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Spironolactone and Hydrochlorothiazide Decrease Vascular Stiffness and Blood Pressure in Geriatric Hypertension

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Abstract

Objectives—The efficacy of spironolactone (SPIRO) and hydrochlorothiazide (HCTZ) as monotherapy in older hypertensive patients in blood pressure control and measures of vascular stiffness is unknown.

Design/Setting/Participants/Intervention—45 hypertensive subjects (24 men, 21 women, mean age 69 yrs) were randomized (double blind) and completed 6 months HCTZ (n=21) or SPIRO (n=24) therapy titrated to a target SBP < 140 mmHg.

Measurements—Baseline (following 4 week antihypertensive drug wash out) and 6-month 24-hr ambulatory BP data were obtained. Pulse pressure was calculated as the difference between the 24-hour average SBP and DBP. Pulse wave velocity (PWV) was determined by non-invasive recordings of the carotid and femoral artery pulse waves.

Results—Six months of HCTZ and SPIRO treatment was associated with significant decreases in 24-hr and nocturnal SBP and DBP (ANOVA $P < 0.001$). At the 6-month time period, average 24-hr and nocturnal SBP were both lower in the SPIRO compared to the HCTZ group ($P < 0.001$). Pulse pressure and PWV also decreased significantly with both HCTZ and SPIRO treatments (ANOVA $P < 0.001$).

Conclusions—Six months of therapy with either HCTZ or SPIRO resulted in comparable reductions in 24-hr average and nocturnal SBP and DBP, pulse pressure and PWV in older hypertensive subjects.

Keywords

Aldosterone; Pulse Wave Velocity; Vascular Stiffness; Ambulatory Blood pressure monitoring

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Sponsor's Role

None of the study sponsors had a role in the design, methods, subject recruitment, data collections, analysis or preparation of this manuscript.

Conflict of Interest

This study was supported by the VA Medical Research Service, the Ann Arbor and Salt Lake City VA Geriatric Research Education and Clinical Centers, NIA K07 AG28403 (MAS) and M01-RR00042 to the University of Michigan Clinical Research Center. Neither author has a proprietary interest in any product mentioned in this manuscript nor any financial conflicts to disclose. Mark A. Supiano had full access to all of the data in this study and accepts full responsibility for its accuracy and the data analysis.

Author Contributions

P.A. Kithas: analysis and interpretation of data, and preparation of manuscript. M.A. Supiano: obtaining funding, concept and design, acquisition of subjects and/or data, analysis and interpretation of data, and preparation of manuscript.

INTRODUCTION

The most commonly encountered form of hypertension in the older population is an elevated systolic blood pressure (SBP) associated with a high pulse pressure (PP) (1). Increased arterial stiffness is the major pathophysiologic characteristic of geriatric hypertension and this accounts for the elevations in both SBP and PP. Increased adiposity, specifically abdominal adipose tissue, higher aldosterone levels and insulin resistance have been shown to be associated with arterial stiffness (2,3). Even within the normal physiologic range, higher aldosterone levels have been associated with increased blood pressure and the subsequent development of hypertension in individuals who had normal blood pressure at baseline (4). In addition, the discovery of aldosterone receptors in the vasculature and myocardium led to the important observation that aldosterone may promote the development of vascular stiffness and myocardial fibrosis (5–6). In this context, the increased aldosterone levels that occur with aging may play an important role through its associations with insulin resistance, inflammation, oxidative stress, sodium retention, and vascular stiffness. This study was performed to test the hypothesis that the mineralocorticoid antagonist spironolactone (SPIRO) would be as effective as HCTZ in decreasing measures of vascular stiffness and lowering 24-hr average and nocturnal blood pressures in an older hypertensive subject population.

METHODS

Subject Selection and Treatment Protocols

Ninety three subjects between the ages of 60 and 80 years were screened for participation in this study. This age range was chosen to facilitate identifying subjects with simple hypertension likely to meet the following study criteria. The primary inclusion criteria were essential hypertension, good general health apart from their hypertension, and signed informed consent. Subjects were excluded if their body mass index was <19 or >40 kg/m² (as both underweight and morbid obesity are known to influence glucose metabolism and sympathetic nervous system function), they used medication that interferes with glucose metabolism or sympathetic nervous system function, their SBP exceeded 180 and/or DBP exceeded 110 mmHg, their antihypertensive treatment consisted of two or more drugs, or evidence of orthostatic hypotension, renal insufficiency (serum creatinine > 2.0 mg/dl); cognitive impairment (MMSE < 26); anemia; type 2 diabetes (fasting plasma glucose > 126 mg/dl or a glucose value > 200 mg/dl at the 2 hour time point of a screening oral glucose tolerance test); contraindication to SPIRO or HCTZ; evidence for secondary hypertension or other significant laboratory or resting ECG abnormalities determined during a screening visit evaluation. Subjects completed an informed consent process and signed a consent form that was approved by the Institutional Review Boards of the University of Michigan – where the study was conducted – and the University of Utah.

