GP152

Effects of hydrocortisone on the regulation of blood pressure – Results from an RCT

J. Werumeus Buning[1]*, M. van Faassen[2], P. Brummelman[1], R.P.F. Dullaart[1], G. van den Berg[1], M.M. van der Klauw[1], M.N. Kerstens[1], C.A. Stegeman[3], A.C. Muller Kobold[2], I.P. Kema[2], B.H.R. Wolffenbuttel[1], A.P. van Beek[1]

[1]Department of Endocrinology, University of Groningen, University Medical Center Groningen, The Netherlands
[2]Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, The Netherlands
[3]Department of Nephrology, University of Groningen, University Medical Center Groningen, The Netherlands

BACKGROUND

The association between excessive levels of glucocorticoids and increased blood pressure is well recognized. However, the exact mechanism behind this association remains unknown. Effects of physiological concentrations of glucocorticoids have hardly been studied in controlled trials. We therefore studied the effects of hydrocortisone substitution dose on blood pressure and regulating mechanisms in patients with secondary adrenal insufficiency in a randomized, double blind cross-over study.

MATERIALS AND METHODS

Patients

Patients with secondary adrenal insufficiency were randomized to either first receive a lower dose of hydrocortisone (0.2-0.3 mg/kg body weight) for 10 weeks, followed by a higher dose (0.4-0.6 mg/kg body weight) for 10 weeks, or in reversed order. HC substitution was administered thrice daily with the highest dose in the morning.

Protocol

At the end of each treatment period patients returned to the hospital for automated office blood pressure measurement in sitting position, and collection of blood and 24-h urinary samples. Blood pressure was measured three times with an automated device and reported as the mean of the three measurements.

Statistics

Data is presented as mean (SD) or median [IQR]. Outcome measures on both hydrocortisone doses were compared by using the Wilcoxon Signed Rank Test for paired observations.

Table 1. Anthropometric measures, biochemical and hormonal analysis (N=46)

	Lower dose	Higher dose	P-value
Plasma total cortisol, 1hr after ingestion (nmol/L)	500 [389; 602]	745 [676; 880][a]	<0.001
Plasma total cortisol, 5hrs after ingestion (nmol/L)	117 [76; 211]	232 [171; 311]	<0.001
Plasma total cortisone, 1 hr after ingestion (nmol/L)	65 [53; 70]	63 [55; 71][a]	0.852
Plasma total cortisone, 5hrs after ingestion (nmol/L)	30 [21; 40]	44 [36; 57]	<0.001
SBP (mmHg)	133 (14)[a]	138 (16)[a]	0.011
DBP (mmHg)	76 (10)[a]	78 (9)[a]	0.050
Weight (kg)	82.8 (14.0)	83.3 (14.3)	0.060
Body mass index (kg/m²)	26.9 (4.0)	27.1 (4.0)	0.045
Plasma sodium (mmol/L)	142 [141; 143]	142 [141; 143]	0.099
Plasma potassium (mmol/L	3.9 [3.7; 4.0]	3.8 [3.6; 4.0]	0.048
Plasma creatinine (µmol/L)	82 [66; 88]	80 [68; 89]	0.109
Serum CBG (µg/ml)	53.2 [49.1; 63.0][a]	56.5 [49.0; 62.5][a]	0.102
Plasma renin concentration (pg/mL)	11.6 [6.7; 17.3][b]	8.6 [5.9; 14.9][b]	0.051
Serum aldosterone (pmol/L)	150 [77; 256][a]	107 [43; 235][a]	0.020
ARR (pmol/ng)	13.8 [7.3; 21.3][b]	11.0 [6.1; 19.8][b]	0.044
TTKG	7.42 [6.12; 9.48][c]	7.47 [6.00; 9.18][b]	0.352
Plasma copeptin (pmol/L)	3.7 [2.5; 5.0][b]	3.4 [2.5; 4.9][b]	0.819
Urine sodium (mmol/24hr)	142 [119; 206][a]	161 [112; 200][c]	0.534
Urine potassium (mmol/24hr)	77 [64; 96][a]	83 [69; 103][c]	0.032
Creatinine clearance calculated (mL/min)	117 (37)[a]	117 (29)[c]	0.700

Fourteen patients received blood pressure lowering medication. [a] N=45, [b] N=43, [c] N=44.

