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A Patient with Bilateral Primary Aldosteronism Refractory to Oral Eplerenone Who Responded to Esaxerenone with Increased Renin Activity

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Patient: Male ,45-year-old
Final Diagnosis: Bilateral primary aldosteronism
Symptoms: Hypertension
Medication: Mineralocorticoid receptor blocker
Clinical Procedure: Segmental adrenal venous sampling and medication
Specialty: Cardiology

Objective: Adverse events of drug therapy

Background: When mineralocorticoid receptor antagonist therapy is initiated for primary aldosteronism, the response of plasma renin activity indicates the level of cardiovascular risk. The purpose of this article was to compare the effect of mineralocorticoid receptor blockers on plasma renin activity levels in a patient with primary aldosteronism.

Case Report: The patient was a 45-year-old male with severe hypertension. Because his aldosterone/renin ratio was high and a saline infusion test was positive, primary aldosteronism was diagnosed. Computed tomography revealed a low-density mass measuring 10 mm in the left adrenal gland. Segmental adrenal vein sampling demonstrated bilateral primary aldosteronism, so pharmacotherapy was started. Before treatment, his plasma renin activity was 0.5 ng/mL/hour. Eplerenone was commenced and the dose was increased to 100 mg/day. However, his plasma renin activity was still 0.8 ng/mL/hour and the maximum dose of eplerenone did not elevate plasma renin activity above 1 ng/mL/hour. Since plasma renin activity remained below 1 ng/mL/hour with mineralocorticoid receptor antagonist therapy, this patient was considered to have a higher cardiovascular risk than patients with essential hypertension. Accordingly, eplerenone was switched to esaxerenone, a new generation mineralocorticoid receptor blocker that became available in May 2019. After switching to esaxerenone (5 mg/day), the patient's plasma renin activity increased to 1.8 ng/mL/hour and subsequently remained at 1 ng/mL/hour or higher.

Conclusions: This is the first case report to present interesting changes of plasma renin activity in a primary aldosteronism patient after switching from eplerenone to esaxerenone. Elevation of plasma renin activity by esaxerenone in our primary aldosteronism patient reflected a mineralocorticoid receptor antagonistic effect that may have alleviated excessive mineralocorticoid receptor activation and volume expansion.

MeSH Keywords: Hyperaldosteronism • Hypertension • Mineralocorticoid Receptor Antagonists • Renin-Angiotensin System

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Background

It has been reported that cardiovascular risk is reduced in primary aldosteronism patients if plasma renin activity (PRA) is 1.0 ng/mL/hour or higher following initiation of treatment with a mineralocorticoid receptor (MR) antagonist [1]. However, if PRA remains below 1.0 ng/mL/hour, MR antagonist therapy is not sufficient to improve cardiometabolic outcomes such as death and atrial fibrillation in primary aldosteronism patients compared to patients with essential hypertension [1]. The objective of this report was to present the different effect of MR blockers on PRA levels in a patient with primary aldosteronism.

Case Report

The patient was a 45-year-old male. Despite oral administration of telmisartan (80 mg/day) and nifedipine (80 mg/day), his blood pressure remained high (≥170/100 mmHg) and he was considered to have severe hypertension. Since secondary hypertension was suspected, screening for endocrine diseases was conducted. Antihypertensive therapy was switched to only calcium channel blockers (amlodipine at 10 mg/day and nifedipine at 80 mg/day). Laboratory tests revealed hypokalemia, with potassium being 3.5 mmol/L. PRA was 0.4 ng/mL/hour and the plasma aldosterone concentration (PAC) was 194 pg/mL. The aldosterone-renin ratio (ARR) was high (484). The blood sampling was always obtained under supine position. Computed tomography (CT) demonstrated a low-density mass measuring 10 mm in the left adrenal gland, and an adrenal adenoma was suspected (Figure 1). A saline infusion test was conducted by administering 2 L of saline over 4 hours. Pre-infusion PRA was 0.5 ng/mL/hour and pre-infusion PAC was 129 pg/mL, while post-infusion PRA was 0.1 ng/mL/hour and post-infusion PAC was 88.3 pg/mL. Because post-infusion PAC was ≥60 pg/mL, the result was positive [2]. Primary aldosteronism was diagnosed. The patient selected curative treatment by partial adrenalectomy, so segmental adrenal vein sampling (S-AVS) was conducted [3]. If excess aldosterone production from the lesion was confirmed by S-AVS, partial adrenalectomy including the tumor could be performed to preserve the function of the residual gland.

