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Aliskiren Reduces Morning Blood Pressure in Hypertensive Patients with Diabetic Nephropathy on Hemodialysis

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Abstract

Our previous study indicated that the exchange from an angiotensin receptor blocker (ARB) to aliskiren reduced morning blood pressure and albuminuria in hypertensive patients with diabetic nephropathy. We extended the above study and assessed the effects of exchanging from an ARB to aliskiren on home blood pressure in hypertensive patients with diabetic nephropathy on chronic hemodialysis. The patients who were persistently hypertensive despite antihypertensive therapy, including ARB, were considered as candidates for the exchange from the ARB to aliskiren. Patients' age and durations of diabetes and hemodialysis were averaged as 62 ± 9 years old, 15 ± 8 and 7 ± 3 years, respectively. Aliskiren decreased morning systolic blood pressure (149 ± 14 to 144 ± 13 mm Hg, $n = 30$, $P < .01$) and plasma renin activity (3.5 ± 1.1 to 1.2 ± 0.6 ng/mL/h, $P < .01$) without changes in serum potassium. Aliskiren also reduced interdialytic weight gain (2.7 ± 0.6 to 2.5 ± 0.5 kg/interval, $P < .05$) and attenuated the magnitude of intradialytic declines in systolic (−20 ± 11 to −17 ± 10 mm Hg, $P < .05$) and diastolic blood pressure (−9 ± 6 to −5 ± 5 mm Hg, $P < .01$). The exchange from an ARB to aliskiren is safe and useful to control home blood pressure in hypertensive hemodialysis patients with diabetic nephropathy. Aliskiren reduced both intradialytic blood pressure drops and interdialytic weight gain in patients with DN.

Keywords: diabetes, home blood pressure, nitric oxide, thirst, renin–angiotensin system

INTRODUCTION

Diabetic retinopathy and nephropathy (DN) is a leading cause of blindness and renal replacement therapy in adults (1). The increasing prevalence of diabetes and its complication is a socioeconomical problem all over the world. The prognosis of hemodialysis patients from DN was worse than that from the other underlying renal diseases (2). Many diabetic patients had already showed significant cardiovascular diseases when they initiated hemodialysis (3,4). Control of glycemia and blood pressure seem crucial for preventing complication in hemodialysis patients with DN. However, most patients with DN manifested autonomic neuropathy (5). Thus, the ability for appropriate vasoconstriction that was required to maintain blood pressure during ultrafiltration was diminished in hemodialysis patients with DN (6). Furthermore, interdialytic weight gain was large in patients with DN, partly because of thirst from hyperglycemia. Advanced atherosclerosis in diabetes may elevate blood pressure variability (7). These make fine control of blood pressure difficult for hemodialysis patients with DN.

We recently demonstrated that in hypertensive patients with DN not yet on hemodialysis, aliskiren reduced albuminuria and morning blood pressure without altering eGFR (8). Morishita et al. depicted that aliskiren manifested antihypertensive effects in hemodialysis patients for a long term with reductions of cardiovascular biomarkers, including BNP and hsCRP (9,10). However, to our knowledge, the effects of aliskiren on home blood pressure have not been assessed in hemodialysis patients with DN. In the present study, we extended our previous study and examined the effects of the exchange from an angiotensin receptor blocker (ARB) to aliskiren in hypertensive patients with DN on hemodialysis. Our data indicated that aliskiren reduced morning blood pressure without altering serum potassium in hemodialysis patients with DN.

METHODS

Retrospective studies were performed to characterize the effects of a direct renin inhibitor, aliskiren, on 30 hemodialysis patients with DN. Hypertensive patients with DN

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who regularly visited our office at the Saitama Medical University were listed for the study when they accepted an informed consent for collection of clinical data. Hypertension was defined as systolic blood pressure more than 140 mm Hg, diastolic blood pressure exceeding 90 mm Hg, and/or administration of antihypertensive drugs. DN was diagnosed by medical history as underlying renal diseases. According to the guideline from the Japanese Society of Hypertension (11), the patients persistently hypertensive despite treatment with antihypertensives including ARB were considered as candidates for the exchange from the ARB to aliskiren. Initially, aliskiren was started at 150 mg/day once in the morning and increased up to 300 mg/day once in the morning when the brachial blood pressure was over 130/80 mm Hg. The usage of the other antihypertensive drugs was permitted. The data were analyzed in the patients whose doses of all other drugs remained unchanged throughout the observation period (12).

