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How hydrocortisone substitution influences the quality of life and the bone metabolism of patients with secondary hypocortisolism

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Abstract

Background Even in the setting of chronic glucocorticoid substitution in hypocortisolaemic patients, severe side-effects will eventually occur when the dosage is inappropriately high. This study evaluates the effect of usual hydrocortisone substitution dosages on the well-being of the patients and on parameters of the bone metabolism to establish an optimum substitution dosage.

Design In a double blind study nine patients with secondary hypocortisolism, being divided in three groups of three, received different doages of hydrocortisone (15, 20, 30 mg per day). Well-being was assessed using three different, validated questionnaires. Markers of bone metabolism were measured in blood and urine.

Results The patients' quality of life was not impaired even at low dosages of hydrocortisone (15 or 20 mg per day). Of all laboratory parameters only osteocalcin significantly changed, decreasing at higher dosages.

Conclusions Our study shows that a risk of bone loss may be avoided with a substitution dosage of 20 mg or even 15 mg hydrocortisone per day, without influencing the well-being of the patient.

Keywords Hypocortisolism, hydrocortisone substitution, well-being, bone metabolism.
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Introduction

In the substitution of hypocortisolism with cortisol, the right substitution dosage of hydrocortisone (HC) is important. Chronically elevated cortisol concentrations may lead to weight gain, centripetal obesity, moon face, purple striae, easy bruisability, proximal myopathy, hypertension and glucose intolerance. Usually, these symptoms appear if the dosage of 40 mg HC per day is exceeded. If too little HC is administered the following symptoms occur: weakness, tiredeness, fatigue, anorexia, nausea and vomiting. With optimum substitution therapy patients feel well and strong. The dosage of substitution therapy is calculated according to the cortisol production. Until now it was considered to be 12–15 mg m^{-2} per day [1,2], but recent research has shown that the production is considerably lower at 6 mg m^{-2} per day [3,4].

To monitor the substitution of chronic adrenal insuffiency the control of serum electrolytes is recommended; the appetite should be good and the patients should feel well [5,6].

The question is, what effects have the usual HC substitution dosages on the well-being of the patients and on the parameters of the bone metabolism and which is the optimum substitution dosage.

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Patients and methods

In a double blind study nine patients with secondary hypocortisolism received different dosages of HC. Four of the patients were women and five were men. Their ages ranged between 23 and 60 years, their weight between 55 and 124 kg. Morning serum cortisol concentration of the patients was $<82{\cdot}8$ nmol L^{-1} and after stimulation with 100 μg CRH or insulin tolerance test (blood glucose <40 mg dL^{-1}) it was $<157{\cdot}3$ nmol L^{-1}. The replacement

therapy of HC, and if necessary the substitution of sex and thyroid hormones as well as the administration of desmopressin, had not been changed for at least 6 months.

The patients were divided into three groups of three who received 15, 20 and 30 mg of hydrocortisone in different orders each for 2 weeks. The other medication was not changed in the 6-week study. Before the study and on the last day of each week the patients filled out three different questionnaires: the Basler Befindlichkeits-Skala (BBS [7]), the Befindlichkeits-Skala (Bf-S [8]) and the Beschwerdeliste (BL [9]). Moreover, blood pressure, pulse and weight were measured, blood was taken and a 24-h urine sample was collected. Serum cortisol (FPI, TDx, Abbott, Wiesbaden, Germany), aldosterone (RIA, DPC, Biermann, Bad Nauheim, Germany), renin (IRMA, Nichols, San Juan Capistrano, USA), sodium, potassium, alkaline phosphatase, its bone-specific subunit (BAP) (RIA, DPC, Biermann, Bad Nauheim, Germany), osteocalcin (RIA, Sorin, Biomedica, France), crosslaps (ELISA, Osteometer; Biotech, Denmark), serum calcium and phosphate were determined. In a 24-h urine sample urinary free cortisol (UFC), pyridinium cross-links (EIA, DPC, Biermann, Bad Nauheim, Germany), calcium and phosphate were also measured.

Due to the small group of patients an analysis of variance could not be employed. To detect changes in the different variables nonparametric statistics (Wilcoxon and Friedman test) were applied. A $P < 0{\cdot}05$ was accepted as significant.

