

Original Paper

A Comparison of the Antihypertensive and Anti-Inflammatory Effects of Aliskiren and Ramipril Add-On Therapy in Peritoneal Dialysis Patients – A Pilot Open Label Study

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Key Words

Arterial hypertension • Peritoneal dialysis • Aliskiren • Ramipril • Inflammation

Abstract

Most hypertensive dialysis patients are currently treated with angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB). Aliskiren, the direct renin inhibitor, has not been specifically studied in peritoneal dialysis patients. The aim of the study was to compare hypotensive effects of aliskiren and ramipril and their influence on serum potassium and inflammatory parameters in hypertensive peritoneal dialysis patients. Eighteen hypertensive patients on chronic peritoneal dialysis were enrolled in an open-label comparative fixed-order study. The patients had been off RAAS blocking drugs for ≥ 4 weeks prior to an inclusion. At each of 3 study visits (baseline and after each of the treatment periods) blood pressure, serum lipids, potassium, renin, aldosterone, C-reactive protein (CRP) and monocyte chemoattractant protein-1 (MCP-1) were measured. After the baseline visit aliskiren was started (150 mg/d) and after 12 weeks replaced with ramipril (5 mg/d) for the next 12 weeks. Blood pressure was $142/88 \pm 15/11$ mmHg at baseline, $137/84 \pm 10/8$ mmHg after aliskiren (ns) and $126/81 \pm 11/7$ mmHg after ramipril ($p < 0.05$ vs baseline and aliskiren). No incidents of hyperkalemia were observed. Plasma renin concentration increased significantly during aliskiren treatment compared to ramipril ($227,6 \pm 844$ vs $58,3 \pm 765$ pg/mL). CRP was similar after both therapies ($8,8 \pm 34$ vs $8,4 \pm 32$ $\mu\text{g/mL}$) but MCP-1 concentration was significantly lower after aliskiren than after ramipril ($294,0 \pm 172,6$ vs $358,9 \pm 183,3$ pg/mL). Aliskiren 150 mg/day decreases blood pressure less effectively than ramipril 5 mg/day in peritoneal dialysis patients. It does not influence serum potassium. The decrease of MCP-1 concentration after aliskiren treatment may provide an indirect evidence for its blood pressure independent cardioprotective and anti-inflammatory effects.

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Introduction

High blood pressure (BP) increases the risk of cardiovascular complications in both the general population and chronic dialysis patients [1, 2]. Arterial hypertension (HTN) is diagnosed in up to 80% of peritoneal dialysis patients [3] and its cardiovascular consequences such as left ventricular hypertrophy are even more common among peritoneal dialysis than hemodialysis patients [4]. Due to the complex pathogenesis of HTN in dialysis patients involving both the neurohormonal activation and chronic volume expansion the resistance to antihypertensive treatment is frequently observed [5]. One of the key pathogenic factors in dialysis patients with HTN is the increased activity of the renin-angiotensin-aldosterone system (RAAS) [5, 6]. Therefore the drugs that inhibit the RAAS such as angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) are frequently prescribed to dialysis patients [5-8]. Alternative drugs suppressing the RAAS activity such as spironolactone or eplerenone are not recommended in end-stage kidney disease largely due to an increased risk of hyperkalemia [3, 9].

Direct renin inhibitors, which suppress the RAAS in the initial activation stage, are the latest class of antihypertensive drugs that has been commercially available [10]. Aliskiren is currently the only drug from this class. So far several studies have shown that aliskiren effectively decreases blood pressure with the side-effect profile similar to placebo [8, 11, 12]. Since aliskiren is excreted with bile and does not require dose reduction in case of decreased glomerular filtration rate it could become a preferred drug for the treatment of hypertension in end-stage kidney disease [10]. Furthermore aliskiren decreases the activity of the sympathetic nervous system to a similar extent as ACEIs and ARBs but although all these agents decrease a concentration of angiotensin I and II and aldosterone only aliskiren increases plasma renin concentration with a parallel decrease of its plasma activity [8, 13, 14].

It has been shown that an increase of RAAS activity could induce a proinflammatory effect and leads to endothelial dysfunction and left ventricular hypertrophy, and thereby may be linked to faster progression of kidney disease [6, 8]. Some studies showed that the drugs suppressing RAAS such as ACEIs or ARBs may have anti-inflammatory action [15-17]. It was also found that aliskiren may decrease the concentration of inflammatory and antifibrotic factors but the evidence has so far been scarce [18-20].

