Aliskiren reduces sympathetic nerve activity and blood pressure in chronic kidney disease patients

Laima Siddiqi¹, P. Liam Oey² and Peter J. Blankestijn¹

¹Department of Nephrology and Hypertension, University Medical Centre Utrecht, Utrecht, The Netherlands and ²Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Utrecht, The Netherlands

Abstract

Background. Hypertensive chronic kidney disease (CKD) patients often have sympathetic hyperactivity. In this pilot study, we evaluated the effect of 6 weeks treatment with aliskiren on sympathetic activity in hypertensive Stages 2–4 CKD patients.

Methods. In 10 CKD patients (8 males, aged 44 ± 11 years, estimated glomerular filtration rate (57 ± 22 mL/min/1.73 m²),
blood pressure and sympathetic activity [quantified by assessment of muscle sympathetic nerve activity (MSNA)] were assessed, while taken off renin-angiotensin blocker, and during the 6 weeks of treatment with aliskiren 300 mg/day. Ten other CKD patients served as control and were studied twice with an interval of 6 weeks without any change in medication, to quantify within subject reproducibility.

**Results.** In the aliskiren study group, MSNA was reduced from 36 ± 8 to 26 ± 8 bursts/min (P = 0.01). Aliskiren lowered supine systolic and diastolic blood pressure from 147 ± 10 to 120 ± 8 and from 96 ± 7 to 83 ± 7 mmHg, respectively (both P < 0.05). MSNA changed in patients treated with aliskiren [−9.6 bursts/min with 95% confidence interval (CI) −10.4 to −8.8; P-value = 0.003] but not in controls (−0.7 bursts/min with 95% CI −2.2 to 4.0; P-value = 0.6). The mean difference in change between aliskiren group and the control group was −8.9 with 95% CI of −15 to −3; P = 0.005.

**Conclusion.** In hypertensive CKD patients, 6 weeks aliskiren treatment lowers blood pressure and MSNA (Clinical trial government identifier number: NCT00719316).

**Keywords:** aliskiren; chronic kidney disease; hypertension; muscle sympathetic nerve activity; sympathetic activity

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**Introduction**

Chronic kidney disease (CKD) patients often demonstrate sympathetic hyperactivity, which appears to contribute to the pathogenesis of hypertension and cardiovascular organ damage [1–3]. Kidney hypoxia seems to be of crucial importance in the pathogenesis of increased activities of both the renin-angiotensin system and sympathetic nervous system [4]. Increased afferent renal nerves and/or circulating angiotensin II (AngII) activate the central nervous system to increase sympathetic outflow. Previously, we have shown that angiotensin-converting enzyme inhibitors (ACEi) and AngII receptor blockers (ARBs) reduce but do not normalize such sympathetic hyperactivity [2, 5–9]. These findings support the idea that the renin-angiotensin system is involved in the pathogenesis of the sympathetic hyperactivity and also suggest that it might be worth investigating options that may more effectively reduce sympathetic hyperactivity in CKD.

As renin catalyses the first and rate-limiting step of the renin-angiotensin system cascade, interruption of the generation of AngII by renin inhibitors at this specific initial step of the cascade is an interesting therapeutic goal. In this study, we assessed the effect of the renin inhibitor aliskiren on muscle sympathetic nerve activity (MSNA) in hypertensive patients with CKD. The primary objective of this study was to assess the effect on sympathetic activity and to compare this with effects of ACEi or ARB obtained in our previous studies. We hypothesize that aliskiren reduces MSNA in hypertensive CKD patients.

**Materials and methods**

**Subjects**

We selected 15 CKD (Stages 2–4) patients from our outpatient’s clinics. The patients were included, if they had stable CKD [defined as estimated glomerular filtration rate (eGFR) showing ≤5% variability during 3 months prior to inclusion in the study], were hypertensive (i.e. using antihypertensive drugs and/or blood pressure >145/90 mmHg when off medication) and were willing to sign informed consent. Exclusion criteria were renal replacement therapy, patients with diabetes mellitus, nephrotic syndrome, renal transplantation and pregnancy. None of the patients had undergone unilateral nephrectomy.