On the basis of these criteria, 58 subjects were enrolled and began a monitored 4 week antihypertensive drug withdrawal phase. In addition to weekly clinic BP measurements, patients were provided an automated home BP device (Omron) and instructed to report any SBP values > 180 mmHg. Four subjects failed this phase due to persistent elevations in SBP > 180 mmHg and were withdrawn; 2 subjects were excluded due to remaining normotensive off of medication. Fifty-two subjects were ultimately randomized to treatment with either HCTZ or SPIRO. Starting doses were 12.5 mg for HCTZ and 25 mg for SPIRO and were titrated over a 2 month period to a target SBP of < 140 mmHg. Subjects were followed weekly to assess BP response, titrate medication (increments of 12.5 mg for HCTZ and 25 mg for SPIRO) and evaluate potassium (K⁺) levels. A KCl supplement or placebo was provided to maintain K⁺ levels > 3.5 mEq/L. Maximum drug doses were 50 mg for HCTZ and 100 mg for SPIRO. Seven subjects withdrew during the 6 month drug treatment: 2 for

unspecified drug intolerance (one from each group), 1 due to an intervening surgical procedure (HCTZ) and 4 for BP non-response (1 HCTZ and 3 SPIRO) defined *a priori* as an average SBP > 160 mmHg at the end of the 2 month dose titration phase. Thus, results from 45 subjects (21 HCTZ, 24 SPIRO) who successfully completed the 6 month randomized treatment phase are presented.

24-hour Blood Pressure Protocol

For 3 days prior to and during study measurements of 24-hr BP (baseline and 6 months) subjects were provided a weight maintaining metabolic diet containing 150 mEq of sodium. There were no activity restrictions placed on the subjects. Baseline and 6 month 24-hr ambulatory blood pressure data were obtained using Spacelabs 24-hr monitors. Measurements were made every 30 minutes during the day and every 60 minutes during the night. Pulse pressure was determined as the difference between 24-hr mean SBP and mean DBP. Nocturnal period was defined as midnight to 0600 and daytime as 1000 to 2000. A subject's nocturnal blood pressure profile was characterized as "dipper" when the ratio of the average nocturnal to daytime SBP was less than 90% and "non-dipper" when the ratio was 90% or higher.

Pulse Wave Velocity Protocol

Subjects reported fasting to the University of Michigan Clinical Resource Center for the pulse wave velocity (PWV) measurement. A venous blood sample was obtained. PWV was determined by non-invasive recordings of the carotid and femoral arteries by applanation tonometry by a trained technician utilizing the SphygmoCor Blood Pressure Analysis System (AtCor Medical) as previously reported (3).

Plasma renin activity and plasma aldosterone levels were measured with a commercially available radioimmunoassay (Diagnostic System Laboratories).

Statistical Methods

Values are presented as means with standard deviations. Comparisons of group characteristics at baseline were performed using non-paired t-tests (Table 1; Prism 4.0, GraphPad Software, Inc.). The effect of treatment – baseline to six-month (the time factor) – between the two drug groups (HCTZ and SPIRO drug factor) was analyzed by two-way repeated measures ANOVA (Table 2; Sigmaplot 11.0, Aspire Software International). Within group post-hoc comparisons to analyze 1) the baseline to six-month comparisons (time) within each of the two drug groups individually, and 2) the HCTZ to SPIRO drug group comparison at each time point (baseline and six month) were performed with the Holm-Sidak method, using a P value < 0.01 to indicate statistical significance to adjust for multiple comparisons. Linear regression analyses were performed to compare the percent change in 24-hour SBP and the percent change in PWV for all subjects combined and within each drug treatment group (Figure 2; Prism 4.0, GraphPad Software, Inc.).

