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High Incidence of Abnormal Circadian Blood Pressure Profiles in Patients on Steroid Replacement Therapy due to Secondary Adrenal Insufficiency and Congenital Adrenal Hyperplasia without Overt Hypertension - Initial Results

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Abstract

Patients on steroid replacement therapy are at an increased risk of cardiovascular complications owing to the fact that disruptions in the cortisol diurnal rhythm may affect the blood pressure (BP) profile.

Aim: To evaluate the circadian BP profiles of patients with secondary adrenal insufficiency (SAI) and congenital adrenal hyperplasia (CAH) on steroid replacement therapy and to compare BP profiles of patients receiving hydrocortisone (HC) in different dosing schedules.

Methods: The study included 33 patients: 15 SAI and 18 CAH (mean age 13.2 years 95CI 11.3-15.1). There were no patients with previously diagnosed overt hypertension. Patients with SAI received a mean of 7.39 mg/m^2 of HC in 3 daily doses (in the morning (M) 50%, in the afternoon (A) 25%, in the evening (E) 25%), CAH patients 17.9 mg/m^2 of HC in the following dosing schedules: 5 patients in 3 equal doses, 7 patients received M: 40% A: 40% E: 20%, the remaining 6 patients had the same dosing schedule as patients with SAI. Fludrocortisone (FC) was given to 13 patients with CAH in 2 equal daily doses. The total dose of HC/FC as well as the dosing schedule of HC was adjusted individually based on clinical and biochemical outcomes. Standard 24-hour BP monitoring (ABPM) was performed using an Ambulatory BP Monitor (Space labs 90217, USA).

Results: The majority of the patients (almost 70% SAI, 80% CAH) presented with an abnormal 24-hour BP profile. There were no significant differences in ABPM results between SAI and CAH patients, and no differences between CAH patients treated with and without FC. There was no correlation between HC and FC doses [mg/m^2] and ABPM results except that mean night SBP values increased with greater HC doses ($r=0.51$, $p<0.05$). Among the CAH group the highest percentage of abnormal ABPM results was observed in patients who received HC in doses: M: 50% A: 25% and E: 25%, the most favorable BP profile was observed in patients with dosing schedule: M: 40%, A: 40%, E: 20%. However there were no significant differences between patients with different treatment protocols, the results suggest that observed disruptions of the BP profile could be related to the HC dosing schedule.

Conclusions: The incidence of abnormal BP profiles in patients on steroid replacement therapy due to SAI and CAH without overt hypertension is high. The disruptions of the BP profiles are not associated with the dose of HC or FC. The abnormal BP profiles in patients with SAI or CAH may be related to the HC dosing schedule. 24-hour ABPM seems to be a useful, non-invasive and safe method for the monitoring of HC and FC replacement therapy in patients with adrenal insufficiency. Further investigations in the larger groups of patients are needed.

Keywords: Congenital adrenal hyperplasia; Secondary adrenal insufficiency; Hypertension; ABPM; Cortisol replacement

Abbreviations: ABPM: Ambulatory Blood Pressure Monitoring; ACTH: Adrenocorticotropic Hormone; ADH: Anti-diuretic Hormone; BP: Blood Pressure; CAH: Congenital Adrenal Hyperplasia; dDBP: Mean Day-Time Diastolic BP; dMAP: Mean Day-Time Arterial Pressure; dSBP: Mean Day-Time Systolic BP; FC: Fludrocortisone; FSH: Follicle-Stimulating Hormone; GH: Growth Hormone; HC: Hydrocortisone; LH: Luteinizing Hormone; MAP: Mean Arterial Pressure; nDBP: Mean Night-Time Diastolic BP; nMAP: Mean Night-Time Arterial Pressure; nSBP: Mean Night-Time Systolic BP; SAI: Secondary Adrenal Insufficiency; TSH: Thyroid-Stimulating Hormone

Introduction

Serum cortisol levels and blood pressure (BP) both have well-documented circadian rhythms. Normally, cortisol levels peak in the early morning and drop to their lowest concentration at night [1,2]. The BP circadian rhythm is typically characterized by minor fluctuations throughout the day and night, with an overall dipping that occurs during the night. In normotensive subjects there is typically a 10% to 20% reduction in BP during sleep [3-5]. Most studies that examine cortisol and BP rhythms tend to look at them in isolation, which could