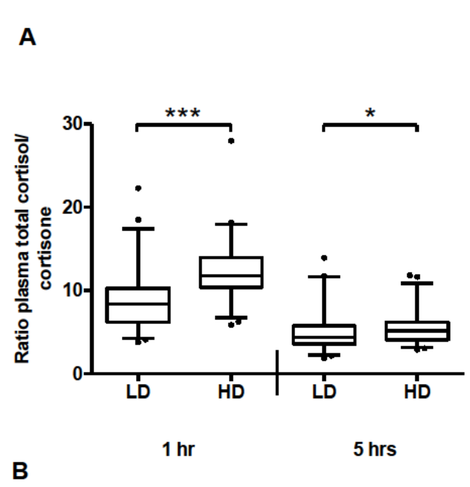

Figure 1. Ratio of plasma total cortisol/cortisone (A), (THF+alloTHF)/THE (B), and UFF/UFE (C) on the two doses of hydrocortisone.
THE: tetrahydrocortisone, THF: tetrahydrocortisol, allo-THF: allo-tetrahydrocortisol, UFE: urinary free cortisone, UFF: urinary free cortisol.
*** P < 0.001, * P<0.05.

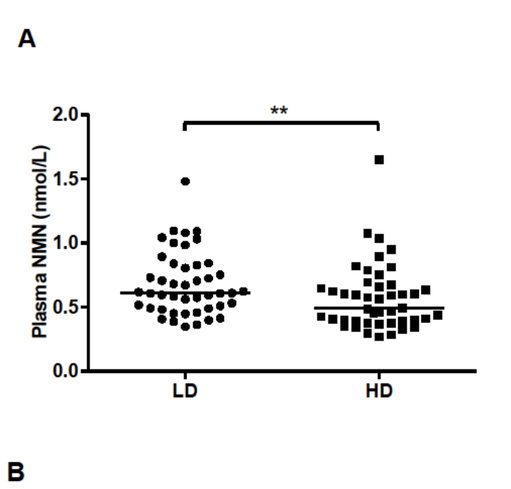

Figure 2. Plasma NMN(A), urinary NMN(B) and urinary 3-MT (C) concentrations on the two doses of hydrocortisone.
3-MT: 3-methoxythyramine, HD: high dose hydrocortisone, LD: low dose hydrocortisone, MN: metanephrine, NMN: normetanephrine.
** P < 0.01, ***P<0.001.

RESULTS

Forty-six patients participated (28 men, 18 women, mean age 51 (14) years, range 19-73). The higher dose of HC resulted in an increase in systolic blood pressure, and a borderline significant increase in diastolic blood pressure (Table 1). Plasma potassium concentration decreased, whereas urinary potassium excretion increased. Plasma renin and serum aldosterone concentration decreased, indicating suppression of the renin-angiotensin-aldosterone system. There was a change in 11β-hydroxysteroid dehydrogenase enzyme activity, thereby favoring enhanced cortisol exposure on the higher dose of HC (Figure 1A-C). Sympathetic nerve activity was decreased on the higher dose as shown by the decreases in plasma normetanephrine and urinary normetanephrine and 3-methoxythyramine (Figure 2A-C).

CONCLUSION

A higher dose of hydrocortisone increased blood pressure and resulted in changes in blood pressure regulating mechanisms, with most pronounced effects found in the renin-angiotensin-aldosterone system, 11β-hydroxysteroid dehydrogenase enzyme activity and sympathetic nerve activity.

* E-mail: j.werumeus.buning@umcg.nl

Presentation supported by a travel grant from Goodlife Healthcare and NVE