Before S-AVS, infusion of synthetic adrenocorticotropic hormone (tetracosactide acetate) was commenced at 0.1 mg/hour. We performed S-AVS under guidance with biplane cine angiography [4]. Then a microcatheter was advanced through the guiding catheter into the segmental adrenal tributary vein. Figure 2 shows images of the adrenal veins obtained in the frontal view and the lateral view. Contrast enhancement of 3 branches was noted, and blood sampling from those branches was possible. Despite searching for the mass previously observed in the left adrenal gland by CT, it was not clearly identified. Blood sampling was performed at 16 sites (Figure 3). Confirmation that the catheter had been inserted into the adrenal vein was based on a plasma cortisol concentration (PCC) (≥200 μg/dL) following adrenocorticotropic hormone (ACTH) stimulation [5], and a PCC >5 times that in the inferior vena cava [6]. Aldosterone hypersecretion was defined as PAC ≥14 000 pg/dL in the adrenal vein following ACTH

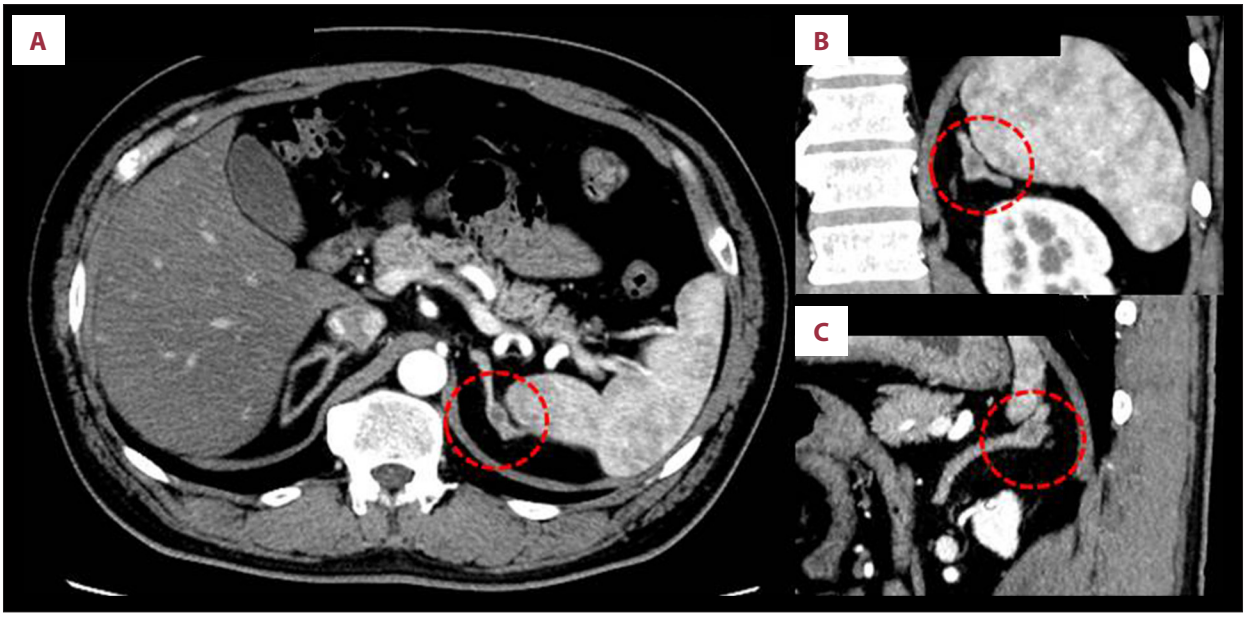

Figure 1. Enhanced computed tomography (CT). Enhanced CT shows a 10 mm mass in the cephalodorsal region of the left adrenal gland. Due to its low density, an adrenal adenoma was suspected. (**A**) Transverse image; (**B**) coronal image, (**C**) saggital image.