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obscure the potential links between them. There are only a few studies that confirm an association between cortisol levels and BP fluctuations [2,6-9]. An elegant study performed by Holt-Lunstad and Steffen in 302 healthy adult volunteers revealed that a decreased diurnal variation in cortisol levels was associated with a decreased diurnal variation in BP, whereas normal cortisol levels were a significant and independent predictor of normal BP dipping [2]. An abnormal BP circadian rhythm, and in particular a non- dipping phenomenon is associated with increased health risks including left ventricular hypertrophy [10-13], cerebrovascular stroke [14], cardiovascular morbidity [12], kidney damage [14], and increased mortality [15,16]. Thus, disrupted circadian cortisol and in consequence BP rhythms may have important long-term health implications. All patients with adrenal insufficiency on life-long hydrocortisone (HC) replacement therapy are at risk of both cortisol rhythm and BP profile disruption and their sequelae. Thus the HC supplementation regimen could be crucial. Under normal circumstances the secretion of cortisol and adrenal androgens is under the dominant control of pituitary ACTH. In contrast, aldosterone, which has a predominantly mineralocorticoid function, is primarily regulated by the renin-angiotensin system. It is also additionally influenced by sodium, potassium, dopamine, and serotonin levels [17].

Secondary adrenal insufficiency (SAI) (central hypoadrenalism) characterized by a deficit of ACTH is commonly found in patients with multihormonal pituitary deficiency (GH, TSH, LH, FSH, ADH) [17]. The most common cause of congenital adrenal hyperplasia (CAH) is 21-hydroxylase deficiency [18], which leads to a decrease in cortisol and aldosterone synthesis (in 75% of cases). Lack of cortisol leads to an increase in ACTH and stimulation of the adrenal cortex, with accumulation of cortisol precursors that are shunted to the sex hormone pathway [18].

The current treatment of SAI and CAH consists of the administration of glucocorticoids, and in the case of CAH mineralocorticoids as well (Fludrocortisone, FC) if necessary. The goal of treatment in both diseases is replacement of cortisol to prevent adrenal crisis, and to suppress the abnormal secretion of adrenal androgens in CAH [17,18]. Hydrocortisone (HC) is considered the drug of choice in these two cases. For the reason that modern techniques which measure cortisol production rates have suggested that the mean total daily production is 10 mg/m^2, that dose of HC is recommended [17,19,20]. In order for it to correlate with the circadian rhythm, the dose should be administered three times a day, usually 50% of the dose in the morning, 25% around lunchtime, and 25% in the early evening [17,20,21]. In order to initially decrease markedly elevated sex hormone levels in CAH patients during infancy, doses of up to 25 mg/m^2 of HC may be required, however in growing children a typical dosing schedule is 10-15 mg/m^2 three times a day. After achieving adult height, patients are often switched to longer-acting glucocorticoid preparations that can be given once or twice a day to maximize convenience and androgen synthesis inhibition. Some authors recommend using a reverse circadian pattern of HC replacement therapy to optimize androgen suppression, because glucocorticoid given before bedtime suppresses the ACTH night-time surge [22-24]. Others advocate giving the highest glucocorticoid dose in the morning or even waking the patient up at 3:00 am in an attempt to approximate the normal physiological timing of cortisol secretion [25-28]. Nevertheless no current glucocorticoid therapy is able to mimic normal cortisol circadian rhythms, and in consequence BP rhythms which may contribute to suboptimal clinical outcomes. The patients on steroid replacement are undoubtedly at higher (in comparison to general population) risk of overt hypertension. Moreover, even if they present with normal results of the casual BP measurements, they may have disruptions of the circadian BP rhythm [2,7-9]. To date, investigators have failed to determine unequivocally what is the frequency of such disorders and what are the main determinants and risk factors [2,7-9].

The Aim of the Study

To evaluate daily BP profiles in patients with SAI and CAH on HC replacement therapy [1,2]. To compare BP profiles in patients with CAH treated with HC in three different dosing schedules.

Patients and Methods

The studied group of this pilot study consisted of 33 patients with adrenal insufficiency, of which 15 had secondary adrenal insufficiency (8 girls and 7 boys) and 18 (11 girls and 7 boys) congenital adrenal hyperplasia due to 21 hydroxylase deficiency (the diagnosis was established based on the results of urinary steroid profile analysis using gas chromatography/mass spectrometry).

