Comparison of eplerenone and spironolactone for the treatment of primary aldosteronism

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Short title: Aldosterone blockade in primary aldosteronism

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Abstract

Background: The mineralocorticoid receptor (MR) is expressed in the kidneys and in adipose tissue, and primary aldosteronism (PA) is associated with metabolic syndrome. This study assessed the effects of MR blockade by eplerenone and spironolactone on blood pressure and metabolic factors in patients with PA.

Methods and Results: Fifty-four patients with PA were treated with one of two MR antagonists, eplerenone (25-100 mg daily, n=27) or spironolactone (12.5-100 mg daily, n=27), for 12 months. Visceral (VAT) and subcutaneous adipose tissue (SAT) were quantified using CT and FatScan imaging analysis software. Body mass index (BMI), homeostasis model assessment-insulin resistance (HOMA-IR), serum creatinine, potassium and lipids, urinary albumin excretion and plasma aldosterone (PAC) and PRA were measured before and after treatment. Eplerenone and spironolactone decreased blood pressure and increased serum potassium levels to similar degrees. PAC and PRA did not differ between the two groups. Although treatment with the MR antagonists did not change HOMA-IR or serum lipids, they significantly decreased urinary albumin excretion and VAT ($p<0.05$).

Conclusion: These results suggest that eplerenone and spironolactone are effective and safe for the treatment of PA. The long-term metabolic and renal effects of these MR antagonists should be further investigated.

Keywords: primary aldosteronism, eplerenone, spironolactone, adipocyte, metabolic syndrome

Introduction

Primary aldosteronism (PA) is the most common form of secondary hypertension, with an estimated prevalence of 5-15% in all hypertensive patients [1, 2]. Excess aldosterone has adverse cardiovascular and renal consequences in patients with hypertension and in patients with diabetes mellitus or chronic renal disease [3, 4]. We have previously reported that PA patients have a higher incidence of cardiovascular complications than age- and sex-matched patients with essential hypertension [5]. Several studies have shown that PA is common in patients with resistant hypertension, with a prevalence of approximately 20% [6], and PA is associated with a significant increase in risk of end-organ damage and cardiovascular events compared with more easily controlled hypertension [7].

Patients with aldosterone-producing adenoma (APA) or unilateral adrenal hyperplasia are often treated with unilateral laparoscopic adrenalectomy. Although surgical removal of APA improves hypertension by up to 30–50% [8], there are no data to show that adrenalectomy is superior to medical treatment. Spironolactone and eplerenone, which both directly antagonize the mineralocorticoid receptor (MR), are the most appropriate therapeutic agents in patients with PA [9]. Spironolactone has been widely used for the treatment of PA, but its use is limited by adverse effects such as gynecomastia, mastodynia, menstrual abnormalities and impotence due to androgen receptor antagonist activity. Eplerenone is a more specific MR antagonist and has very few side effects [4].

Patients with PA have a significantly higher prevalence of metabolic syndrome than those with essential hypertension (EHT) [10, 11,12]. The mineralocorticoid receptor (MR) is expressed in the kidneys and in adipose tissue. Eplerenone improves obesity-related insulin resistance through the reduction of fat reactive oxygen species (ROS) production, inflammatory processes, and induction of cytokines in ob/ob mice. [13]. We examined the effects of MR blockade by eplerenone and spironolactone on blood pressure, renal function and serum potassium and metabolic factors in patients with PA.

Methods

Subjects

The protocol and informed consent form were reviewed by the appropriate Independent Ethics Committee or Institutional Review Board prior to enrollment of any study patients. The clinical trial registration No. was UMIN000004581. To be included in the trial, men and non-childbearing women were at least 18 years of age with hypertension (seated diastolic BP≥90 and ≤120 mmHg with systolic BP<200 mmHg), serum potassium more than 3.0 and less than 5.0 mmol/L. Exclusion criteria included history of accelerated/malignant hypertension, sex hormone therapy, reduced renal function (serum creatinine >1.5 mg/dL in men and 1.3

mg/dL in women), liver disease based on transaminases more than two times the upper limit of normal, and a history of heart failure, myocardial infarction, stroke or serious cardiovascular event within 6 months. Fifty-four hypertensive patients (24 men and 30 women; aged 56 ± 10 years) were diagnosed with PA according to The Japanese Society of Endocrinology Guidelines for the Management of PA [14] in the Kanazawa University Hospital and two municipal hospitals. Thirty-nine patients underwent adrenal venous sampling (AVS); 9 subjects had unilateral aldosterone hypersecretion (4 patients in the SPL group and 5 patients in the EPL group), and 30 subjects had bilateral production of aldosterone (17 patients in the SPL group and 13 patients in the EPL group). AVS was not performed in 15 patients because they did not want to undergo the operation (6 patients in the SPL group and 9 patients in the EPL group).