The aim of our study was to compare a hypotensive effect of the direct renin inhibitor aliskiren and ACEI ramipril in chronic peritoneal dialysis patients. Additionally, we assessed the effect of aliskiren on serum potassium and serum biomarkers of inflammation.

Patients and Methods

Eighteen hypertensive patients undergoing chronic peritoneal dialysis (12 treated with automated peritoneal dialysis – APD and 6 with continuous ambulatory peritoneal dialysis - CAPD) for more than 6 months (mean 18.1±22.4 months, median 9.5, range 7-78 months) and in a stable clinical condition (14 M, 4 F; mean 59.4±12.3 years, median 61, range 34-70 years) ; BMI 27.3±4.6 kg/m², median 26, range 19-34 kg/m²) were enrolled into a pilot open-label comparative study with fixed-order design. All patients had preserved residual diuresis and a target total weekly Kt/V_{urea} of >1.7. Mean time from the diagnosis of kidney disease to end-stage kidney disease was 45.9±35.0 months (median 32, range 15-107 months). In all patients the peritoneal dialysis was the first form of renal replacement therapy. Kidney disease was caused by arterial hypertension in 4 patients, chronic glomerulonephritis (5 patients), diabetic nephropathy (3 patients), tubulointerstitial nephritis (2 patients), adult polycystic kidney disease (1 person), and unknown in 3 patients. All patients had been treated for hypertension for at least 3 months and BP had been satisfactory controlled (systolic blood pressure <150 mmHg). Most were on a combination antihypertensive therapy including calcium antagonists (14 patients), betablockers (12 patients) and centrally acting sympatholytics (9 patients) (mean number of antihypertensive drugs 2.5±0.7). The patients had been off any drugs that directly inhibit RAAS for at least 4 weeks before an enrollment. All antihypertensive drugs used at the time of the qualification to the study were continued in unmodified doses throughout the whole duration of the

Table 1. Baseline clinical and biochemical characteristics of the study group.

Parameter (units)	mean ± SD
Age (years)	59 ± 14
Body mass index (kg/m ²)	27.1 ± 4.5
Time since initiation of PD (months)	18.1 ± 22.4
Systolic blood pressure (mmHg)	141.7 ± 15.9
Diastolic blood pressure (mmHg)	88.0 ± 11.2
Serum total cholesterol (mmol/L)	4.7 ± 0.9
Serum triglycerides (mmol/L)	1.9 ± 1.1
Serum potassium (mmol/L)	4.68 ± 0.59
Serum sodium (mmol/L)	140.1 ± 3.0
Serum creatinine (μmol/L)	658 ± 289
Serum urea (mmol/L)	18.2 ± 5.0

study treatment. The patients with episodes of hyperkalemia (defined as serum potassium >6 mmol/L) or acute inflammatory conditions for 3 months prior to the study were excluded. The patients were not receiving any immunosuppressive drugs. Liver and heart insufficiency (NYHA class 2-4) or any vascular incidents in the last 3 months were additional exclusion criteria. The baseline clinical and biochemical characteristics of the study subjects are shown in Table 1. The study protocol was approved by the local Ethics Committee.

During each of the three study visits (baseline and after each of the treatment periods) blood pressure was measured in triplicate and blood was collected for measurements of serum sodium, potassium, creatinine, urea, total cholesterol, triglycerides, renin, aldosterone, C-reactive protein (CRP) and monocyte chemoattractive protein-1 (MCP-1). Following the recruitment visit aliskiren was immediately started in a fixed dose of 150 mg/day once per day for 12 weeks. After that period aliskiren was replaced with ramipril administered in a dose of 5 mg/day for another 12 weeks.

Mean arterial pressure (MAP) was calculated as diastolic blood pressure + 1/3 of systolic – diastolic blood pressure.

Total cholesterol and plasma triglycerides were measured with standard automated laboratory methods, serum sodium and potassium with flame photometry. Serum high-sensitive C-reactive protein and MCP-1 were measured with immunoenzymatic method (Quantikine, R&D Systems Europe, Ltd., Abington, UK), plasma renin and aldosterone with radioimmunoassay.

Data are shown as mean ± SD and median and range as appropriate. To assess the differences between the visits ANOVA for repeated measurements and paired t-test or Wilcoxon test for non-normally distributed data were used. Significance was set as $p < 0.05$.

