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Eplerenone Improves Carotid Intima-Media Thickness (IMT) in Patients with Primary Aldosteronism

Running head: Eplerenone improves IMT in PA

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ABSTRACT

Primary aldosteronism (PA) is associated with a higher rate of cardiovascular events than essential hypertension. Although adrenalectomy has been reported to reduce carotid intima-media thickness (IMT) in patients with PA, the effects of the selective aldosterone blocker, eplerenone, on vascular damage in these patients remains unclear. To evaluate the effects of eplerenone on vascular status in PA patients, we sequentially measured carotid IMT using the computer-based average IMT for accurate and reproducible evaluation in 22 patients with PA, consisting of 8 patients treated by unilateral adrenalectomy and 14 patients treated with eplerenone for 12 months. Patients who underwent adrenalectomy showed significant reductions in aldosterone concentration (from 345 ± 176 pg/mL to 67 ± 34 pg/mL; $P < 0.01$) and IMT (from 0.67 ± 0.07 mm to 0.63 ± 0.09 mm; $P < 0.05$) 6 months after surgery. Patients treated with eplerenone showed significant reductions in IMT from baseline (0.75 ± 0.10 mm) to 6 (0.71 ± 0.11 mm; $P < 0.05$) and 12 (0.65 ± 0.09 mm; $P < 0.01$) months, although plasma aldosterone level increased significantly, from 141 ± 105 pg/mL to 207 ± 98 pg/mL ($P < 0.05$). Eplerenone treatment of patients with PA reduces blood pressure and increases serum potassium level, as well as improving vascular status. Carotid IMT may be a useful marker for evaluating the effectiveness of eplerenone in patients with PA.

INTRODUCTION

Primary aldosteronism (PA) is characterized by excessive secretion of the mineralocorticoid hormone aldosterone and is frequently caused by an aldosterone-secreting adrenocortical adenoma or adrenal hyperplasia [1,2]. PA is the most frequent form of secondary hypertension and has been estimated to affect 5-15% of hypertensive patients [3-5]. Moreover, the prevalence of PA has been found to correlate with the severity of hypertension [6, 7], and patients with PA are at higher risk for cardiovascular events than those with essential hypertension [8-10]. Non-invasive assessment of vascular status revealed that excessive aldosterone caused both structural and functional vascular alterations, characterized by endothelial dysfunction and increases in arterial stiffness and intima-media thickness (IMT) [11-16].

Unilateral adrenalectomy is recommended for patients with unilateral PA. However, medical treatment with a mineralocorticoid receptor (MR) antagonist, spironolactone or eplerenone, has been recommended for patients unable or unwilling to undergo surgery [2]. Although the MR antagonist potency of eplerenone is 60% that of spironolactone, eplerenone is a more selective MR antagonist, without the antiandrogen and progesterone agonist effects of spironolactone [2].

Whereas adrenalectomy has been shown to improve carotid IMT in patients with PA [17], the effects of eplerenone on IMT have not been evaluated.

METHODS

Patients

The study population comprised 22 patients with PA, including 8 (4 males and 4 females; age range 32-76 years) who underwent adrenalectomy and 14 (2 males and 12 females; age range 46-71 years) who were treated with eplerenone. Patients in the latter group were started on 50 mg/day eplerenone; if blood pressure or IMT was not improved, the dose of eplerenone was increased to 100 mg/day.

PA was diagnosed according to the clinical guidelines of the Japan Endocrine Society [18], based on the ratio of plasma aldosterone concentration (PAC; pg/mL) to plasma renin activity (PRA; ng/mL/hr) measured simultaneously in patients with hypertension and/or adrenal lesions. Patients found to have a PAC/PRA ratio (ARR) >200 underwent confirmatory tests for PA, including captopril-challenge, upright furosemide-loading, and saline-loading tests. Patients with positive results on at least 2 of these confirmatory tests were subjected to adrenal venous sampling to determine the laterality of aldosterone hypersecretion.

Measurement of IMT

The IMT of the carotid arteries was measured at a 10-MHz scanning frequency in the B-mode using ultrasonic diagnosis equipment (SDU-2200; Shimadzu Co., Ltd., Kyoto, Japan) that was programmed with the IMT measurement software, Intimascope (Media Cross Co., Ltd., Tokyo, Japan). This software is able to automatically recognize the edges of the internal and external membranes of blood

vessels and measure the distance at a sub-pixel level, using a three-dimensional polynomial measurement formula [19, 20]. Images were obtained in the 20-mm region proximal to the origin of the bulb at the far wall of the right common carotid artery. The average value of 250 computer-based points in the region was calculated and defined as the average IMT.

Biochemical assays

PAC and PRA were measured by radioimmunoassay. Serum concentrations of total cholesterol, triglyceride, fasting blood glucose, and glycosylated hemoglobin (HbA1c) were measured by standard procedures.