Study Design

This was an open-label, non-controlled study. After a 2-week washout period, patients with PA underwent randomization with the envelop method: 27 patients received spironolactone (25 mg) and 27 received eplerenone (50 mg) as the first dose. If blood pressure (BP) was not at the goal level (<140/90 mmHg) after 4 weeks of treatment, the dose of spironolactone or eplerenone was increased up to 100 mg. If BP remained uncontrolled after 8 weeks, a calcium channel blocker was added. The duration of hypertension was 7.7 ± 8.9 (eplerenone group) and 6.0 ± 8.7 years (spironolactone group). We assessed the visceral and subcutaneous fat area, insulin resistance as represented by HOMA-IR, lipid parameters and urine albumin excretion at baseline and after MR blockade treatment. The study was performed in accordance with the principles of the Declaration of Helsinki, and the investigational protocol was approved by the Ethics Committee for Human Studies at the Kanazawa University Hospital. All patients provided written informed consent.

Laboratory Measurements

Body mass index (BMI) was calculated as weight (kg) divided by height (cm) squared. Venous blood samples were obtained after a 12 h overnight fast after a 15 min rest in the supine position in the morning. Serum lipids, potassium, glucose, and creatinine were determined by standard procedures. HbA1c was measured by high-pressure liquid chromatography. Urinary albumin was measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit. Plasma immunoreactive insulin (IRI) was measured using ELISA, and blood glucose was measured using the glucose oxidase method. The insulin resistance index was calculated based on HOMA-IR [fasting glucose (mg/dL) ×fasting insulin (mU/mL)/405]. The plasma aldosterone concentration (PAC), plasma renin activity (PRA) and serum cortisol concentration were measured by radioimmunoassay as previously reported [15].

Measurement of Abdominal Adipose Tissue by CT

CT scans were performed using a 64-channel multi-detector row CT (MDCT) (GE Healthcare, Little Chalfont, Buckinghamshire, England). All subjects underwent CT at the umbilical level to measure the cross-sectional

abdominal subcutaneous adipose tissue (SAT) area and visceral adipose tissue (VAT) area using FatScan software (N2 System Corp, Osaka, Japan) [16]. FatScan software enables multiple image rendering and geometric measurements of a specific region with a specified CT number (in Hounsfield units). A single cross-sectional scan at the level of the umbilicus was selected for quantification. Adipose tissue was determined by setting the attenuation level within the range of -190 to-30 Hounsfield units, and the acquired image corresponded to the total fat region. The region of visceral fat was defined by manual tracing of its contour, and the total fat region was divided into visceral and subcutaneous fat regions. Finally, the VAT was calculated by the software.

Statistics

Data are expressed as the means ± S.Ds. All of the analyses were conducted using SPSS software version 18.0 for Windows (SPSS, Chicago, IL). Two-sided tests of treatment differences, based on analysis of covariance (ANOCOVA) with baseline as a covariate and treatment and center as factors were used to compare the effects of spironolactone and eplerenone.

Results

No significant differences in the clinical data were observed between the two groups (Table 1). There were 11 metabolic syndrome patients, three diabetic patients, and fifteen dyslipidemic patients in the spironolactone group at baseline. There were eight metabolic syndrome patients, four diabetic patients, fourteen dyslipidemic patients in the eplerenone group at baseline. Additional antihypertensive drugs and other medications used at the end point are shown in Table 2. Two patients had successfully decreased blood pressure with 25 mg/day of SPL, so their dose of SPL was reduced to 12.5 mg/day; these patients maintained their target blood pressure. Table 3 summarizes the effects of mineralocorticoid receptor antagonists (MRAs) on BP, PAC, PRA, serum potassium, renal function, and serum metabolic factors. Figure 1 shows treatment with spironolactone or eplerenone significantly decreased systolic BP and diastolic BP ($p<0.001$). Serum potassium levels did not exceed 5.0 m Eq/L in any patients. Estimated GFR tended to decrease, but urinary albumin excretion (UAE) was significantly improved by MR antagonist treatment ($p=0.024$). The differences between the effects of eplerenone and spironolactone on systolic and diastolic BP, PRA, PAC, serum potassium, eGFR, UAE, and metabolic factors are shown in Table 3. The blood pressure lowering effects between the two agents did not differ. Spironolactone significantly increased PAC compared with eplerenone ($p=0.007$). PRA, serum potassium, eGFR and UAE did not differ between the two groups. The metabolic factors did not significantly differ between the two groups. Body weight, BMI, waist circumference, VAT and SAT area were not different between the two groups. Although BMI and VAT area were significantly decreased in all patients ($p<0.05$), no significant differences in BMI, VAT and SAT area were observed between the two groups. Two patients treated with spironolactone experienced gynecomastia. No patients treated with eplerenone showed

gynecomastia.

