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Original article

Successful Treatment of Hypertension in Anuric Hemodialysis Patients with a Direct Renin Inhibitor, Aliskiren

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Abstract

Objective: A direct renin-inhibitor (DRI), aliskiren, was administered to anuric patients to investigate whether it can be a new optional therapy against hypertension in hemodialysis (HD) patients.
Patients: The patients that received aliskiren comprised 8 males and 2 females with a mean ± SD age of 63 ± 8 years (43-72 years). They were exposed to dialysis therapy for 118 ± 73 months (8-251 months), with diabetes mellitus in 4 cases, chronic glomerulonephritis in 4 cases, and other diagnoses in 2 cases.
Methods: After the plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were measured before an HD session, aliskiren, 150 mg as an initial dose, was administered to the patients. PRA and PAC were also examined a week after initiating aliskiren. The blood pressure (BP) levels at the start of each HD session for a period of 2 weeks (6 HD sessions) were compared between before and after administration of aliskiren. The change of doses in other antihypertensive agents was also counted.
Results: The averaged reduction of mean blood pressure was 4 ± 5 mmHg, and doses of antihypertensives other than aliskiren were reduced in 4 patients. Of the examined parameters, only the reduction rate of PRA x PAC seemed correlated with the BP lowering effect of aliskiren, which was calculated as the sum of the mean BP reduction in mmHg and drug reduction with 1 tablet (capsule)/day considered to be 10 mmHg.
Conclusion: A DRI, aliskiren, was effective even in anuric dialysis patients, and monitoring of PRA and PAC was valuable for selecting cases responsive to aliskiren.

Key words: prorenin, vascular RAS, antihypertensive drugs

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Introduction

A direct renin inhibitor (DRI), aliskiren, was developed by structure-based design as the first inhibitor of the catalytic effect of renin a decade ago[1]. Aliskiren features only an antihypertensive agent suppressing plasma renin activity[2], a blood pressure lowering effect unrestricted to hyperreninemic condition[3, 4], renoprotection[2, 5, 6] and few adverse reactions[7, 8] besides a report of acute renal failure[9].

Hypertension is one of the serious problems in dialysis patients, and lowering blood pressure (BP) results in improved patient survival[10, 11]. However, appropriate control of blood pressure is still difficult in a certain population of dialysis patients, because a variety of factors are involved in elevating BP. Aliskiren might have a limited effect on BP in anuric patients, since urinary sodium excretion and subsequent regulation of blood pressure is diminished in such a population. However, renal blood flow and renin production are preserved even in anuric patients. Moreover, the extrarenal effect of the renin-angiotensin-aldosterone system (RAS) on BP was recently addressed[12]. Therefore, it is noteworthy to evaluate the effect of aliskiren on BP in dialysis patients not only for exploring a new class of antihypertensive agents in this field, but for clarifying the role of the RAS in developing HT in anuric patients.

Patients and Methods

In maintenance hemodialysis patients of Toride Kyodo General Hospital, ten hypertensive patients with a urine volume of less than 100 ml/day, and undergoing thrice a week hemodialysis therapy were enrolled in this study after their informed consent was verbally obtained with respect to administration of aliskiren, the purpose and the results of examinations and the disclosure of obtained data that could not specify the individual private information. As Table 1 shows, the patients were 8 males and 2 females who were 63 ± 8 (43-72) years old. The period of dialysis in the patients was 118 ± 73 (28-251) months. The causes of renal failure were CGN in 4 cases, diabetes mellitus in 4 cases, reflux nephropathy in 1 case and renal failure with acute-onset and unknown etiology in 1 case. BP of the patients was mea-

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Table 1 Patient characteristics

Case	Sex	Age	Dialysis period (month)	Disease	BP		
					Systolic	Diastolic	Mean
1	F	66	171	CGN	186	74	111
2	M	69	132	ARF by unknown cause	183	88	120
3	F	67	144	CGN	188	96	126
4	M	56	28	DM	176	94	121
5	M	62	32	DM	182	101	128
6	M	43	251	Reflux Nephropathy	173	102	126
7	M	62	156	CGN	172	99	123
8	M	61	147	CGN	163	99	121
9	M	72	32	DM	160	76	104
10	M	67	83	DM	169	94	119
Total	M:F 8:2	63 ± 8	118 ± 73		175 ± 10	92 ± 10	120 ± 7