The mean age was 13.2 years with a confidence interval of 95CI (11.3-15.1).

The exclusion criteria were: presence of previously diagnosed overt hypertension, anti-hypertensive treatment and other endocrinological disorders except secondary thyroid insufficiency and growth hormone deficiency on hormonal replacement therapy.

In the group of patients with secondary adrenal insufficiency all were affected by multiple pituitary insufficiency, 12 had congenital defects of the pituitary gland and 3 acquired pituitary insufficiency due to pituitary tumors.

There were no significant differences with regard to age and auxological parameters (Table 1).

The daily hydrocortisone dose was significantly higher in the CAH group (13 patients were also treated with FC). In all patients with SAI, hydrocortisone was administered in 3 daily doses: 50% of the daily dose was given in the morning (M), 25% in the afternoon (A) and 25% in the evening (E). In the CAH group, 5 patients received hydrocortisone in 3 equal doses, 7 received: M: 40%, A: 40%, E: 20%, 6 patients had a dosing schedule similar the one in patients with SAI (M: 50%, A: 25%, E: 25%). The total dose of HC as well as the dosing schedule was adjusted individually based on clinical and biochemical outcomes

Parameters	Secondary adrenal insufficiency mean [95% CI]	Congenital adrenal hyperplasia mean [95% CI]	p
N	15	18	-
Age [years]	13.2 [11.3-15.1]	11 [9.2-12.7]	0.07
Height [SDS]	-0.49 [-1.25-0.26]	-0.52 [-1.3-0.25]	0.79
BMI [SDS]	0.04 [-0.5-0.6]	0.21[-0.4-0.8]	0.61
Hydrocortisone daily dose mg/m^2	7.39[6.1-8.6]	17.9[15.4-20.3]	0.002
Fludrocortisone daily dose mg/m^2	-	0.03[0.01-0.04]	-

Table 1: Characteristics of the studied groups: secondary adrenal insufficiency (SAI) and congenital adrenal hyperplasia (CAH).

such as: growth velocity, body weight, bone age, blood pressure, 17-hydroxyprogesteron levels in the blood and 17-ketosteroid levels in the urine. Fludrocortisone (FC) was given in 2 daily doses, the total dose was adjusted based on plasma renin activity and BP.

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, using a stadiometer (Harpenden, UK) and a balanced scale. As the standard of reference normal values from the local population were used [29].

24-hour BP monitoring was performed using an Ambulatory BP Monitor (Space labs 90217, USA), with a cuff which was the same size as the one used to measure casual blood pressure. It was set to take a reading every 15 minutes (day 6 a.m.-10:59 p.m.), and every 30 minutes (night 11:00 p.m.-5:59 a.m.). The monitoring was performed in a standard setting, patients went to sleep at 9-10 p.m. and got up at 6-7 a.m. Sleep and wake periods were established based on a diary completed by the child's parents. Recordings with at least 70% valid readings and at least one reading every hour were considered for the analysis. The following parameters were analyzed: mean 24-h systolic (SBP), diastolic (DBP), and mean arterial pressure (MAP), mean day-time systolic (dSBP), diastolic (dDBP), and MAP (dMAP), mean night-time systolic (nSBP), diastolic (nDBP), and MAP (nMAP). Blood pressure load was calculated separately for the awake and asleep periods. BP load was defined as the percentage of valid BP measurements above a set threshold (95th percentile for sex and the height) value [4,5]. Loads in excess of 30% were considered elevated. Loads in excess of 50% were considered severely elevated. The calculation of nocturnal dipping was based on a formula by the American Heart Association: [(dSBP–nSBP)/dSBP] × 100. Normal dipping was defined as a ≥10% decline in BP [3,5].

In order to compare the two groups the two-sided Mann-Whitney U-test and ANOVA tests were used. Spearman ρ was used to measure the strength of association between pairs of variables. The level of significance was set at $p<0.05$. Calculations were performed using the STATISTICA 10.0 PL soft ware (Poland).

Results

The majority of the patients presented with abnormal 24-hour BP profile: almost 70% with SAI 80% with CAH. The patients with normal BP profiles were significantly younger in comparison to individuals with BP profile abnormalities (mean 9.6 vs. 12.8 years).