Results

Blood pressure tended to decrease after 12 weeks of aliskiren treatment but the difference did not reach statistical significance ($p=0.11$ vs baseline for systolic and mean blood pressure and $p<0.05$ for diastolic blood pressure). In contrast, after the treatment with ramipril blood pressure significantly decreased ($p=0.001$ vs both baseline and aliskiren) (Fig. 1). Serum potassium did not change during the study (Fig. 2) and there were no episodes of hyperkalemia during the whole study (defined as serum potassium >6 mmol/L with or without clinical symptoms). As expected, plasma renin concentration was significantly higher during aliskiren treatment in comparison to baseline and ACEI therapy ($p=0.011$ and $p=0.009$, respectively). There were no changes of aldosterone concentration during the treatment (ns). Serum CRP was similar at all visits, but MCP-1 concentration decreased significantly during aliskiren ($p=0.01$) but not ramipril treatment (Table 2). Serum urea (18.2 ± 5.0 at baseline, 17.6 ± 3.5 after aliskiren and 18.8 ± 4.7 mmol/L after ramipril) and creatinine was unchanged during the study (658 ± 288 , 690 ± 278 and 788.379 μmol/L, respectively). There were also no significant changes of total serum cholesterol, serum triglycerides and serum sodium during the study.

Table 2. Plasma renin, aldosterone, C-reactive protein (CRP) and monocyte chemoattractant protein-1 (MCP-1) assessed at baseline and after 12-week treatment with aliskiren and 12-week treatment with ramipril.

Parameter (units)	Baseline	Aliskiren	Ramipril
Renin (pg/mL)	76.2 ± 86.2	227.6 ± 124.4*	58.3 ± 76.5
Aldosterone (pg/mL)	112,5 ± 60.0	118,6 ± 51.4	163,9 ± 118.8
CRP (g/mL)	0.48 ± 0.41	0.55 ± 0.42	0.65 ± 0.47
MCP-1 (pg/mL)	473.0 ± 182.2	294.0 ± 172.6 [#]	359 ± 183.3

* p=0.01 vs baseline, [#] p=0.01 vs baseline

Fig. 1. Systolic, diastolic and mean blood pressure (MAP) at baseline (visit 1), after 12-week treatment with aliskiren (visit 2) and after 12-week treatment with ramipril (visit 3).

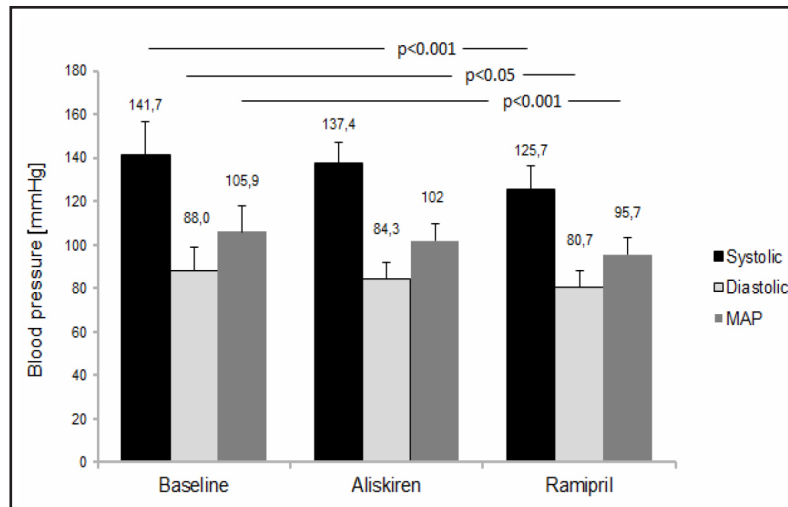
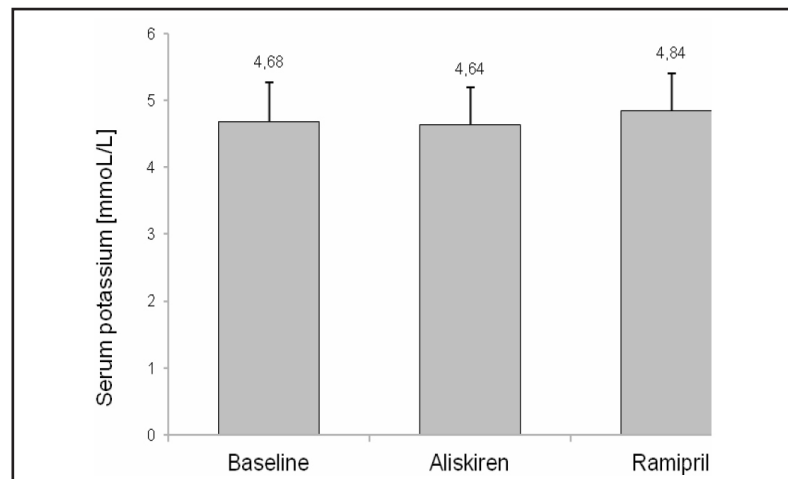