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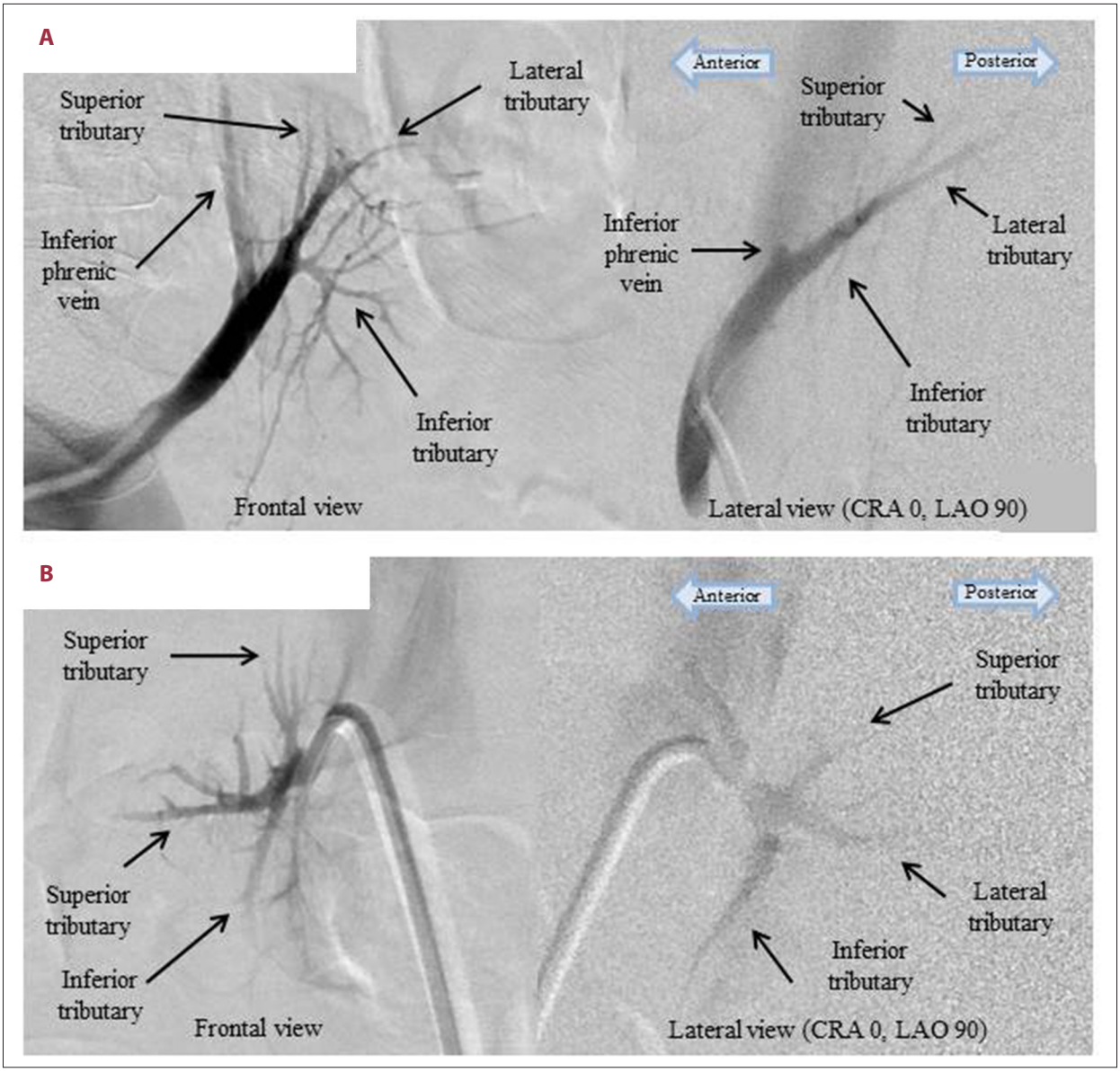

Figure 2. Comparison between the frontal and lateral views during segmental adrenal vein sampling. (**A**) Left adrenal vein in the frontal and lateral views. (**B**) Right adrenal vein in the frontal and lateral views. Retrograde contrast enhancement shows the adrenal veins on both sides. Three tributary adrenal veins are clearly seen on both the left and right sides. The mass observed on computed tomography scans is not seen in the left adrenal gland in the angiogram.