Discussion

Spironolactone has been successfully used in the treatment with PA for more than four decades as monotherapy or in combination with other antihypertensive drugs [9]. Eplerenone is approved for the treatment of essential hypertension in the United States and Japan, but not in Europe [17]. Both eplerenone and spironolactone inhibit activation of the human mineralocorticoid receptor, and spironolactone is more potent than eplerenone in blocking the aldosterone activation of mineralocorticoid receptors [18]. Weinberger et al. [19] reported that the blood pressure reduction with spironolactone 50 mg b.i.d. was greater than with eplerenone 50 mg b.i.d. or 100 mg/day. There are limited data on the effects of eplerenone in patients with PA. Two recent studies compared the efficacy of eplerenone and spironolactone on blood pressure reduction in patients with PA. Karagiannis et al. [20] showed that treatment with eplerenone (from 50 to 200 mg/day) or spironolactone (from 50 to 400 mg/day) for 16 weeks in 34 patients with IHA resulted in an equally effective reduction in blood pressure. Parthasarathy et al. [21] reported that the antihypertensive effects of spironolactone (from 75 to 225 mg) were significantly greater than those of eplerenone (from 100 to 300 mg) in 141 patients with PA including APAs. Two studies reported the adverse events associated with spironolactone treatment, which included gynecomastia, breast pain in females and impotence. The early trials of spironolactone demonstrated its efficacy at doses up to over 200 mg, whereas lower doses of spironolactone have recently been used to avoid dose- and time-dependent adverse events while maintaining the drug's antihypertensive effects [22, 23]. Our data with lower doses of spironolactone or eplerenone might be more practical. Calcium channel blockers decrease aldosterone synthesis in human adrenocortical cells [24] and in hypertensive patients [25]. Nakamura et al. reported that eplerenone potentiates the protective effects of amlodipine against cardiovascular injury in salt-sensitive hypertensive rats independently of blood pressure [26]. In this study, 30-40% of patients needed to use amlodipine to achieve BP <140/90 mmHg. Other blood pressure lowering agents such as ACE inhibitors, angiotensin II receptor blockers and thiazide diuretics were not used. Our data suggest that calcium channel blockers are useful add-ons for the treatment of PA.

Recent in vitro studies have suggested that aldosterone and the MR might influence adipocyte behavior. Caprio et al. [27] reported that aldosterone promotes maturation of pre-adipocytes to adipocytes in a time-, dose-, and MR-dependent manner. Brines et al. [28] reported that adipocytes produce aldosterone, which regulates adipocyte differentiation and vascular function in an autocrine and paracrine manner. In addition, a higher prevalence of glycemic abnormalities and of the metabolic syndrome has been demonstrated in patients with PA compared with those with essential hypertension [29]. Although a cause-effect relationship has not been established, the available evidence indicates that VAT might be a common element linking the

many facets of the metabolic syndrome, including glucose intolerance, hypertension, dyslipidemia, and insulin resistance [30]. We found that treatment with MRAs decreased VAT but not SAT in patients with PA; however, serum lipids and HOMA-IR were not influenced by the medical treatment. Catena et al. [31] reported that treatment with surgery or MR antagonists rapidly and persistently restores normal sensitivity to insulin in patients with PA, which was independent of plasma potassium levels. In their report, HOMA-IR was decreased at 6 months after treatment and increased to the baseline levels over an average period of 5.7 years. Kosmala et al. [32] reported that treatment with spironolactone in patients with metabolic syndrome resulted in a significant decrease in biomarkers of collagen synthesis, left atrial dimension, left ventricular wall thickness and mass. The beneficial effects of MR antagonists on cardiovascular and metabolic factors should be further investigated.