Fig. 2. Serum potassium at baseline (visit 1), after 12-week treatment with aliskiren (visit 2) and after 12-week treatment with ramipril (visit 3).



Discussion

In this study we assessed a hypotensive effect of a direct renin inhibitor aliskiren in chronic peritoneal dialysis patients with arterial hypertension. We showed that the addition of 150 mg/day of aliskiren to an antihypertensive therapy that excluded drugs that inhibit RAAS was safe but the hypotensive effect of the therapy was inferior to ramipril in a dose of 5 mg/day.

Several clinical studies with aliskiren in hypertensive patients without renal impairment showed its satisfactory antihypertensive effects [6, 11, 12, 18, 21-24]. The lack of a significant BP decrease in our study might have been due to several reasons including relatively well-controlled BP with conventional therapy at baseline and the dose of aliskiren

that was lower than in most other studies [14, 23-25]. Unfortunately the experience with aliskiren in patients with renal impairment has so far been very limited. In an open-label uncontrolled study in a group of 30 hemodialysis patients Morishita et al. [26] found that 150 mg of aliskiren once daily for 8 weeks reduced systolic and diastolic blood pressure by 15.3 and 5.1 mmHg, respectively the effect that was larger than in our study (5 and 4 mmHg, respectively). The study of Siddiqi et al. in patients with chronic kidney disease stage 2-4 proved that a dose of 300 mg/day of aliskiren, i.e. twice larger than in our study, effectively lowered blood pressure along with the reduction of the sympathetic activity [14]. Gradman et al. compared the influence of different daily doses of aliskiren (150 mg, 300 mg, and 600 mg) with irbesartan (150 mg/24h) on arterial pressure in patients with hypertension but without renal impairment [12]. They showed that aliskiren in the dose of 150 mg/d caused a similar decrease of blood pressure than 150 mg/24h of irbesartan. Furthermore 300 mg/d was even more effective but 600 mg/24h did not give any additional benefits as there were no further lowering of blood pressure and side-effects were more frequent [12]. What is more, Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (ALTITUDE), that aimed to assess the efficiency and safety of adding aliskiren to other RAAS suppressing drug (ACEI or ARB) in diabetic patients with chronic kidney disease has been discontinued due to an increased frequency of side-effects in the group of patients treated with aliskiren (more renal events, hyperkalemia, hypotension, and stroke) [27]. A thorough analysis of this study showed however that most side effects occurred when aliskiren was given in a combination with other RAAS inhibiting drug in a dose of 300 mg/day.

Nevertheless, in our study which compared the hypotensive efficacy of ACEI and aliskiren we observed that ramipril in a daily dose of 5 mg significantly lowered blood pressure in contrast to aliskiren in a dose of 150 mg/day. There were only few studies directly comparing ACEI and aliskiren and none of them included patients with advanced or end-stage kidney disease. Uresin et al. [28] compared a hypotensive efficacy of 300 mg aliskiren with 10 mg ramipril and the combination of these two drugs in a large group of hypertensive patients with type 2 diabetes. They showed that ramipril and aliskiren showed similar antihypertensive effect and combined therapy was more effective. Unlike in ALTITUDE, they did not however note an increased risk of side effects in any of the groups [27, 28]. In a study of Andersen et al aliskiren 150 mg/day provided better BP control than ramipril 5 mg/day [18] that is opposite to our results. However that study was performed in patients with arterial hypertension but without chronic kidney disease. It could be speculated that a response to a direct renin inhibitor might be altered in the presence of severely impaired renal function however there has been not enough evidence to support such concept. One has however need to take into account the fact that on the one hand renal failure leads to a stimulation of RAAS and on the other increased renin and prorenin release caused by aliskiren has been found to induce several potentially detrimental effects by the increased generation of angiotensin II in the membrane-bound phase and activation of signal transduction pathways involved in tissue damage, stimulation of profibrotic and inflammatory mediators [29].