stimulation [7]. Based on these definitions, aldosterone hypersecretion was observed at 4 sites in the left adrenal gland and 4 in the right adrenal gland. In the left adrenal venous system, PAC ≥14 000 pg/mL was detected at the common stem, the superior tributary vein near where the mass was considered to exist, and the lateral tributary vein. And in the right adrenal venous system, PAC ≥14 000 pg/mL was detected in an inferior tributary vein, lateral tributary vein, and the main right adrenal vein, but not the superior tributary vein. We considered that the left adrenal gland might contain both an aldosterone-producing adenoma and microadenoma. And the microadenomas might be scattered through the right adrenal gland. In addition, other possibility was considered that the patient might have bilateral scattered idiopathic hyperaldosteronism and left non-functioning tumor. The diagnosis of bilateral primary aldosteronism was supported by lateralized ratio: 2.0 (39/20) and contralateral ratio: 1.5 (20/13) [8]. Since the patient was shown to have bilateral primary aldosteronism, it was considered that curative surgical treatment would be difficult, and pharmacotherapy was selected instead.

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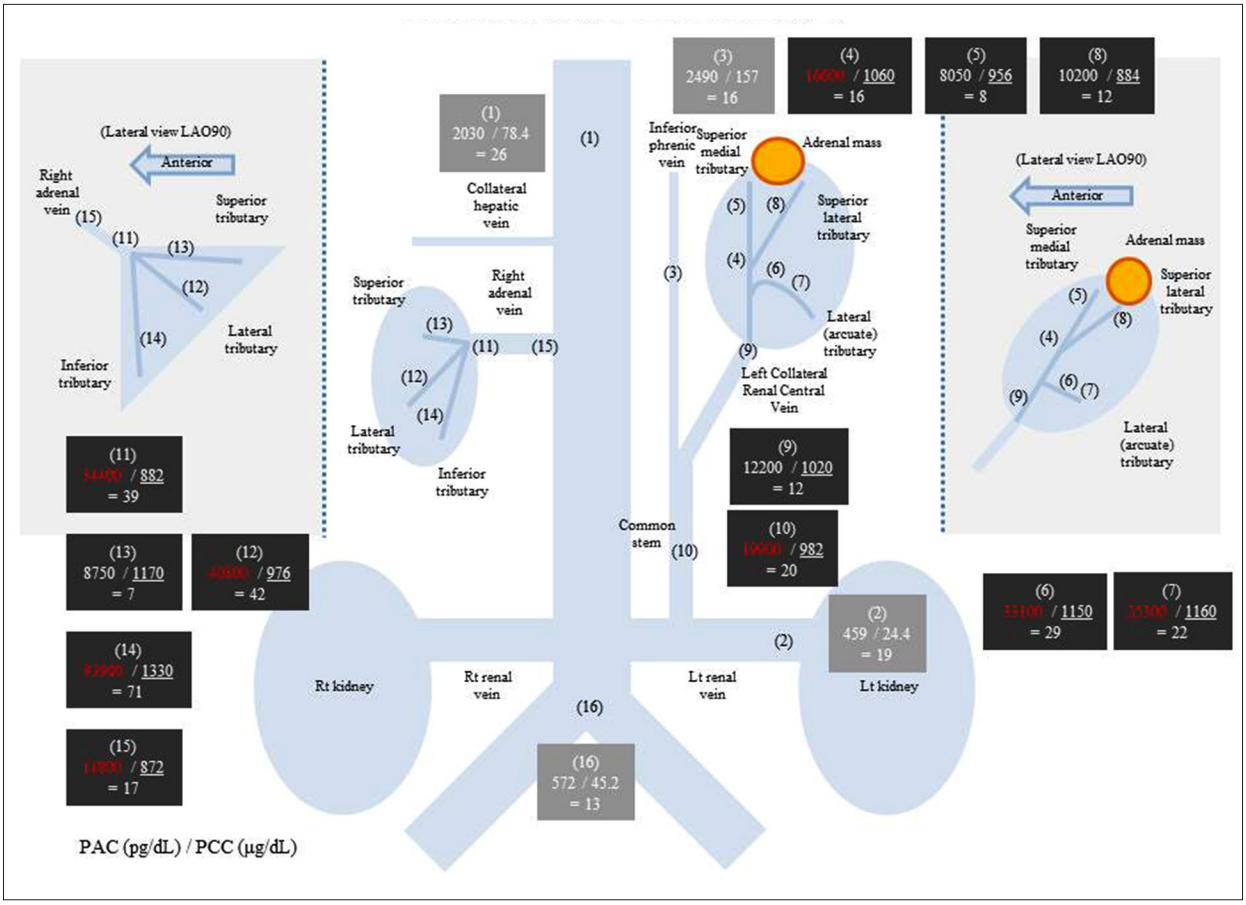