Table 2 PRA, PAC and antihypertensive drugs before aliskiren therapy

Case	PRA (ng/mL/hour)	PAC (pg/mL)	Drugs
1	8.1	354	3: CaB,α_1B, ARB
2	0.2	54.8	7: CaB, α_1B, α_2S, βB, ACEI, ARB × 2
3	0.8	243	2: CaB, ARB
4	5.3	52.2	4: CaB, α_1B, ACEI, ARB
5	2.6	134	2: CaB, α_1B
6	9.6	51.3	2: CaB, ARB
7	4.2	94.9	4: CaB × 2, βB, ARB
8	0.7	154	0
9	8.9	77.5	3: CaB × 2, ARB
10	4.7	61.8	3: CaB × 2, ARB
Total	4.5 ± 3.5	127.8 ± 100.0	3 ± 2

CaB: calcium blockers, α_1B: α1-blockers, ARB: angiotensin-II receptor blockers, ACEI: angiotensin converting enzyme inhibitors, βB: β-blockers. The actual prescribed drugs were nifedipine (N), doxazosin (D) and telmisartan (T) in case 1; N, D, guanabenz, atenolol, enalapril, olmesartan (O) and valsaratan (V) in case 2; N and T in case 3; N, D, T and V in case 4; amlodipine (A) and D in case 5; N and O in case 6; manidipine, N, celiprolol and O in case 7; azelnidipine, N and candesartan in case 9; and cilnidipine, A and T in case 10.

sured in the supine position on a bed before each dialysis session. Before initiating aliskiren, the patients' averaged systolic, diastolic, and mean BPs taken at the start of each HD sessions for 2 weeks (6 sessions) were 175 ± 10, 92 ± 10 and 120 ± 7 mmHg, respectively. They had already received 3 ± 2 (0 - 7) antihypertensive drugs before aliskiren treatment (Table 2). Blood samples for measuring serum potassium (K), plasma renin activity (PRA), plasma aldosterone concentration (PAC) and plasma prorenin were obtained through the blood accesses for hemodialysis 30 minutes after beginning bed rest and just before each dialysis session. PRA was measured by the established enzyme activity assay using angiotensinogen as an enzyme substrate[13]. PAC was measured by a competitive radioimmunoassay[14]. Plasma prorenin was directly measured using a double-antibodies sandwich assay (AlphaLISA Renin/Prorenin Kit, PerkinElmer Inc., Waltham, MA, U.S.A.). The principles of the assay were as described in a previous report[15], although a chemiluminescent measurement was used instead of a radiometric method.

Aliskiren, 150 mg/day as an initial dose, was orally administered to the patients after every evening meal to avoid hypotension during HD sessions and to improve adherence to the drug by the simple prescription style. Their BP was monitored during HD sessions as a routine clinical procedure. The averaged systolic, diastolic, and mean BPs at the beginning of the HD sessions for 2 weeks after aliskiren therapy were compared with the BPs before initiating aliskiren. Two weeks are supposed to be a sufficient period for aliskiren to reach to its plateau levels. In 4 patients, a few

Table 3 Effect of aliskiren on BP

Case	ΔsBP	ΔdBP	ΔmBP	Score for BP lowering effect	Drugs
1	−14	−13	−13	13	0
2	+1	−2	−1	1	0
3	−1	+3.5	+2	15	−1.7: D/C 20 mg (2 C) of nifedipine and 80 mg (2 T) of telmisartan on the day of HD
4	−1	−3.5	−3	27	−2.4: D/C 20 mg (1 T) of nifedipine, 5 mg (1 T) of amlodipine and 80 mg (2 T) of valsartan on the day of HD
5	−9	−12	−11	21	−1: D/C 1 mg (1T) of doxazosin
6	−2	−4	−3	3	0
7	+4	+4	+4	6	−1: D/C 10 mg (1T) of manidipine
8	−8	−4	−5	5	0
9	−8	−4	−5	5	0
10	−2	−10	−7	7	0
Total	−4	−4	−4	10	−0.6