There were no significant differences in ABPM results between SAI and CAH patients. The mean values of the 24h SBP, day time SBP and night time SBP were slightly higher in the CAH group, however the differences were not significant (SBP: 108.8 vs. 112.2 mmHg, dSBP: 111.7 vs. 114.2 mmHg, nSBP: 100.6 vs. 105.2 mmHg in SAI and CAH groups respectively). The mean 24-hour SBP loads were also comparable: an elevated SBP load was observed in 20% of patients with SAI and in 17% of CAH patients (in 6% of CAH patients elevation was severe). Day time SBP load was elevated in 20% of SAI and 12% of CAH patients (severely elevated in 6% CAH patients). Interestingly, the night time SBP seems to be more affected in CAH group since the night time SBP load was elevated in 26% (13% seriously elevated) of SAI, and 34% (28 seriously elevated) of CAH patients.

There were also no significant differences among 24h DBP, day time DBP and night time DBP mean values between SAI and CAH patients (66.5 vs. 67.2 mmHg, 69.7 vs. 69.3 mmHg, 56.6 vs. 59.5 mmHg respectively). An elevated 24-h DBP load was observed in 13% of SAI and in 11% of CAH patients. 27% of SAI patients presented an elevated day time DBP load (severely elevated in 7%), but interestingly it was not observed in any patient with CAH. Night time DBP load elevation was present in 27% of SAI patients (severely elevated in 7%), and in 23% of CAH patients (severely elevated in 17%).

The mean values of the 24h MAP, day time MAP and night time MAP were comparable in both groups: 24h MAP 81.5 vs. 82.8 mmHg, dMAP 84 vs. 84.6 mmHg, nMAP 71.5 vs. 75.8 mmHg in SAI and CAH patients respectively.

In 21 patients 8 (53%) with SAI and 13 (72%) with CAH (of which 11 patients were on FC) there was no significant night time dip. Nevertheless there was no significant difference in the mean value of the nighttime dip between SAI and CAH patients (9.91 vs. 7.88%). There were no significant differences in ABPM results between CAH patients treated with or without FC (Table 2).

There was no correlation between HC and FC doses [mg/m^2] and 24 hour ABPM results except that mean night SBP values increased with greater HC doses ($r=0.51$, $p<0.05$).

Among the CAH group the highest percentage of abnormal ABPM results was observed in patients who received HC in doses: M: 50% A: 25% and E: 25%, the most favorable BP profile was observed in patients with dosing schedule: M: 40%, A: 40%, E: 20% (Table 3). However there were no significant differences between patients with different treatment protocols, the results suggest that observed disruptions of the BP profile could be related to the HC dosing schedule.

Discussion

The circadian rhythm of blood pressure is maintained within normal limits through the interplay of various mechanisms including the secretion of cortisol and aldosterone [1,2]. Unfortunately when these hormones are exogenously administered they are not under the regulatory feedback mechanisms that maintain BP homeostasis. The results of the present study show that long term HC and/or FC replacement therapy do not seem to be associated with overt hypertension in young people with SAI or CAH when using casual BP references. This observation is in agreement with previously published data [7]. Even though no single case of overt hypertension was noted, almost 70% of SAI and 80% of CAH patients presented with

	Fludrocortisone	no fludrocortisone	p
HC dose [mg/m^2]	17.7	18.3	0.55
mean 24h SBP (mmHg)	111.1	115.2	0.3
mean 24h DBP (mmHg)	65.8	70.8	0.1
mean 24h MAP (mmHg)	81.6	85.8	0.27
mean dSBP (mmHg)	113.1	117.4	0.12
mean dDBP (mmHg)	68	72.8	0.13
mean dMAP (mmHg)	83.6	87.4	0.13
mean nSBP (mmHg)	105	106	0.8
mean nDBP (mmHg)	58.3	62.6	0.2
mean nMAP (mmHg)	75	77.8	0.3
24h SBP load (%)	14.3	19.7	0.4
dSBP load (%)	12	16.9	0.3
nSBP load (%)	22	27.1	0.9
24h DBP load (%)	10.7	17.8	0.1
dDBP load (%)	9.5	13.9	0.2
nDBP load (%)	15.4	31	0.1
night time dip (%)	7.1	9.6	0.5

Table 2: Outcome variables in patients with CAH with and without fludrocortisone replacement therapy.