The following patients were excluded; patients treated with corticosteroid or immunosuppressant, patients with myocardial infarction or stroke including transient ischemic attack within 6 months, patients with unstable angina pectoris, patients with valvular heart diseases or persistent arrhythmia, patients with aortic aneurysm or aortic replacement with artificial vessels, patients with heart failure or left ventricular ejection fraction of 40% or less, or with a disorder that had been treated by physician's opinion. The patients were educated to take 6 g salt, 1 g/kg protein, and 35 Cal/kg daily with restriction of potassium and phosphate (13–15).

Office blood pressure was measured on the arm, in which a shunt has been formed, at the time of HD using an oscillometric device equipped within hemodialysis machine. All patients received hemodialysis for 4 hour/session and 3 times/week, and office blood pressures were measured in lying position. Edema-free dry weight was carefully determined by taking the blood pressure cardio-thorax ratio into consideration. Echocardiography and natriuretic peptides were assessed only if necessary. After overnight fast, the blood samples were taken before the exchange and 6 months later (16).

After being shown how to measure their own blood pressure, the patients were instructed to record their blood pressure at home in the sitting position (17). Blood pressure was measured twice a day; once in the morning before breakfast after voiding within one hour of awaking and once in the evening within 1 hour before going to a bed. Each blood pressure was measured after 3–5 minutes rest in sitting position. Home blood pressure was measured using semiautomatic devices, which operate on the cuff-oscillometric principle. All devices were calibrated with sphygmomanometer at the time of instruction, and the devices showing blood pressure difference less than 5 mm Hg were applied for the study. Weekly averaged blood pressure was used to assess the divergence of blood pressure by medication.

Table 1. Patient backgrounds at study entry

Age (y/o)	62 ± 9	
Sex (male/female)	18/12	
Body weight (kg)	67 ± 11	
Height (cm)	163 ± 12	
Hemoglobin A1c (%)	6.1 ± 1.4	
Duration of diabetes (y)	15 ± 8	
Duration of hemodialysis (y)	7 ± 3	
Serum creatinine (mg/dL)	10 ± 2	
ARB used previously	Number of patients	Mean dose (mg)
Losartan	4	88 ± 25
Candesartan	5	10 ± 2
Irbesartan	3	83 ± 29
Olmesartan	6	37 ± 8
Valsartan	5	96 ± 36
Telmisartan	7	74 ± 15

Abbreviation: ARB – angiotensin receptor blocker.

Data were expressed as means ± SD. Student *t* test and Fisher exact test were used. $P < .05$ was considered statistically significant.

RESULTS

The patient background is detailed in Table 1. We did not restrict the patients regarding ARB usage, and then the patients treated with various ARBs were enrolled. At the end of the study, the doses of aliskiren were averaged to 225 ± 76 mg/day. Predialysis serum creatinine reached 10 mg/dL, and only three patients voided urine once or twice a day. Although the exchange to aliskiren might enhance diuresis, considerable increases in urination were not observed. Exchanging to aliskiren did not alter either body (dry) weight (Figure 1) or hemoglobin A1c (to 6.2 ± 1.5%). Thus, glycemic control was maintained throughout the study.

The exchange of renin–angiotensin system (RAS) inhibitor resulted in improvement in home blood pressure (Figure 2). Morning systolic pressure was reduced by the exchange to aliskiren (149 ± 14 to 144 ± 13 mm Hg, $P < .01$). Indeed, aliskiren decreased plasma renin activity (3.5 ± 1.1 to 1.2 ± 0.6 ng/mL/h, $P < .01$) significantly (Figure 3). However, significant changes were seen neither in morning diastolic blood pressure (74 ± 7 to 73 ± 6 mm Hg) nor in evening blood pressure (132 ± 11/71 ± 7 to 131 ± 10/71 ± 7 mm Hg) by altering ARB to aliskiren.