In this study, MR blockade therapy decreased urinary albumin excretion in patients with PA. We have previously reported that spironolactone reduced urinary albumin excretion in diabetic patients [33]. Nagase et al. [34] reported that eplerenone improved podocyte damage and retarded the progression of proteinuria and glomerulosclerosis. Iwakura et al. showed that in 111 patients with bilateral hyperaldosteronism treated with mineralocorticoid receptor antagonists, urinary albumin excretion and eGFR were significantly decreased at 12 months after treatment; these results were consistent with the results from our study [35]. Iwakura et al. noted that patients with higher urinary albumin excretion prior to treatment had the greatest reduction in eGFR. Recently, Ando et al [36] reported that the addition of low-dose eplerenone to renin-angiotensin system inhibitors had renoprotective effects through the reduction of albuminuria in non-diabetic hypertensive patients. A limitation of this current study is that in keeping with ethical practices, the study could not be controlled with a placebo. We did not provide enrolled subjects a special diet program to change their lifestyles, but the patients in both the spironolactone group and eplerenone group might have changed their lifestyles of their own volition. BMI decreases during treatment occurred, and lifestyles might have changed. Francis et al. showed that aldosterone stimulates salt appetite, and MRA administered intracerebroventricularly or intraperitoneally significantly reduced salt ingestion in congestive heart failure model rats [37].

Eplerenone was as effective as spironolactone for the treatment of hypertension in patients with PA and showed fewer side effects. The beneficial effect of both drugs on VAT is of interest and should be further investigated.

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Conflicts of interest

The authors declare no conflicts of interest

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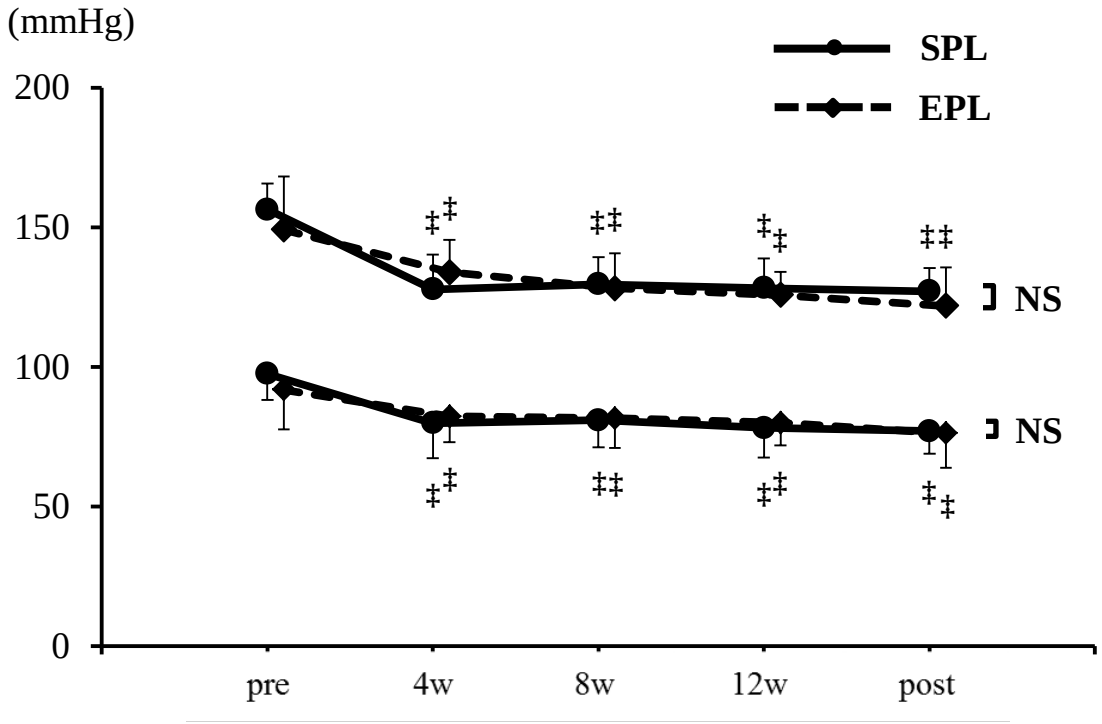
Figure.1 Effect of spironolactone (SPL) or eplerenone (EPL) on blood pressure in PA subjects.



‡ p<0.001; **v.s. pre.**

Table.1 Baseline characteristics

	SPL (n=27)	EPL (n=27)	*P value*
Age(years)	56.1±9.9	54.9±10.7	0.660
male/female	11/16	13/14	
sBP(mmHg)	157±19	150±19	0.104
dBP(mmHg)	96±11	92±14	0.060
s-K(mEq/l)	3.9±0.3	3.9±0.3	0.912
PRA（ng/ml/hr）	0.3±0.3	0.4±0.3	0.322
PAC(pg/ml)	128±55	140±60	0.424
p-aldo/PRA ratio	602±443	470±271	0.191

Data are the mean±S.D. BP, blood pressure; s-K, serum potassium PRA; plasma renin activity; PAC, plasma aldosterone concentration.