RESULTS

Baseline characteristics of the 45 subjects – 21 randomized to HCTZ and 24 to SPIRO – who completed baseline and 6-month evaluations are presented in Table 1. The groups were well matched with respect to age, gender, BMI, nocturnal BP pattern (dipper characterization), and renin and aldosterone levels (all P > 0.05). Mean achieved study drug doses were 42 ± 3 mg for HCTZ and 71 ± 7 mg for SPIRO. Subjects randomized to HCTZ required an average KCl supplementation dose of 23 ± 6 mEq daily. Potassium levels remained in the normal range throughout the study (HCTZ: 3.8 ± 0.4 to 3.8 ± 0.4 ; SPIRO: 4.1 ± 0.2 to 4.2 ± 0.3 mEq/l; baseline and 6 month respectively (ANOVA time effect P=

0.20, drug effect $P < 0.001$). At the 6-month time period, potassium levels were significantly higher in the SPIRO group ($P < 0.001$). There were no reported instances of hyperkalemia, hypokalemia or gynecomastia. Renin levels increased significantly at 6 months (HCTZ 12 ± 3 ng/ml/hr and SPIRO 17 ± 3 ng/ml/hr; ANOVA time effect $P < 0.001$, drug effect $P = 0.36$). Post-hoc multiple comparison testing identified a significant effect of time for the increase in renin levels only within the SPIRO group ($P < 0.001$). There was a significant drug x time interaction effect noted for the change in aldosterone levels at 6 months (HCTZ 157 ± 9 ng/dL and SPIRO 300 ± 37 ng/dL; $P = 0.002$). Post-hoc multiple comparison testing identified a significant effect of time for the increase in aldosterone levels only within the SPIRO group as well as higher levels compared with HCTZ at the 6-month time period (both $P < 0.001$).

Upon completion of 6 months of therapy with HCTZ and SPIRO the decreases in SBP and DBP were significant within each group and qualitatively comparable throughout the 24-hr monitoring period between the two groups (Figure 1). Twenty-four hour average SBP and DBP were significantly decreased in both groups at 6 months compared with baseline (time and drug effects as well as effect of time within each drug group all $P < 0.001$; Table 2). Similarly, for average nocturnal SBP and DBP, both HCTZ and SPIRO treatments were associated with statistically significant decreases at 6 months (time effect as well as effect of time within each drug group all $P < 0.001$; Table 2). At the 6-month time period, average 24-hr and nocturnal SBP were both lower in the SPIRO compared to the HCTZ group ($P < 0.001$).

Approximately two-thirds of each treatment group was characterized by a “dipper” nocturnal BP pattern at baseline (Table 1). Following six-months of therapy, 57% of the HCTZ group and 70% of the SPIRO group met the dipper criteria. There was not a statistically significant effect of treatment group with respect to the nocturnal BP dipping pattern following treatment. There was a significant overall effect of time noted for 24-hr average heart rate ($P < 0.001$), but the within drug group time effects were not statistically significant. There were no changes observed for either drug or time effect with respect to average nocturnal heart rate.

Both indicators of vascular stiffness – pulse pressure and PWV – were significantly lower following treatment with both HCTZ and SPIRO (time effect as well as effect of time within each drug group all $P < 0.001$; Table 2). At the 6-month time period there were no significant differences in either PP or PWV between HCTZ and SPIRO groups.

At baseline, as expected, PWV was strongly associated with 24-hr average SBP ($r^2 = 0.15$; $P = 0.008$). This association was also noted in the combined subject group following treatment ($r^2 = 0.09$; $P = 0.04$). Following six months of treatment, the decrease in PWV (percent change) was not significantly associated with the percent change in SBP when the two drug groups were combined (Figure 2; $r^2 = 0.055$; $P = 0.13$). However, while there was no association noted between percent change PWV and percent change in SBP in the HCTZ treated group ($r^2 = 0.00009$; $P = 0.97$), there was a trend toward a significant direct association in the SPIRO treated group ($r^2 = 0.16$; $P = 0.06$); no interaction was identified between these two relationships.

DISCUSSION

The major results from this investigation demonstrate that six months of treatment with either HCTZ or the mineralocorticoid antagonist SPIRO resulted in comparable lowering of 24-hr average and nocturnal BP in an older hypertensive patient population. At the 6-month time period the 24-hr average and nocturnal SBP were significantly lower among the SPIRO treated group. In addition, HCTZ and SPIRO treatments were associated with comparable

benefits in reducing pulse pressure and pulse wave velocity, suggesting a reduction in vascular stiffness. There were no significant adverse events and both drugs were well tolerated.