ΔsBP, ΔdBP, and ΔmBP indicate the differences of after and before administration of aliskiren for the systolic, diastolic, and mean blood pressure, respectively. D/C is an abbreviation for discontinuation. The score for the BP lowering effect was calculated as the sum of the reduced mean blood pressure in mmHg and discontinued antihypertensive drugs, where 1 tablet (T) or capsule (C) per day was assumed to be equal to a 10-mmHg reduction in blood pressure, as in (2 + 2) × 3 / 7 = 1.7 in case 3. Since the blood pressure was rather elevated (+ 2 mmHg), the score for the BP lowering effect was calculated as follows, 1.7 × 10 − 2 = 15 (see the formula in the text).

antihypertensive drugs other than aliskiren were discontinued within 2 weeks, because of hypotension that caused difficulties in continuing HD therapy. To compare the effect of aliskiren on BP in these four patients with the other six patients, the score for the BP lowering effect was counted, as described below.

The score for the BP lowering effect = (averaged lowering of the mean BP in mmHg for two weeks) + (10 mmHg x reduced daily tablets or capsules of antihypertensive drugs) after aliskiren treatment.

For instance, if the averaged lowering of the mean BP for two weeks by the administration of aliskiren is 10 mmHg and one tablet of an antihypertensive drug can be discontinued during that period, the score for the BP lowering effect will be calculated as follows,

$10 + 1 \times 10 = 20$.

The data are shown as the mean ± SD, unless otherwise specified. The paired *t*-test and regression analysis were performed using Excel 2007 (Microsoft Inc., Redmond, WA, U.S.A.).

Results

PRA and PAC before aliskiren treatment in each patient are described in Table 2. Administration of aliskiren to the ten anuric HD patients significantly suppressed the systolic, mean and diastolic BP before HD sessions (Figure 1), and reduced the administered doses of antihypertensives in 4 patients. The averaged BPs before/after aliskiren treatment were 175 ± 10 / 171 ± 11 mmHg for systolic, 120 ± 7 / 116 ± 10 mmHg for the mean and 93 ± 10 / 88 ± 13 mmHg for diastolic. In 6 patients without changing antihypertensives, these BPs were 172 ± 11 / 167 ± 12 mmHg for systolic, 117 ± 8 / 111 ± 10 mmHg for the mean and 89 ± 12 / 83 ± 14 mmHg for diastolic. These BP changes were also significant ($p < 0.05$). The total effect of aliskiren was estimated by calcu-

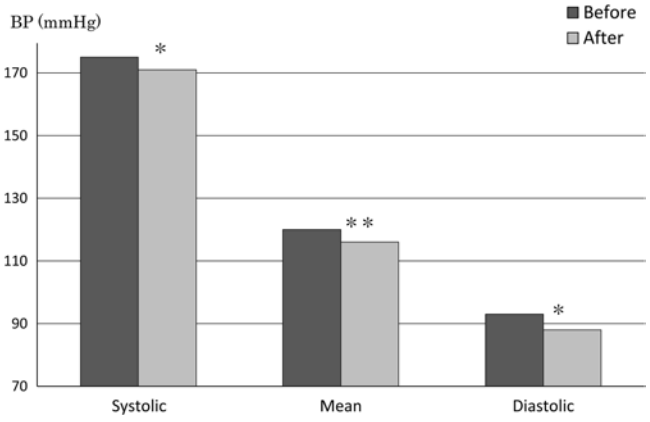

Figure 1 Effect of aliskiren on BP.
Systolic, mean, and diastolic BP were averaged for before and after administration of aliskiren for 2 weeks (6 measurements before HD sessions). *: $p < 0.05$. **: $p < 0.01$.