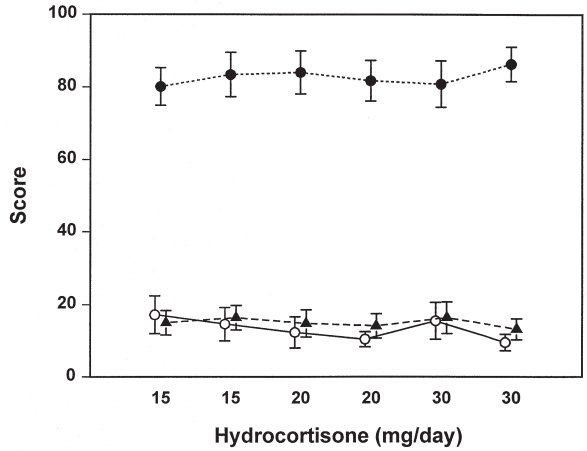

Figure 1 Sum scores of the questionnaires, Basler-Befindlichkeits-Skala (●), Befindlichkeits-Skala (○) and Beschwerdeliste (▲) investigated the well-being and subjective impairment due to physical symptoms at 15 mg, 20 mg and 30 mg HC day^{-1} in nine patients (scores of normal individuals: BBS, 77·6 ± 1·2; Bf-S, 12·2 ± 0·2; BL, 14·2 ± 0·3). Data are shown as mean ± SEM.

Results

The excretion of cortisol in the 24-h urine sample increased significantly depending on the substitution dosage. With 15 mg HC day^{-1} the excretion was 298 ± 26 nmol day^{-1} (mean ± SEM), with 20 mg it was 454 ± 43 nmol day^{-1} and with 30 mg 819 ± 59 nmol day^{-1} (Table 1). The mean scores of the psychological questionnaires did not change significantly during the whole study. The scores of the BBS were 81·8 ± 3·9, 82·8 ± 3·9 and 83·6 ± 3·9 with 15, 20 and 30 mg HC day^{-1}, the sores of the Bf-S were 15·9 ± 13·4, 11·3 ± 2·6 and 12·5 ± 2·8, respectively, and the BL scores were 15·7 ± 2·3, 14·4 ± 2·5 and 14·8 ± 2·6, respectively (Fig. 1). Of all the laboratory parameters only osteocalcin changed significantly. The osteocalcin concentration was 2·3 ± 0·49 μg L^{-1} at 15 mg day^{-1} and decreased significantly to 2·1 ± 0·42 μg L^{-1} at 20 mg and to 1·8 ± 0·38 mg L^{-1} at 30 μg day^{-1} ($P < 0{\cdot}05$).

Table 1 Urinary free cortisol at 15, 20 and 30 mg HC day^{-1}, given as mean ± SEM

HC (mg/day)	UFC (nmol/day)
10	298 ± 26
20	454 ± 43
30	819 ± 59
Normal	147–535

Discussion

The most important parameters in determining the correctness of the substitution dosage of HC in secondary hypocortisolism are the well-being and quality of life of the patients [5,6]. Therefore we analysed general health perception in a randomized double-blind study using three questionnaires for self-rating [10].

In our patients the sum scores of these three questionnaires did not change significantly over the entire period of the study and with different dosages of HC (Fig. 1). The quality of life was not influenced by the different dosages of HC. Even at the lower dose of 15 or 20 mg HC day^{-1} the patients' well-being was not impaired and the patients did not have more complaints than with the conventional substitution dose of 30 mg HC day^{-1}.

Another important variable is the UFC [11]. Despite the short period of only 2 weeks for each dosage, we noted a significant increase of UFC with increasing amounts of HC. The cortisol excretion at 15 and 20 mg day^{-1} was found within, and at 30 mg HC day^{-1} above the normal range (Table 1). This suggests that a long-term dosage of 30 mg HC day^{-1} leads to elevated UFC.

It has been shown that GC influence bone metabolism [12]. As an enzymatic marker of osteoblastic activity we

measured AP and its bone-specific isoenzyme BAP. As a highly specific marker of bone formation serum concentrations of osteocalcin were measured. Osteocalcin is completely synthesized from the osteoblasts [13]. A decrease in serum levels of osteocalcin reflects depression of the osteoblastic function.

Studies on bone mineral density measurement have shown that long-term treatment with a replacement dosage of 30 mg HC day^{-1} induces bone loss in men with Addison disease [14]. Adult patients with congenital adrenal hypoplasia (21-hydroxylase deficiency) showed a decrease of bone mineral density during substitution therapy with more than 10–15 mg m^{-2} HC day^{-1} [15].

Our study is in agreement with these findings, as osteocalcin decreased significantly with increasing HC doses, suggesting a risk of bone loss in our patients.

We conclude that different dosages of HC (15, 20 or 30 mg day^{-1}) have a similar influence on the quality of life in patients with secondary hypocortisolism. With 15 or 20 mg HC day^{-1} patients feel nearly as well as normal healthy individuals. A level of 30 mg HC day^{-1} reduces serum osteocalcin levels, indicating a depression of osteoblastic activity. Long-term treatment with a high replacement dose of GC (HC 30 mg day^{-1}) may induce bone loss [14]. Our study suggests that this risk may be avoided with a substitution dose of 20 mg or even 15 mg HC day^{-1}, without impairing the well-being of the patient.

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