As shown in Figure 4, the exchange to aliskiren failed to alter predialysis office blood pressure (154 ± 14/78 ± 8 to 153 ± 13/78 ± 8 mm Hg). Regardless of the RAS inhibitor used, blood pressures were significantly decreased until the end of hemodialysis (ARB: to 134 ± 11/70 ± 8 mm Hg; aliskiren: to 136 ± 10/73 ± 7 mm Hg, $P < .01$ for all). However, the magnitude of drops in systolic (−20 ± 11 to −17 ± 10 mm Hg,

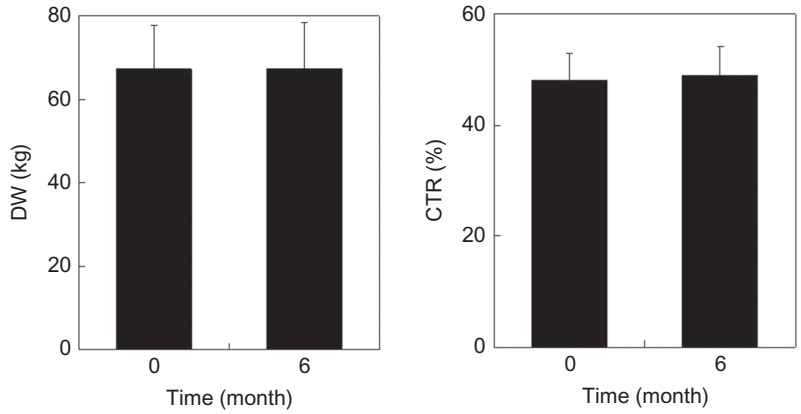

Figure 1. Null influences of the exchanging from angiotensin receptor blocker to aliskiren on dry weight (DW) and cardiothoracic ratio (CTR).

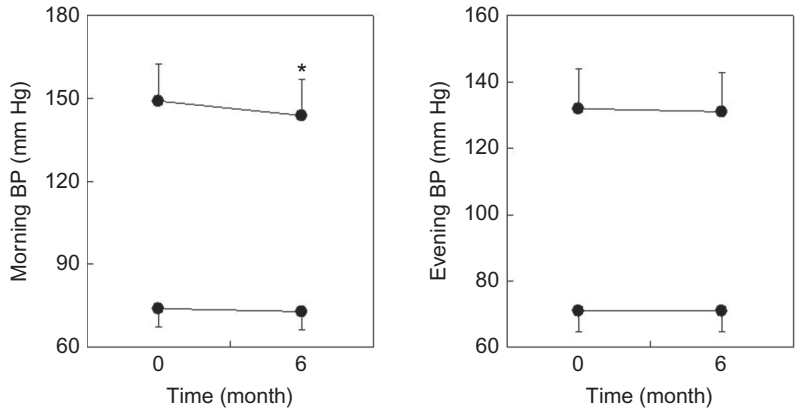

Figure 2. The effects of exchanging from angiotensin receptor blocker to aliskiren on morning and evening blood pressure (BP).
Note: *Describes significant difference from basal value.

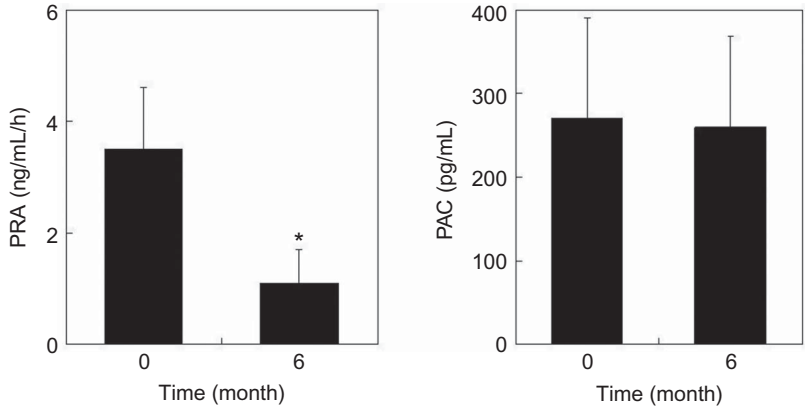

Figure 3. The influences of the exchange from angiotensin receptor blocker to aliskiren on plasma renin activity (PRA) and plasma aldosterone concentration (PAC).
Note: *Indicates significant difference from basal value.