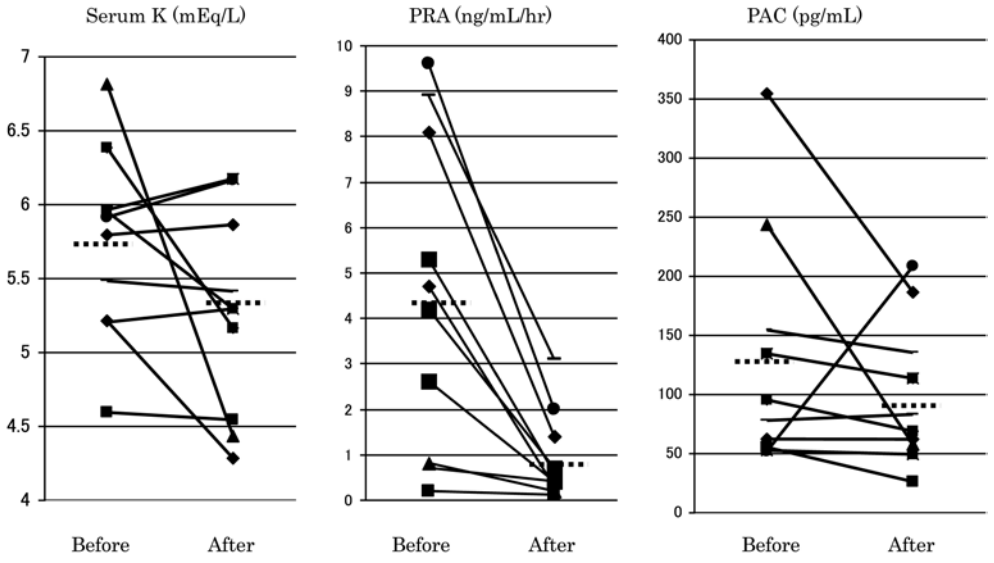

Figure 2 Changes of serum K, PRA and PAC after administration of aliskiren.
Only PRA was significantly reduced. PAC was rather elevated in 2 patients.

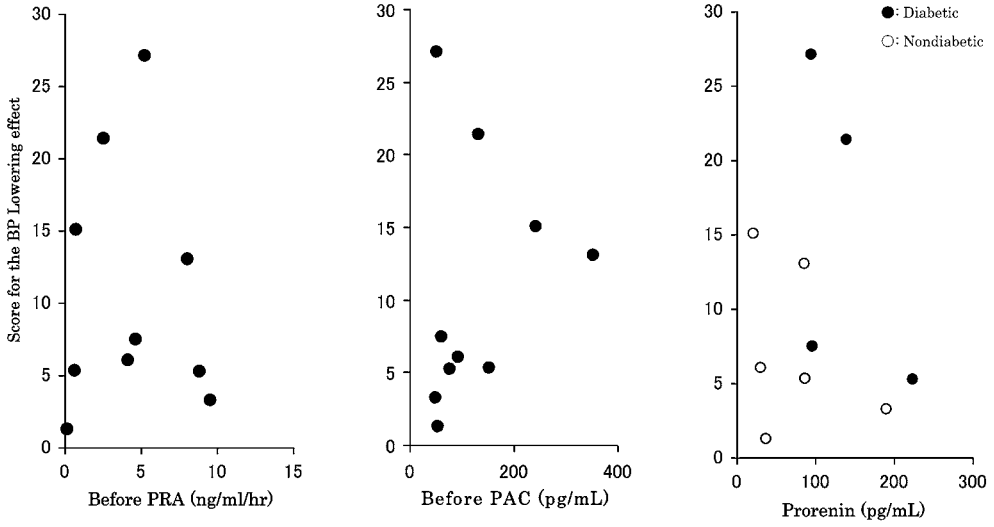

Figure 3 PRA, PAC before treatment and prorenin after treatment and their correlation with the score for the BP lowering effect.
These values were not significantly correlated. The correlation coefficients of the score and PRA, PAC and prorenin were 0.06, 0.21 and 0.08, respectively.

lating the scores for the BP lowering effect and summarized in Table 2.

As Figure 2 shows, serum K and PAC were not significantly changed by administrating aliskiren. Meanwhile, PRA was significantly suppressed.

The level of PRA or PAC before aliskiren treatment did not predict the overall effect (Figure 3). However, a pecent reduction rate of (PRA × PAC), calculated by the formula described below, above 80% may reflect the effectiveness of aliskiren (Figure 4).

percent reduction rate of (PRA × PAC) = 100 × {(PRA × PAC)$_{before}$ – (PRA × PAC)$_{after}$}/(PRA × PAC)$_{before}$, where before and after indicate before and after the administration of aliskiren, respectively.

