCORTISONE DOSES

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INTRODUCTION

- Adrenal insufficiency (AI) is a life-threatening disease resulting from impaired corticosteroid hormone secretion.[1]
- In primary AI (PAI; Addison's disease), impaired aldosterone secretion can result in clinical signs and symptoms of mineralocorticoid deficiency, such as hypotension, weakness, salt craving and electrolyte disturbances (hyperkalaemia, hyponatremia).[2]
- Mineralocorticoid replacement therapy (i.e. fludrocortisone) is therefore used in addition to glucocorticoid (GC) replacement therapy (e.g. hydrocortisone) to treat patients with PAI.
- Based on published calculations, however, it can be estimated that the standard dose (20 mg) of hydrocortisone has the same mineralocorticoid activity as 0.05 mg of fludrocortisone.[2,3]
- Therefore, it has been suggested that patients with PAI receiving low doses of hydrocortisone may require higher doses of mineralocorticoid replacement therapy and *vice versa*.

AIMS

- The aim of this study was to investigate the association between doses of hydrocortisone and fludrocortisone in patients with PAI.

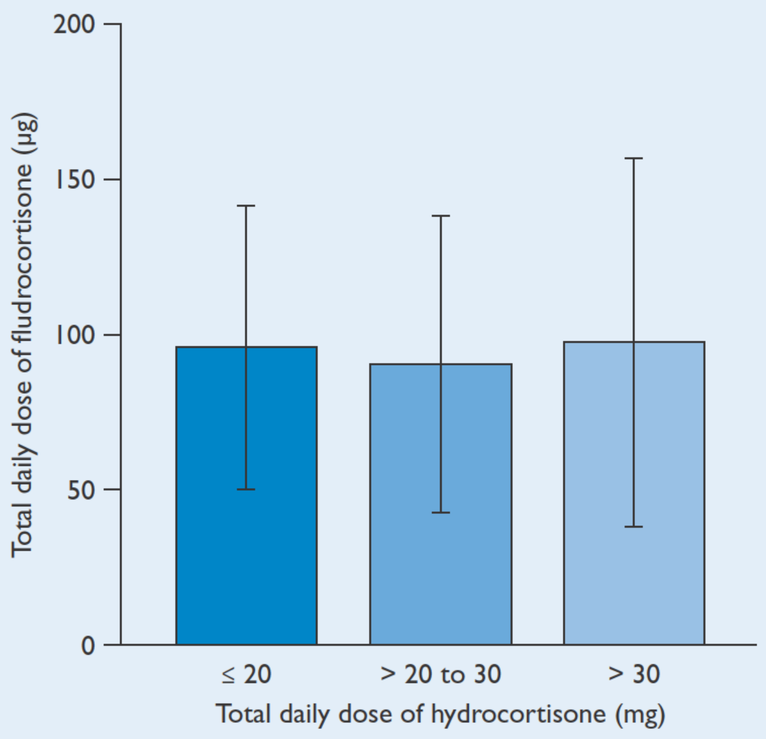
METHODS

- The European Adrenal Insufficiency Registry (EU-AIR), which is sponsored by Shire and involves 20 centres across Germany, the Netherlands, Sweden and the UK, was initiated in August 2012 to monitor the long-term safety of modified-release hydrocortisone and conventional GC replacement therapy during routine clinical practice in patients with chronic AI (ClinicalTrials.gov identifier: NCT01661387).
- Written informed consent/assent is provided by each patient and/or their parent(s)/legal guardian(s) before enrolment in EU-AIR.
- Comprehensive baseline data are collected at enrolment, as described previously.[4]
- The EU-AIR protocol offers no guidance or instructions for patient management. All decisions regarding treatment and patient care are made by the treating physician and/or patient.
- This descriptive analysis presents baseline data in patients with a diagnosis of PAI (including congenital adrenal hyperplasia [CAH]) who are receiving hydrocortisone, cortisone acetate or modified-release hydrocortisone alongside fludrocortisone. Implausible outliers were not included. Patients receiving fludrocortisone doses greater than 300 µg were excluded.
- For cortisone acetate, hydrocortisone-equivalent doses were calculated by multiplying the dose of cortisone acetate by 0.8.
- This descriptive analysis examined the mean total daily dose of fludrocortisone taken by patients with PAI receiving hydrocortisone-equivalent daily doses that fell into one of three groups: 20 mg or less, from greater than 20 mg to 30 mg, and greater than 30 mg. The analysis further examined the association between fludrocortisone and hydrocortisone-equivalent dosing in all included patients.

RESULTS

- As of 5 November 2014, baseline data on fludrocortisone use were available for 474 patients with PAI (including CAH) who were receiving hydrocortisone or hydrocortisone-equivalent therapy; 377 patients (79.5%) were receiving fludrocortisone at baseline.

Figure 1. Mean (± SD) daily dose of fludrocortisone taken by patients with primary adrenal insufficiency who are receiving daily hydrocortisone-equivalent doses of ≤ 20 mg, > 20 mg to 30 mg, and > 30 mg.



SD, standard deviation.