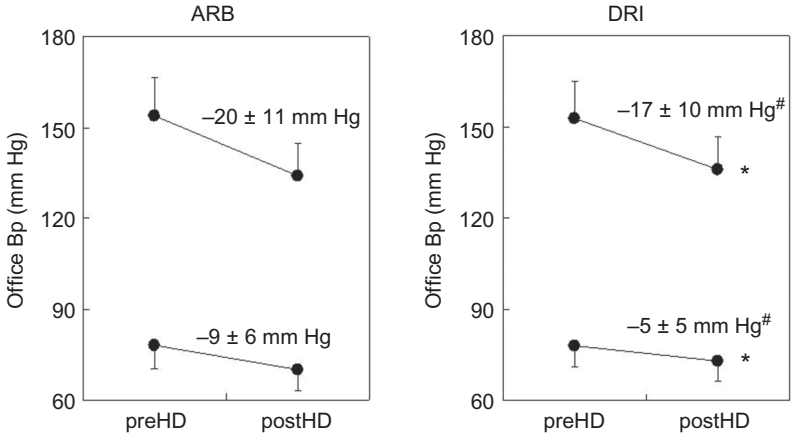

Figure 4. The effects of the exchange from angiotensin receptor blocker (ARB) to aliskiren (DRI) on intradialytic blood pressure (BP). preHD and postHD mean before and after hemodialysis.
Notes: *Depicts significant difference from respective basal value. #Shows significant difference from the value in ARB period.

$P < .05$) and diastolic blood pressure (-9 ± 6 to -5 ± 5 mm Hg, $P < .01$) during hemodialysis was attenuated when the patients were taking aliskiren, compared to those on an ARB.

Of interest, exchanging from ARB to aliskiren slightly but considerably decreased interdialytic body weight gain (Figure 5: 2.7 ± 0.6 to 2.5 ± 0.5 kg/interval, $P < .05$). However, dry weight (to 68 ± 11 kg) and cardiothoratic ratio (48 ± 5 to $49 \pm 5\%$) did not differ between ARB and aliskiren treatments (Figure 1), suggesting that volume status was similar throughout the observation period. Plasma aldosterone concentration (272 ± 121 to 260 ± 109 pg/mL) was not reduced by the exchange to aliskiren (Figure 3). Furthermore, aliskiren did not alter serum potassium (5.3 ± 0.5 to 5.4 ± 0.5 mEq/L), as shown in Figure 5.

DISCUSSION

In 2011, the number of patients on renal replacement therapy exceeded 300 000 in Japan, largely due to increases in DN (18). Most patients with DN are hypertensive because of fluid retention, the activation of RAS, and decreased nitric oxide bioavailability (19,20). Blood pressure variability is also substantial in DN (7). Furthermore, high variability of blood pressure as well as hypertension itself is a risk for cardiovascular diseases and events. Sander et al. reported that diurnal systolic blood pressure variability is the strongest predictor of early carotid atherosclerosis (21). Collectively, not only lowering absolute value of blood pressure but also reducing blood pressure variability appears important for the patients with DN to prevent cardiovascular death.

Our recent study demonstrated that exchanging from an ARB to aliskiren decreased both morning blood pressure and albuminuria (8). Aliskiren has a very long half-life over 40 hours, possessing long-acting antihypertensive effects (22). Indeed, Palatini et al. described that the magnitude of worsening blood pressure control by a missed dose of aliskiren was less than that of irbesartan (23). Our present data constitute new demonstrations that aliskiren reduced morning blood pressure in hemodialysis patients with DN compared to ARBs. We enrolled DN patients who had taken various ARBs. It was reported that irbesartan had longer half-life than the

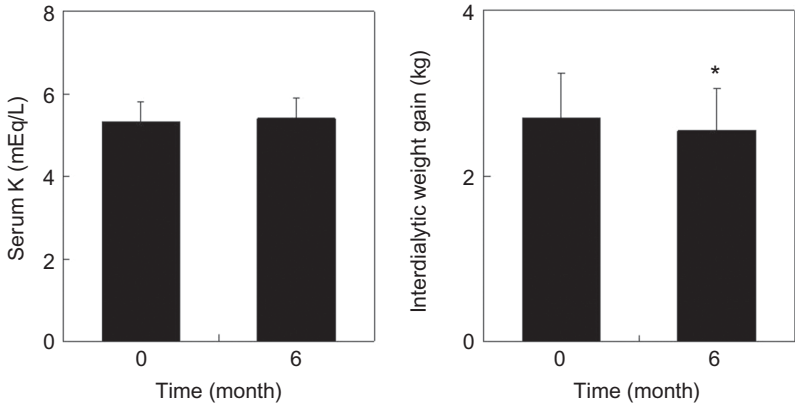

Figure 5. The impacts of exchanging from angiotensin receptor blocker to aliskiren on serum potassium (K) and interdialytic weight gain.
Note: *Describes significant difference from basal value.