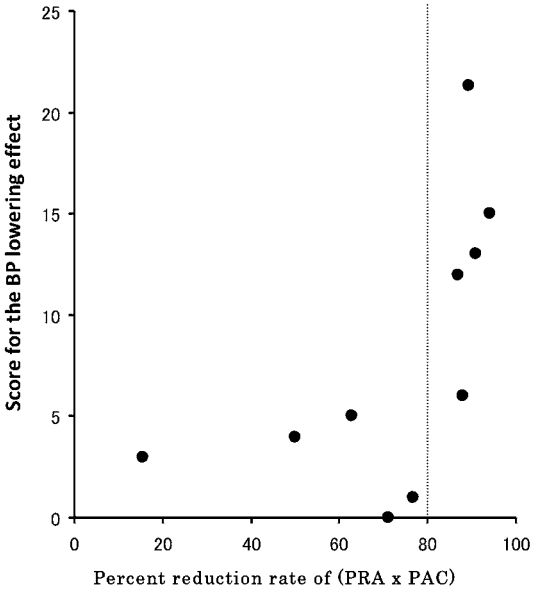

Figure 4 Reduction rate of (PRA × PAC) and the score for the BP lowering effect.
These values were not significantly correlated (Y = 0.12X – 0.78, r = 0.44, p = 0.20), but high BP lowering effects (score > 5) were observed only in the cases showing a high percent reduction rate (> 80%).

No adverse reaction after administration of aliskiren was observed during the observation period, except for arm pain caused by hypotension in one patient who continued to receive aliskiren.

Discussion

Lowering BP is not always beneficial to HD patients because HD would be more easily carried out in a hypertensive, rather than hypotensive, condition. To avoid such troubles related to hypotension during HD sessions, anti-hypertensives except for aliskiren were reduced in 4 patients. Meanwhile, this protocol caused a difficulty in analyzing the real effect of aliskiren on BP. We assumed a reduction of one tablet or capsule in a day, irrespective of the kinds of drugs, was equivalent to lowering BP by 10 mmHg, which seemed an anticipated level for physicians to prescribe a new antihypertensive drug. Otherwise, the effect of aliskiren in a study population could not be evaluated as a whole, and the patients should be separated into two populations: one in whom the prescribed antihypertensives are reduced and another in whom the drugs are not changed. Apparently, the former group includes patients with a better response to aliskiren. Hence, the precise quantification of effectiveness seems difficult in HD patients. Moreover, such a protocol inevitably decreases the size of the population for analysis. Therefore, we proposed a score for the BP lowering effect as an index for evaluating the effect of alskiren in patients receiving hemodialysis therapy.

Based on the score for the BP lowering effect, the DRI, aliskiren, was certainly useful as an antihypertensive in dialysis patients, although the function and regulation of the RAS in dialysis patients are inconsistent and have not been fully elucidated[16]. These differences may be derived from levels of residual renal function or concurrent problems, such as diabetes mellitus[14]. In dialysis patients, the RAS in the brain, heart and vascular wall may be involved in elevating BP. However, aliskiren cannot pass the blood brain barrier and does not have inotropic action on the heart. Hence, the RAS in the vascular wall may be suppressed by aliskiren. In fact, renin production in the vascular wall was found and increased in the patients with congenital genetic processing abnormalities of preprorenin that manifest progressive renal failure[17]. A similar phenomenon may happen in anuric HD patients, although no direct evidence has been reported until the present.

Since PRA did not predict the effectiveness of aliskiren in a previous report[4], we also examined prorenin, which exists mostly (98%) in the inactive, hinged form[13], and may be activated in the vascular wall. However, the levels of prorenin were not related to the effectiveness of aliskiren, as shown in Figure 3. Moreover, no other clinical parameters that predicted the effectiveness of aliskiren on blood pressure were identified in this study of anuric hemodialysis patients. Of the parameters, the reduction rates of PRA × PAC by the administration of aliskiren, rather than the absolute value of PRA × PAC, were more related to the BP lowering effect of aliskiren, which suggested that PRA and PAC in blood sampling might reflect only some fraction of the RAS. As described before, the vascular stiffness could be a target for aliskiren besides the kidney. However, further studies are needed to evaluate such possibilities, since the recent case series study also reported certain BP-lowering effects of aliskiren in anuric dialysis patients in Japan[18].

In conclusion, a DRI, aliskiren, was effective in lowering BP in anuric dialysis patients. Further studies are needed to elucidate the mechanism and to select patients responsive to aliskiren.

Conflict of Interest

The first author, Y. Maeda, received honoraria from Novartis (Basel, Switzerland) for serving as a speaker.

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