Figure 3. Results of segmental adrenal vein sampling. Blood samples were collected at 16 sites. The site number, PAC, PCC, and PAC/PCC ratio following ACTH stimulation are indicated. If blood samples from the adrenal gland are defined as PCC ≥200 μg/dL with ACTH stimulation, blood from the adrenal gland was sampled at sites 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15. In the left adrenal venous system, PAC was ≥14 000 pg/mL at the junction of the common stem, superior tributary vein, and lateral tributary vein (sites 4, 6, 7, and 10), indicating a diagnosis of aldosterone-producing adenoma and microadenoma. In the right adrenal venous system, PAC was ≥14 000 pg/mL in the inferior tributary vein, lateral tributary vein, and main right adrenal vein, but not the superior tributary vein (sites 11, 12, 14, and 15). It was considered that microadenomas secreting a large amount of aldosterone were present in the right adrenal gland. PAC – plasma aldosterone concentration; PCC – plasma cortisol concentration; ACTH – adrenocorticotropic hormone.

The patient's oral medications and laboratory results are shown in Figure 4. First, amlodipine (10 mg/day) and nifedipine (80 mg/day) were administered. After S-AVS, nifedipine was decreased to 40 mg/day and eplerenone (50 mg/day) was added. Eplerenone was subsequently increased to 100 mg/day, and nifedipine was discontinued. Prior to starting eplerenone, serum potassium, PAC, PRA, and ARR levels were 3.6 mmol/L, 129 pg/mL, 0.5 ng/mL/hour, and 258, respectively. After 2 months of treatment with eplerenone at 100 mg/day, serum potassium, PAC, PRA, and ARR were 3.7 mmol/L, 323 pg/mL, 0.8 ng/mL/hour, and 404, respectively. Thus, the maximum dose of eplerenone did not elevate PRA beyond 1 ng/mL/hour. Because PRA remained below 1 ng/mL/hour during treatment with an MR antagonist, this patient was considered to have a higher cardiovascular risk than patients with essential HT [1]. We wanted to increase the MR antagonist dose further to achieve more potent MR blockade, but the maximum dose of eplerenone allowed under the Japanese health insurance system is 100 mg/day, and use of eplerenone with spironolactone is contraindicated.

Accordingly, we hypothesized that switching from eplerenone to a new generation MR blocker, esaxerenone, might elevate PRA, and we switched from eplerenone (100 mg/day) to esaxerenone (5 mg/day). After 1 month, serum potassium, PAC, PRA, and ARR levels were 3.9 mmol/L, 365 pg/mL, 1.8 ng/mL/hour, and 203, respectively. PRA was maintained at 1 ng/mL/hour or higher by esaxerenone.

The blood pressure changed from 162/104 mmHg to 158/106 mmHg by exchange from eplerenone to esaxerenone. And the body weight increased from 90.6 kg to 93.3 kg during the last 4 months.