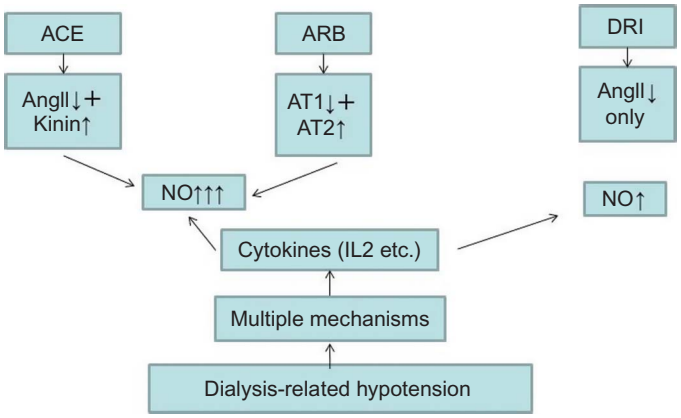

Figure 6. Possible mechanisms that allow aliskiren to decrease the magnitude of intradialytic blood pressure drops.

other ARBs in humans (24). However, in the present study, the degree of reductions in morning blood pressure by the exchange was similar when that was compared among original ARBs. The differing doses of ARBs may account for the discrepancy. The present results suggest that aliskiren induces long-lasting RAS inhibition, being useful to obtain fair blood pressure control over 24 hours in hemodialysis patients with DN.

In 2011, the American Heart Association warned the combined usage of aliskiren with the other RAS inhibitors because significant increases in incidence of hyperkalemia, nonfatal stroke, renal complication, and hypotension in hypertensive patients with DN (25). Our recent study demonstrated that the exchange from an ARB to aliskiren did not alter serum potassium or eGFR in patients with DN not on hemodialysis (8). The present study extended the above and indicated that the exchange from an ARB to alisikren did not elevate serum potassium in hemodialysis patients with DN. In the present study, plasma aldosterone was not decreased by aliskiren despite the reduction of renin activity and morning blood pressure. In addition to RAS, extracellular potassium itself drives aldosterone release from adrenal gland (26). We also recommended the restriction of potassium intake for all hemodialysis patients. Taken together, our data suggest the safety in using aliskiren as a RAS inhibitor in hemodialysis patients with DN.

Surprisingly, the present results indicate that the exchange to aliskiren slightly but significantly reduced both interdialytic weight gain and intradialytic blood pressure drops, suggesting that aliskiren may be beneficial for hemodialysis patients with DN to survive. Although the reasons to decline interdialytic weight gain were unclear from the present data, the possibilities merit comments; one is central and the other is peripheral mechanism. Angiotensin II is a powerful stimulus for thirst as the central mechanism (27). As evident in home blood pressure, aliskiren would induce persistent decrease in angiotensin II, efficiently suppressing drinking behavior in hemodialysis patients with DN. Decreasing interdialytic weight gain could account for attenuating intradialytic blood pressure drops (6). Peripheral mechanism may involve nitric oxide (Figure 6). Dialysis hypotension is mediated by various mechanisms, including the lack in appropriate vasoconstriction and reduced plasma refilling (6,28). Contact with dialysis membrane let blood release various cytokines such as TNF and interleukin, which increase nitric oxide. ARB inhibits AT1 receptors, and the remaining angiotensin II should stimulate AT2 receptors to release nitric oxide. ACEI also inhibits kininase, increasing bradykinin, and nitric oxide. However, aliskiren reduces angiotensin II without modulating nitric oxide, to possibly avoid exposing to too much nitric oxide during hemodialysis.

This study has limitations. First, the study has only one arm, lacking in randomized time control. Blood pressure shows seasonal variations in hemodialysis patients (29). Please note that the patients who started aliskiren in winter were not enrolled. Second, the observation period was relatively short. To assess the effects of aliskiren on cardiovascular events or survival, the study with longer period would be required. Third, great caution is required to extend the present results to non-diabetic hemodialysis patients. Although potential mechanisms may be common for all hemodialysis patients, further studies on hemodialysis patients from non-DN origins are required to assess this issue.

In summary, aliskiren safely decreased morning blood pressure in hemodialysis patients with DN, further reducing interdialytic weight gain and intradialytic blood pressure drops.

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***Declaration of interest*:** The authors report no conflicts of interest regarding this manuscript. The authors alone are responsible for the content and writing of the paper.

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