Table 2. Antihypertensive medications used at end point and treatment for diabetes and dyslipidemia

Mineralocorticoid receptor blocker	SPL (n = 27)	EPL (n = 27)
Dose (mg/day)	32.4±13.1	74.1±28.1
Range (mg/day)	12.5 – 100	25 – 100
Period (months)	12.7±1.5	12.4±1.1
Calcium channel blocker	9 (33.3)	11 (40.7)
α-Blocker	1 (3.7)	1 (3.7)
Treatment for diabetes mellitus	2 (7.4)	4 (14.8)
Sulfonylurea	1 (3.7)	2 (7.4)
Biguanide	1 (3.7)	1 (3.7)
α-glucosidase inhibitors	0 (0)	1 (3.7)
Treatment for dyslipidemia	4 (14.8)	3 (11.1)
Statin	3 (11.1)	3 (11.1)

Data are the mean±S.D. Data represent number (percent).

Table.3 Baseline Metabolic parameters and their changes at end of follow-up in the whole patients, SPL group and EPL group

	ALL		SPL		EPL	
	Baseline	End of study	Baseline	End of study	Baseline	End of study
Systolic BP (mmHg)	153±19	125±12‡	157±19	127±11‡	150 ±19	122±14‡
Diastolic BP (mmHg)	95±12	77±10‡	96±11	77±8‡	92±14	76±12‡
PRA（ng/ml/hr）	0.4±0.3	1.3±1.1‡	0.3±0.3	1.5±1.3‡	0.4±0.3	1.1±1.0‡
PAC (pg/ml)	135±57	213±90‡	128±55	244±84‡	140±60	184±88*
PAC/PRA ratio	543±370	277±256‡	602±443	268±232‡[a]	470±271	286±281*
serum-Potassium(mEq/l)	3.9±0.4	4.2±0.3‡	3.9±0.3	4.3±0.3‡	3.9±0.3	4.2±0.3†
eGFR (ml/min/1.73m^2)	79.9±18.6	74.4±18.0	78.5±18.5	72.5±20.6‡	81.3±18.9	76.3±15.2*
UAE (mg/gCr)	10.4 (5.8-21.9)	6.3 (4.5-15.9)*	10.0 (5.6-21)	5.6 (4.2-15.4)	10.8(5.3-22.4)	7.0 (4.8-16.4)
Fasting plasma glucose (mg/dl)	103±17	104±19	106±21	107±23	99±12	100±13
Plasma insulin	5.6 (4.4-11.0)	6.5 (4.7-9.4)	7.2 (4.2-11.3)	8.1(4.0-9.9)	7.5 (4.4-9.1)	6.5 (5.3-8.0)
HOMA-IR	1.3 (1.0-2.7)	1.5 (1.1-2.4)	1.8(1.0-3.0)	2.1(1.0-2.8)	1.3 (1.1-2.2)	1.5 (1.2-2.1)
HOMA-β	60（44-108）	70 (47-93)	63(39-105)	62(44-82)	57 (46-109)	76 (48-99)
HbA1c (%)	5.3±1.0	5.2±1.2	5.5±0.6	5.1±1.7	5.0±1.2	5.3±0.6
Triglycerides (mg/dl)	109 (76-168)	104 (67-155)	114(81-180)	109(71-161)	106 (74-134)	98 (62-153)
HDL-C (mg/dl)	55±15	54±17	56±17	55±20	53±14	53±13
LDL-C (mg/dl)	117±32	110±30	117±25	110±33	117±37	111±27
Body Weight (kg)	64.4±13.0	63.5±12.8	63.2±12.2	62.5±13.1	65.6±13.8	64.4±12.7
Body mass index (kg/m^2)	24.5±3.0	24.0±3.0*	24.2±2.6	23.6±3.1	24.9±3.3	24.4±2.8
Waist circumstance (cm)	85.7±9.1	85.2±9.0	84.2±8.9	84.3±9.9	86.5±9.3	85.6±8.7
Visceral fat area (cm^2)	94.5±49.0	88.6±51.1*	96.6±54.5	85.8±54.2	93.6±47.1	90.0±50.5
Subcutaneous fat area (cm^2)	162.0±63.0	157.3±58.5	145.2±48.0	137.4±44.9	170.1±68.5	166.9±65.6

（mean±S.D.） ‡; p<0.001, †; P<0.01, *; P<0.05, [a];vs EPL group p<0.001