Parameters		Three equal daily doses	40+40+20%	50+25+25%	P
24h SBP	mean [mmHg]	110	112.1	114.1	0.52
	load [%]	13.9	8.6	25.9	0.42
	percentage of abnormal load values [%]	0	0	33	
24h DBP	mean [mmHg]	66.2	66	68.2	0.78
	load [%]	12.4	9.3	16.9	0.6
	percentage of abnormal load values [%]	0	0	33	
dSBP	mean [mmHg]	112.6	114.1	115.8	0.8
	load [%]	10.4	7.6	22.6	0.38
	percentage of abnormal load values [%]	0	0	33	
dDBP	mean [mmHg]	68.8	69.4	69.7	0.9
	load [%]	9.38	8.9	14	0.8
	percentage of abnormal load values [%]	0	0	0	
nSBP	mean [mmHg]	102.4	104	109	0.55
	load [%]	23.94	9.6	39.3	0.26
	percentage of abnormal load values [%]	20	14	50	
nDBP	mean [mmHg]	59.2	57.9	62	0.45
	load [%]	20.8	10.9	29.3	0.6
	percentage of abnormal load values [%]	20	0	30	
Night time dip	[%]	9.05	8.8	5.7	0.18
	percentage of abnormal load values [%]	80	57	100	

Table 3: Outcome variables in patients with CAH with different HC dosing schedules.

an abnormal 24-hour BP profile. The results of the study shows, those casual, ambulatory BP measurements are not a sufficient tool for the monitoring of long-term cardiovascular risk factors in such patients, because adrenocortical insufficiency and subsequent replacement therapy are not usually associated with overt hypertension, but have often been shown to account for a loss of circadian blood pressure rhythm. Due to the fact that cortisol and BP circadian rhythms are closely linked, 24-hour BP monitoring may be a useful additional tool for the non-invasive monitoring of replacement therapy.

Our results show that the total daily dose of HC was not associated with 24-hour BP profile parameters, except mean night time SBP. The lack of such an association was also showed in the study performed by Ubertini et al. [8]. Our results also show that there was no significant impact of the FC, since there were no significant differences between patients with CAH receiving only HC and combined HC + FC therapy. However in the group of patients receiving FC the incidence of decreased night time dip was higher compared to the group receiving HC alone, but there were no significant difference in the mean values of night time dip between these two groups. Interestingly, decreased night time dip was also observed in the majority (53%) of patients with SAI.

A more important factor which can modulate the circadian variation of BP might be the regimen of HC administration. Only a few studies have been dedicated to the analysis of the relationship between the HC administration model and BP profiles in such groups of patients [6,9]. In these studies the administration of a higher morning dose of HC was associated with a more physiologic BP rhythm and preservation of night time dipping. The authors suggested that patients with SAI on HC replacement therapy could maintain an approximately normal BP rhythm. This has not been confirmed in the present study. Only 46% of SAI patients presented night time dip ≥10%. The problem is even more complicated in patients with CAH. A few recent studies, investigating BP profiles in CAH patients, have reported conflicting results. Even though Ubertini et al. showed no significant differences between CAH patients and the general population concerning BP profiles [8], other authors indicated a higher prevalence of abnormalities, especially a decrease in night time dip in these patients [30,31]. One study with 11 CAH participants showed that a more physiological administration of HC with a higher morning dose was associated with a more physiological BP profile, with greater night time dip, and not associated with poor biochemical parameters of control of the disease [6].

Our results show that the risk of an abnormal BP profile is present in as many as 80% of CAH patients, irrespective of HC replacement schedule and additional treatment with FC. Nevertheless the most favorable profile was observed in patients receiving 40% of their daily dose in the morning, 40% in the afternoon and 20% in the evening. This novel observation needs further examination in larger groups of patients.

Conclusions

The incidence of abnormal BP profiles in patients on steroid replacement therapy due to SAI and CAH without overt hypertension is high. The disruptions of the BP profiles are not associated with the dose of HC neither with FC treatment (in CAH patients). The abnormal BP profiles in patients with SAI or CAH might be related to the HC dosing schedule. 24-hour ABPM seems to be a useful, non-invasive and safe method for the monitoring of HC and FC replacement therapy in patients with adrenal insufficiency. Further investigations in the larger groups of patients are needed.

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