Developed more than 50 years ago, SPIRO has been primarily used as a potassium sparing diuretic in volume overload states such as congestive heart failure and cirrhosis and to treat primary hyperaldosteronism (7). Several early studies demonstrated its effectiveness as a single agent in treating essential hypertension (8,9). More recently, randomized controlled trials have demonstrated that mineralocorticoid antagonists reduced cardiovascular events and improved morbidity and mortality in patients with severe heart failure and in patients following myocardial infarction (10,11). These studies emphasized the importance of “aldosterone escape” during ACE inhibitor therapy and led to a reexamination of aldosterone’s vascular effects. In addition, local, vascular, production of aldosterone has been identified to contribute to vascular stiffness and myocardial fibrosis.

Aldosterone antagonists antagonize the aldosterone-induced upregulation of the angiotensin receptor 1, ACE activity and stimulation of vascular smooth muscle cell growth which may contribute to a decrease in vascular stiffness (12). Given these actions of aldosterone and its potential contribution to the development of vascular stiffness – the major pathophysiologic characteristic of geriatric hypertension – the effect of treatment with the mineralocorticoid antagonist SPIRO on two measures of arterial stiffness is of clinical importance. Significant reductions in pulse pressure and in PWV were identified with SPIRO treatment that were comparable to the reductions achieved with HCTZ treatment. Only one prior study has assessed vascular stiffness outcomes following treatment with the aldosterone antagonist eplerenone (13). This 24-week study also identified a reduction in PWV.

Current guidelines for the pharmacological management of hypertension in older patients recommend thiazide type diuretics for most patients (14). Many randomized trials have shown thiazide diuretics to be equally efficacious in reducing the incidence of cardiovascular events in comparison to the other antihypertensive drug classes (15). However, thiazide diuretics carry a risk for potentially undesirable metabolic side effects such as hypokalemia, hypertriglyceridemia, impaired glucose tolerance and increases in serum cholesterol and uric acid (16). By comparison, despite clinical trial data showing that both selective and non-selective aldosterone antagonists are effective as monotherapy in treating hypertension, these agents have received less attention as alternative therapies (8,9). As a class, these agents antagonize aldosterone’s effect to increase renal sodium reabsorption, alter renal hemodynamics, increase afterload and increase vascular stiffness (2).

The effect of thiazide diuretics to reduce SBP to a greater extent than DBP and lead to a reduction in PP is a feature that is well tailored to the treatment older hypertensive patients. The comparable reduction in pulse pressure noted between HCTZ and SPIRO is clinically important due to concerns about potential harmful effects resulting from excessive reductions in diastolic blood pressure (the J-curve phenomenon) that may occur during treatment of primarily systolic hypertension. Both HCTZ and SPIRO treatment led to larger reductions in SBP relative to DBP and consequently statistically significant reductions in pulse pressure.

The results from the present study demonstrate that HCTZ treatment is associated with a significant reduction in PWV, independent from its BP lowering effect (Figure 2). Previous studies comparing thiazide diuretics to other antihypertensives have not demonstrated a reduction in PWV or other measures of vascular stiffness in association with thiazide

diuretic therapy (17). These studies were of much shorter duration (4 weeks) and therefore may not have allowed for the chronic effects of thiazides to become evident.

Since there were comparable reductions in pulse pressure and PWV in the HCTZ and SPIRO treatment groups, it is possible that the reduction in vascular stiffness was primarily due to the decrease in blood pressure *per se*. The lack of a significant overall relationship between the change in PWV and the change in SBP (Figure 2) argues against this possibility – certainly in the HCTZ treated group. In contrast to the HCTZ treated group, there was a trend for a direct association between the change in PWV and the change in SBP among the SPIRO treated group. Finally, it is important to point out that prior studies have not identified treatment-associated reductions in PWV despite significant reductions in BP across several classes of antihypertensive drugs. For example, a 10-week study of perindopril, atenolol, lercanidipine and bendrofluazide found no effect on PWV with any of these drugs (18).

It has been demonstrated that lower PWV is associated with lower overall cardiovascular risk even after the confounding effects of pulse pressure and blood pressure level are taken into account (19,20). The age-related change in PWV has been estimated to increase by 1.36 m/sec per decade (21). Thus, the magnitude of the decrease in PWV noted in each treatment group – approximately 1 m/sec – is likely to be clinically relevant.

Several studies have demonstrated the advantages of 24-hr ambulatory blood pressure monitoring over office determinations with regard to CV risk prediction (22–24). In particular, nocturnal BP and dipping patterns have been reported to be the best predictors of risk, independent of the average 24-hour blood pressure (25,26). It is thus important to have demonstrated comparable BP lowering effects of SPIRO to HCTZ across the entire 24-hour period. Based on the diurnal variation of aldosterone levels which are known to be higher in the late evening and into the early morning hours, it was thought that SPIRO treatment may exert an enhanced reduction in nocturnal BP relative to treatment with HCTZ. While a reduction in nocturnal BP was identified in both HCTZ and SPIRO groups, nocturnal SBP was significantly less in SPIRO compared with the HCTZ group at the 6-month time point.