Measurement of arterial stiffness

The brachial–ankle pulse wave velocity (baPWV) and ankle–brachial index (ABI) were measured with the subject in a supine position after 15 min of rest using an automatic waveform analyzer, (form PWV/ABI; Omron Colin Co., Ltd., Komaki, Japan). The cardio-ankle vascular index (CAVI), an index reflecting arterial stiffness, was measured automatically using a VaSera VS-1500N instrument (Fukuda Denshi Co. Ltd., Tokyo, Japan).

Follow up

Serum biochemical assays were performed and vascular status evaluated in patients who underwent

adrenalectomy before and 6 months after surgery. In patients treated with eplerenone, serum biochemical assays were performed and vascular status evaluated before and after 1, 3, 6 and 12 months of treatment.

Statistical analyses

Results are presented as mean \pm standard deviation and compared in the 2 groups by Student *t*-tests (for paired sample) or chi-square tests. Multiple regression analysis was performed to evaluate association between the changes in carotid IMT and those in SBP, LDL-cholesterol, plasma aldosterone level and serum potassium level at 6 months after treatment with eplerenone. All statistical analyses were performed using Microsoft Excel 2010 software, with $P < 0.05$ considered statistically significant.

Ethical Consideration

We have performed a follow-up survey for patients with adrenal tumors treated at Kyushu University Hospital [21]. This study protocol was approved by the Kyushu University Institutional Review Board for Clinical Research (protocol number; 26-98).

RESULTS

Of the 22 patients diagnosed with PA, 8 underwent adrenalectomy and 14 were treated with

eplerenone. The baseline clinical characteristics of the 2 groups are shown in Table 1. The adrenalectomy group was significantly younger and had lower systolic blood pressure (SBP) and serum potassium level, and higher plasma aldosterone concentration than the eplerenone group. The lower SBP in the surgical group was likely because of the higher percentage of those prescribed antihypertensive drugs. IMT was significantly higher in the eplerenone than in the adrenalectomy group.

All 8 patients who underwent unilateral adrenalectomy showed significant reductions in plasma aldosterone concentration, from a mean 345 ± 176 pg/mL to 67 ± 34 pg/mL ($P=0.002$) and normalization of serum potassium level from a mean 3.1 ± 0.4 mmol/L to 4.6 ± 0.3 mmol/L ($P<0.001$) (Table 2). Six of these patients discontinued antihypertensive drug therapy, with doses reduced in the other 2. Moreover, IMT was significantly reduced, from a mean 0.67 ± 0.07 mm at baseline to 0.63 ± 0.09 mm 6 months after surgery ($P=0.03$).

Treatment with eplerenone for 6 months resulted in a significant reduction in mean SBP, from 146 ± 15 mmHg to 133 ± 14 mmHg ($P=0.007$), and a significant increase in serum potassium concentration, from 4.0 ± 0.3 mmol/L to 4.2 ± 0.4 mmol/L ($P=0.023$). Although mean plasma aldosterone concentration increased significantly, from 141 ± 105 pg/mL to 207 ± 98 pg/mL ($P=0.03$), mean IMT was significantly reduced, from 0.75 ± 0.10 mm to 0.71 ± 0.11 mm ($P=0.004$).

IMT was sequentially measured after 1, 3, 6 and 12 months of eplerenone treatment. IMT was not altered after 1 month but tended to decrease after 3 months (Fig. 1). Significant improvements in IMT

were observed after 6 and 12 months of treatment with eplerenone.

Changes in IMT observed in a female patient treated with eplerenone are shown in Fig. 2. This patient took eplerenone for 6 months, showing a significant decrease in IMT. However, the treatment with eplerenone was interrupted at 6 months because of low blood pressure. After stopping eplerenone, her IMT returned to baseline level. Her doctor resumed treatment with eplerenone, resulting in an improved IMT after 3 months.

To evaluate whether the effects of eplerenone on IMT are age-dependent, patients were divided into 2 groups, those aged <65 years (7 patients) and those aged ≥ 65 years (7 patients). The younger patients showed a significant decrease in mean IMT after 6 months, with the older group also showing improvement in IMT (Fig. 3), indicated that eplerenone was able to reduce IMT even in elderly patients with PA.

Changes in IMT were not significantly related to those in baPWV, CAVI, ABI, SBP, DBP, LDL-cholesterol and HDL-cholesterol (data not shown). We also performed multiple regression analysis to evaluate association between the changes in carotid IMT and those in SBP, LDL-cholesterol, plasma aldosterone level and serum potassium level at 6 months after treatment with eplerenone. However, no predictors were identified to be associated with the decrease in carotid IMT. SBP, DBP and serum potassium level were improved after 1 month of treatment with eplerenone, thereafter remaining unchanged (Fig. 4).

DISCUSSION

This study showed that the MR antagonist eplerenone was as effective as adrenalectomy in reducing carotid IMT in patients with PA. To our knowledge, this is the first report showing that eplerenone can improve IMT in patients with PA.