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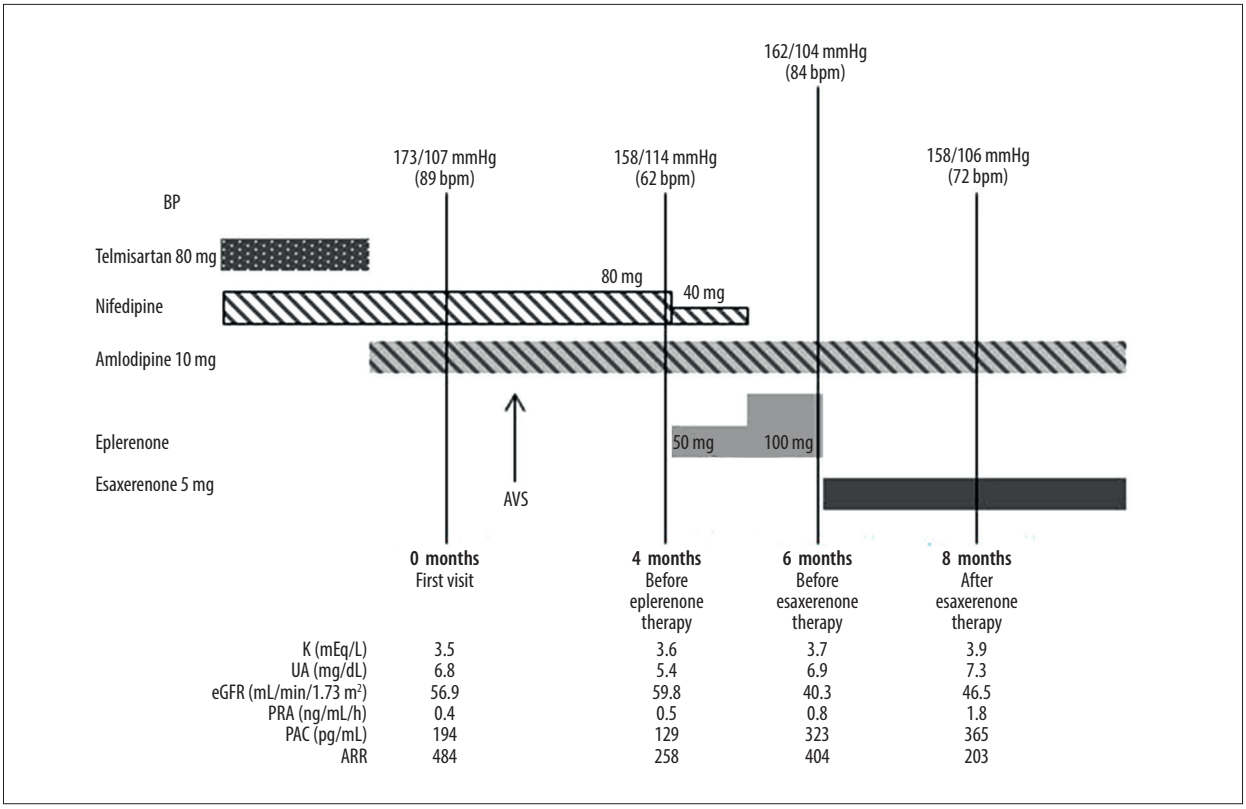

Figure 4. Clinical course. At initial presentation, telmisartan (80 mg/day) and nifedipine (80 mg/day) were commenced. Telmisartan was then switched to amlodipine (10 mg/day). After AVS, nifedipine was reduced to 40 mg/day, and eplerenone (50 mg/day) was added before discharge. Thereafter, eplerenone was increased to 100 mg/day, and nifedipine was discontinued. Prior to starting eplerenone, serum potassium, PAC, PRA, and ARR levels were 3.6 mmol/L, 129 pg/mL, 0.5 ng/mL/hour, and 258, respectively. After 2 months of treatment with eplerenone at 100 mg/day, serum potassium, PAC, PRA, and ARR levels were 3.7 mmol/L, 323 pg/mL, 0.8 ng/mL/hour, and 404, respectively. The maximum dose of eplerenone did not increase PRA above 1 ng/mL/hour. However, 1 month after eplerenone was switched to esaxerenone (5 mg/day), serum potassium, PAC, PRA, and ARR levels were 3.9 mmol/L, 365 pg/mL, 1.8 ng/mL/hour, and 203, respectively. PRA was maintained at 1 ng/mL/hour or higher. AVS – adrenal vein sampling; PAC – plasma aldosterone concentration; ARR – aldosterone-renin ratio.