Several limitations inherent in this study's design deserve comment. The subject population recruited for this investigation was selected to represent a geriatric population with simple hypertension. The 4-week antihypertensive drug withdrawal period was believed to be an important design element to avoid confounding effects of antihypertensive therapy on physiologic measures taken at baseline, but this restricts the study findings to individuals with mild hypertension who are able to tolerate this withdrawal period. Therefore these results may not generalize to older patients with more severe hypertension or those with common co-morbid conditions such as diabetes. The relatively small sample size of this study also imposes limits on its generalizability. In addition, the six-month study duration does not permit extrapolation of these findings to longer term therapy.

In conclusion, in older hypertensive patients, 6 month treatment with SPIRO was demonstrated to be associated with significant reductions in average 24-hr and nocturnal SBP and DBP and measures of vascular stiffness – pulse pressure and PWV – comparable to the reductions in these outcomes in subjects randomized to HCTZ therapy. With recent data revealing potentially important beneficial metabolic effects of mineralocorticoid blockade, the potential physiological and longer term clinical benefits of mineralocorticoid antagonist therapy in this hypertensive patient population should be further investigated.

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Figure 1. 24-hour ambulatory systolic blood pressure monitoring profiles at baseline and following six months of treatment. Diastolic blood pressure profiles (data not shown) were qualitatively similar.

Figure 2.

Relationship between the percent change in pulse wave velocity (PWV) and percent change in 24-hr SBP in the HCTZ (closed diamonds) and SPIRO (open squares) treated subjects. In the combined group, the association was not statistically significant ($r^2=0.055$; $P=0.13$).

Table 1

Baseline Subject Characteristics

	HCTZ n = 21	SPIRO n = 24	P-value
Age (years)	69 ± 6	70 ± 5	0.39
Gender (M:F)	11:10	14:10	0.70
BMI (kg/m ²)	27.6 ± 4.0	27.4 ± 5.4	0.90
Nocturnal "Dipper" BP Pattern (%)	62%	67%	0.75
Renin (ng/ml/hr)	5.3 ± 3.2	4.8 ± 1.9	0.56
Aldosterone (ng/dL)	106 ± 49	107 ± 51	0.93

Values are means ± SD. BMI, body mass index.

Table 2

Ambulatory monitoring 24-hour and nocturnal blood pressure and heart rate, pulse pressure and pulse wave velocity.

	Baseline		Six Month		Time effect P-value	Drug effect P-value	Drug × Time P-value
	HCTZ	SPIRO	HCTZ	SPIRO			
24-hr SBP (mm Hg)	149 ± 9	142 ± 2	136 ± 9	126 ± 9 ^⓪	< 0.001	< 0.001	0.18
24-hr DBP (mm Hg)	84 ± 7	81 ± 8	79 ± 6	74 ± 6	< 0.001	0.05	0.40
24-hr Heart Rate (bpm)	72 ± 8	73 ± 11	75 ± 8	75 ± 11	< 0.001	0.81	0.82
Nocturnal SBP (mm Hg)	135 ± 12	130 ± 9	125 ± 9	116 ± 9 ^⓪	< 0.001	0.005	0.24
Nocturnal DBP (mm Hg)	75 ± 7	73 ± 8	71 ± 5	67 ± 7	< 0.001	0.14	0.73
Nocturnal Heart Rate (bpm)	65 ± 8	64 ± 10	66 ± 10	65 ± 10	0.15	0.71	0.76
Pulse Pressure (mm Hg)	64 ± 8	61 ± 8	57 ± 9	51 ± 8	< 0.001	0.06	0.15
Pulse Wave Velocity (m/sec)	9.9 ± 2.5	9.6 ± 2.2	9.0 ± 1.7	8.6 ± 1.9	< 0.001	0.52	0.73

Values are means ± SD. HCTZ n=21; SPIRO n=24; The time effect factor compares baseline to six-month results and the drug effect factor compares HCTZ and SPIRO groups in the two-way repeated measures analysis.

[Ⓢ] post-hoc multiple comparison within each separate drug group for a baseline vs. 6-month time effect – P < 0.001;

^⓪ post-hoc multiple comparison within six-month time period for HCTZ vs. SPIRO drug effect – P < 0.002. There were no significant drug group differences for any of these comparisons at baseline.