Patients with PA have been shown to have more cardiovascular events than those with essential hypertension [8-10]. Previous clinical studies found that patients with PA have more severe vascular disturbances, such as increased IMT [13, 14] and arterial stiffness [11, 14] and reduced endothelial function [15], than those with essential hypertension. An analysis of small resistance arteries showed that total collagen and type III vascular collagen were higher in patients with PA than in patients with essential hypertension [12]. Aldosterone has been shown to affect blood vessels in patients with endothelial dysfunction, increasing collagen deposition, vascular inflammation, and oxidative stress, and promoting tissue fibrosis and activation of the sympathetic nervous system [22-24]. Inhibition of aldosterone activity in blood vessels of patients with PA may therefore halt the progression of aldosterone-induced vascular damage. Current clinical guidelines recommend unilateral adrenalectomy for patients with unilateral PA [2]. Alternatively, patients unable or unwilling to undergo surgery are recommended to receive medical treatment with a mineralocorticoid receptor antagonist, either spironolactone or eplerenone.

Increased IMT in patients with PA has been reported reversible after adrenalectomy [24]. A very recent study revealed that both adrenalectomy and treatment with spironolactone were effective in

reducing common carotid IMT in patients with PA [25]. The findings presented here showed that eplerenone was also effective in improving IMT in patients with PA.

In patients with bilateral PA, both spironolactone and eplerenone were able to reduce blood pressure and correct hypokalemia [26]. Another double-blind randomized study demonstrated that the antihypertensive effect of spironolactone was significantly greater than that of eplerenone in patients with PA, but that the rates of gynecomastia in men and mastodynia in women were higher those treated with spironolactone than with eplerenone [27]. Evaluation of the effects of these MR antagonists in patients with PA should not consider only the normalization of blood pressure and hypokalemia but also the prevention of aldosterone-induced cardiovascular and renal complications [28]. Direct comparisons of the efficacy of these 2 MR antagonists in improving organ damage, including vascular disturbances, are required.

IMT is considered a surrogate marker for atherosclerosis and a strong predictor of future cardiovascular events [29-31]. However, many methods are used to measure IMT. Manual measurements require rigorous quality control and quality assurance, and are also observer dependent [30]. In this study, average IMT of 250 computer-based points in the region was determined using Intimascope software [19]. This method resulted in accurate and reproducible IMTs, as well as allowing direct comparisons of IMT before and after treatment.

As shown in Fig. 4, SBP and DBP were reduced at one month after treatment with eplerenone.

However, there was no significant correlation between changes in IMT and other factors including

SBP or LDL-cholesterol. These results suggest that reduction of carotid IMT by eplerenone is not simply caused by its blood pressure lowering effect but also by inhibition of aldosterone-induced direct vascular effects [22-24].

Although this study focused on improvements in vascular damage in patients with PA, aldosterone has also been found to contribute to the development and progression of cardiovascular and renal damage, even in patients with essential hypertension [32-34]. Aldosterone blockade with spironolactone or eplerenone in patients with heart failure has been associated with marked reductions in morbidity and mortality rates [35, 36]. The beneficial effects of eplerenone on vascular disturbances observed in our study suggest that this agent would be effective, even in patients with atherosclerosis caused by essential hypertension.

The limitations of our study were its small sample size and sex bias in the eplerenone treatment group (12 females and 2 males). Larger-sized, longer-term studies are needed to further evaluate the effects of eplerenone on vascular damage.

In summary, sequential measurement of carotid IMT in patients with PA revealed that both adrenalectomy and eplerenone treatment were able to improve IMT. Treatment with eplerenone may also reduce cardiovascular risks in patients with PA. Moreover, sequential measurements of IMT may enable the determination of the effectiveness of eplerenone treatment in individual patients with PA.

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DISCLOSURE

The authors declared no conflict of interest.

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FIGURE LEGENDS

Fig. 1. Effects of eplerenone on intima-media thickness (IMT) in patients with primary aldosteronism.

The IMT of the carotid arteries was sequentially measured before and after 1, 3, 6 and 12 months of treatment with eplerenone. The graph shows the mean change and standard error in IMT from baseline at each time point. * $P < 0.05$, compared with baseline.

Fig. 2. Changes in intima-media thickness (IMT) in a patient treated with eplerenone requiring treatment interruption.

Fig. 3. Effects of eplerenone on intima-media thickness (IMT) in 7 patients aged <65 years and 7 aged ≥ 65 years. The graph shows mean and standard error in IMT at baseline (open bars) and after 6 months (closed bars) of treatment with eplerenone. $*P<0.05$, compared with baseline.

Fig. 4. Effects of eplerenone on (A) systolic blood pressure (SBP), (B) diastolic blood pressure (DBP) and (C) serum potassium concentration in patients with primary aldosteronism. SBP, DBP and serum potassium were measured before and after 1, 3 and 6 months of treatment with eplerenone. The graph shows mean changes and standard errors from baseline at each time point. $*P<0.05$, compared with baseline.