Discussion

Primary aldosteronism results in excessive MR activation via renin-independent aldosterone secretion and is associated with a higher risk of cardiovascular events independent of the increase in blood pressure [9]. Surgical adrenalectomy (or partial resection) can decrease the cardiovascular risk associated with excessive aldosterone production. However, physicians tend to hesitate to perform AVS and adrenalectomy [4,10,11]. Accordingly, many primary aldosteronism patients receive oral MR antagonist therapy as an alternative to surgery, including some patients who could be cured by surgery.

Our patient case is the first reported case in which switching eplerenone to esaxerenone resulted in elevation of PRA. There have been reports of antihypertensive effects of esaxerenone in essential hypertension [12], but there are few reports in primary aldosteronism. In addition, there are no data from prospective clinical studies to show whether suppressing PRA by dose escalation or switching an MR antagonist reduces the cardiovascular risk. In primary aldosteronism patients whose PRA does not exceed 1 ng/mL/hour despite oral administration of an MR antagonist, using a higher MR antagonist dose or switching to another drug may result in an increase of PRA. However, a prospective study would be needed to determine if cardiovascular risk is also reduced.

In the present patient case, the hypotensive effect was not strong enough; this may have been due to insufficient diet/exercise therapy, including restriction of salt intake, which led to an increase of body weight. Unfortunately, we didn't analyze urinary sodium and creatinine before and after the administration of esaxerenone. It is also possible that decreasing the dosage of calcium antagonists might have been responsible.

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There have been various reports about the influence of other MR antagonists on hypertension. However, esaxerenone only became available in May 2019, and there are few reports on the use of esaxerenone for hypertension or primary aldosteronism. MR antagonists are effective for treatment-resistant hypertension, and adding spironolactone to standard antihypertensive therapy is effective for decreasing the blood pressure [13]. A combination of the angiotensin-converting enzyme (ACE) inhibitor enalapril and eplerenone has been shown to demonstrate a more potent antihypertensive effect compared to monotherapy with either drug, as well as inhibiting left ventricular hypertrophy and decreasing albuminuria. It is anticipated that MR antagonists will exert diverse effects in patients with primary aldosteronism [14]. Our patient was switched from eplerenone, a conventional MR antagonist, to esaxerenone, which binds to and inhibits the MR, and also reduces re-absorption of water from the collecting ducts by blocking re-absorption of sodium to lower the blood pressure [15,16]. *In vitro* studies have compared conventional steroidal MR antagonists (spironolactone and eplerenone) with esaxerenone, showing that it inhibits binding of aldosterone to the MR at a low concentration and has no influence on glucocorticoid receptors, androgen receptors, and progesterone receptors even at high concentrations [16]. In addition, esaxerenone is well absorbed and has a longer half-life than spironolactone or eplerenone [17–19]. Thus, esaxerenone is a selective and strong MR antagonist, which are characteristics that may have contributed to elevation of PRA in our patient. Esaxerenone inhibited the elevation of blood pressure in a dose-dependent manner in rats with salt-sensitive hypertension [20]. An increase of left ventricular mass is dose-dependently inhibited by spironolactone, eplerenone, and esaxerenone, while esaxerenone dose-dependently decreases the blood level of brain natriuretic peptide [20]. Brain natriuretic peptide was not measured in our primary aldosteronism patient, but we considered that he had volume expansion. An increase of PRA by esaxerenone may have reduced volume overload [21]. In general, volume-overload hypertension is common, and esaxerenone is expected to be effective for patients with treatment-resistant hypertension.

In patients with primary aldosteronism, it was reported that blood pressure reduction showed no difference between spironolactone and eplerenone [22]. In the future, the antihypertensive effect of medical treatment for primary aldosteronism should be compared between conventional therapy such as spironolactone or eplerenone, and esaxerenone, the novel drug used in our patient.

Conclusions

The effects of esaxerenone on primary aldosteronism are interesting, and there have been no previous reports about the changes of PRA when eplerenone was switched to esaxerenone. Based on the results in this case, if the maximum dose of spironolactone or eplerenone does not increase PRA and control aldosterone excess, switching to esaxerenone may bring about a response in some cases. A prospective blinded study of esaxerenone for primary aldosteronism may be warranted.

Conflict of interest

The authors have received honoraria from Otsuka Holdings and Daiichi Sankyo Co., Ltd. and grant support for a clinical trial of ultrasonic renal denervation for treatment-resistant hypertension.

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