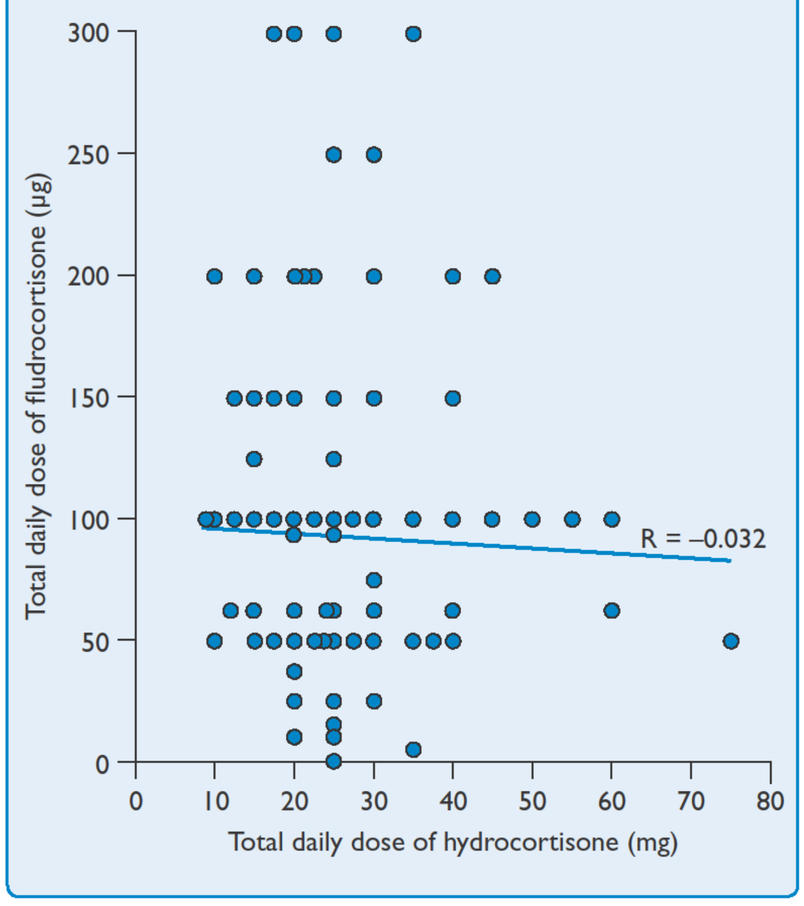
- In total, 345 patients (mean ± standard deviation [SD] age, 50.1 ± 15.7 years; 221 [64.1%] female; body mass index [BMI; kg/m^2] < 25, 43.5%; BMI 25 to < 30, 30.4%; BMI ≥ 30, 17.4%; missing BMI data, 8.7%) receiving fludrocortisone with hydrocortisone, cortisone acetate or modified-release hydrocortisone were included in this analysis (Table 1).
- The median fludrocortisone dose received was 100 µg (range, 0.3–300 µg)[a].
- Approximately half of all patients were receiving hydrocortisone-equivalent doses of 20 mg/day or less (n = 179 [51.9%]) and the remaining patients were receiving doses greater than 20 mg/day (n = 166 [48.1%]; of these, 27 were receiving greater than 30 mg/day).
- Patients receiving hydrocortisone-equivalent daily doses of 20 mg or less, from greater than 20 mg to 30 mg, and more than 30 mg were all receiving approximately the same mean dose of fludrocortisone (Figure 1). However, care should be taken in the interpretation of data relating to the group receiving more than 30 mg, because this group contained a small number of patients.

Table 1. Demographics of patients with primary adrenal insufficiency taking fludrocortisone with hydrocortisone, cortisone acetate or modified-release hydrocortisone.

Parameter	Analysis population (n = 345)
Mean age, years (SD)	50.1 ± 15.7
Mean weight, kg (SD)	74.7 ± 15.6 (n = 327)
Mean height, cm (SD)	168.7 ± 10.1 (n = 319)
Sex, n (%)	
Male	124 (35.9)
Female	221 (64.1)
BMI (kg/m^2) category, n (%)	
Underweight (< 18.5)	2 (0.6)
Normal (18.5 to < 25)	148 (42.9)
Overweight (25 to < 30)	105 (30.4)
Obese (≥ 30)	60 (17.4)
Missing data	30 (8.7)

BMI, body mass index; SD, standard deviation.

Figure 2. The association between the total daily hydrocortisone-equivalent dose and the total daily dose of fludrocortisone taken by patients with primary adrenal insufficiency.



- Overall, there was no association between the total daily hydrocortisone-equivalent dose and the total daily dose of fludrocortisone received by patients with PAI (R = –0.032) (Figure 2).
- Similarly, there was no association between hydrocortisone-equivalent and fludrocortisone doses taken by male (R = –0.114) or female (R = 0.019) patients.
- The total daily dose of fludrocortisone was not associated with BMI in male (R = 0.145) or female (R = 0.086) patients.

CONCLUSIONS

- The results of this descriptive analysis demonstrate that total daily doses of fludrocortisone received by patients with PAI vary widely, and are not associated with total daily hydrocortisone-equivalent doses or BMI.
- The absence of a clear association between the dose of fludrocortisone and the hydrocortisone-equivalent dose suggests that physicians consider the prescription of fludrocortisone independently of GC replacement therapy.
- Heterogeneity in the dosing of fludrocortisone may reflect differences in the mineralocorticoid replacement requirements of individual patients, or inadequate titration of fludrocortisone dosing.
- Neglecting optimal mineralocorticoid replacement could, however, contribute to the failure of GC replacement therapy to restore life expectancy and/or quality of life to normal levels in patients with PAI.

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[a]The lowest reported dose has been queried with the centre that reported the value.

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