It has been well documented that an increase in angiotensin II concentration is not only associated with hypertension, but also leads to release of reactive forms of oxygen and thereby induces oxidative stress [15, 30]. Chadramonachan et al. observed that RAAS stimulation in the kidneys was associated with an increase in MCP-I and PAI expression. MCP-I is the key factor involved in the activation of macrophages and to the influx of proinflammatory cells, resulting in fibrosis and organ damage. The stimulation of the secretion of the inflammatory markers was caused by the increase of angiotensin II concentration associated with the stimulation of intrarenal RAAS [29]. Similar observations were also made by Proudfoot et al. [15].

In our study we compared the effect of aliskiren and ramipril on serum markers of inflammation. While we were able to demonstrate that both ACEI and aliskiren caused a decrease of MCP-1 only the former reduced its concentration significantly. It is unlikely that such an effect was secondary to a blood pressure decrease since that was significantly

larger after ramipril than aliskiren. Our results corroborate those from other studies carried out in different clinical settings i.e. in patients without renal failure and treated with other RAAS blocking agents. Andersen et al. compared the influence of ramipril and aliskiren on inflammatory markers in hypertensive patients without renal function impairment and observed that although both drugs significantly lowered the MCP-1 concentration the decrease was significantly larger after aliskiren [18]. Proudfoot et al. in an experimental study showed that the inhibition of RAAS by two angiotensin II receptor antagonists irbesartan and losartan reduced MCP-1 concentration leading to a suppression of inflammatory markers [15]. Similar results were published by Kato et al. who showed that both ACEI enalapril and ARB candesartan caused the decrease of MCP-1 expression in experimental diabetes but not in non-diabetic animals [16]. Interestingly, MCP-1 reduction correlated with the decrease of proteinuria. The authors drew a conclusion that the activation of RAAS in diabetic nephropathy might have led to an increase in MCP-1 expression. An increase in MCP-1 concentration could result from direct activity of angiotensin II through AT1 on the cells generating MCP-1 [16]. That hypothesis was confirmed by Amann et al. who revealed that angiotensin II stimulated the activation of NF κ B and the synthesis of MCP-1 by the mesangial cells, which led to inflammatory cell infiltration [31].

Nguyen et al. postulated that an increase in the inflammatory markers was not only dependent on angiotensin II generation but also directly on increased renin production. They also showed that that effect was independent of blood pressure [32]. Tang et al. showed that by adding aliskiren to losartan caused a significant decrease of other inflammatory markers independent of blood pressure [33].

In our study neither of the drugs caused a change of serum CRP, which is a common but unspecific inflammatory marker in the dialysis patients including those treated with peritoneal dialysis [34]. Similar observations on the lack of an effect of aliskiren on CRP were made by Andersen et al. [18]. Karakousis et al. compared the influence of various combinations of hypotensive drugs on serum markers of inflammation and showed that despite a similar hypotensive effect combined aliskiren and valsartan therapy led to a significant decrease of hs-CRP compared to a combination of amlodipine and valsartan [19]. Similar effects were also shown by Muller et al. [8].

The use of a direct renin inhibitor holds promise for more potent blockade of the RAAS system in contrast to ACEI and ARB that do not fully inhibit angiotensin and aldosterone production. Moreover the putative direct action of aliskiren on prorenin/renin receptor may explain its action on inflammatory markers that are independent of angiotensin II [35]. Therefore aliskiren has a potential for more effective reduction of inflammation than angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [6, 8].

Currently most recommendations for the treatment of arterial hypertension do not apply to dialysis patients. Despite the lack of any evidence from large randomized trials most dialysis patients are treated with the drugs that inhibit RAAS but despite their common use the problem of uncontrolled or resistant hypertension is more frequent in end-stage renal disease than among patients with normal renal function [5-7]. Whether aliskiren may provide additional benefit in these patients is unknown and our results showing its less effective blood-pressure lowering effect than an ACEI on the one hand but a significant decrease of an inflammatory marker MCP-1 by aliskiren and nor by ramipril on the other clearly show that this question may only be answered in large studies with hard endpoints which are however rarely designed and performed in chronic dialysis patients.

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