In three patients, we did not obtain an analysable MSNA signal and two patients refused the second set of measurements (Figure 1). Data on the 10 remaining patients with poly cystic kidney disease (3), IgA nephropathy (2), obstructive uropathy (1) and unknown cause (4) are presented. Two of the 10 patients were active smokers (average of 10 cigarettes daily). Our standard protocol for CKD patients includes treatment with an ACEi or ARB. When insufficient blood pressure control was obtained with this regimen, a diuretic was added until adequate control was obtained. In the nine patients on diuretics, diuretic dosage was not changed throughout the study. Furthermore, we quantified variability of the MSNA in 10 other CKD patients by assessing MSNA with an ~6-week interval. All CKD patients in this control group were on an ACEi or an ARB. Medication was not changed during the study (see Figure 1).

**Protocol**

The institutional committee for studies in humans at the University Medical Centre in Utrecht approved the protocol (NCT00719316, www.clinicaltrials.gov). All subjects gave written informed consent. Patients were studied under two conditions, i.e. when taken off ACEi or ARB for 4 weeks and during the 6 weeks of aliskiren treatment (300 mg/day). All other medications were continued unchanged throughout the study. None of the patients were receiving antihypertensive medication, other than diuretics. None of the patients were on an erythropoiesis-stimulating agent.

All subjects underwent an identical set of measurements in the supine position in a quiet room with an ambient temperature of 22–24°C. All study sessions were done in the morning between 2 and 5 h after drug intake. These measurements included MSNA measurement, systolic and diastolic arterial blood pressure, heart rate, plasma renin activity (PRA) and standard laboratory tests. Blood pressure was measured semi-continuously at the arm with an automated non-invasive calibrated blood pressure device with the subject in the supine position. Means of five measurements are presented. MSNA was recorded with a unipolar tungsten microelectrode placed in a muscle nerve fascicle of the peroneal nerve using the technique of Valbo et al. [10], as described previously by us [6–8, 11, 12]. The correct position of the electrode is evaluated by means of a Valsalva manoeuvre whereby the patient blows into a mouthpiece of an aeroid manometer to 40 mmHg for 15 s, while blood pressure (Finapres Ohmeda), heart rate [electrocardiogram (ECG)] and MSNA are continuously recorded. The blood pressure overshoot after the restart of breathing is associated with a short pause in neural activity. The neural signal during the blood pressure overshoot is considered as background noise. This procedure is done at the beginning and at the end of each study session. Success rate of obtaining an adequate neural signal is ~85%. The neural signal was filtered (bandwidth, 500–2000 Hz), rectified and integrated (time constant, 0.1 s). Sympathetic bursts were identified by their characteristic morphology and relationship to R waves on the ECG. MSNA was expressed as the number of bursts of sympathetic activity per minute. We have previously reported that intraserver and interserver reproducibilities are 4.5 ± 0.5% and 6.2 ± 0.7%, respectively [5].

After instrumentation, subjects rested for 20 min. Baseline measurements for blood pressure, heart rate and MSNA were obtained and blood was sampled for measurement of PRA, kidney function and other laboratory tests. The patients collected urine at home 24 h before the measurements.

**Laboratory analyses**

eGFR was estimated using the plasma creatinine (at the day of MSNA measurement) by the Modification of Diet in Renal Disease equation and creatinine clearance according to the creatinine clearance Cockcroft–Gault equation. Body mass index (BMI), estimated from weight and height, was measured using the metric imperial formula. PRA was measured by radioimmunoassay [13].

**Data analyses**

Data are given as mean ± SD unless indicated otherwise. Baseline parameter analysis was performed with Student’s unpaired t-test between
Results

The 10 patients (8 men) had a mean age of 44 ± 11 years; BMI of 26 ± 2 kg/m² and eGFR of 57 ± 22 mL/min/1.73 m². BMI and eGFR were stable during the last 3 months before entering the study. Office systolic and diastolic blood pressures at the time of screening, when on an ACEi or ARB, were 130 ± 10 and 86 ± 5 mmHg. Control patients had a mean age of 43 ± 9 years, BMI of 25 ± 2.6 kg/m² and eGFR of 57 ± 28 mL/min/1.73 m². Patients and controls were clinically normovolaemic, i.e. no peripheral or pulmonary oedema evidenced by physical examination and chest X-ray, and no signs of orthostatic hypotension. Patients in the aliskiren study, receiving other prescribed medications including phosphate binders (n = 2), statins (n = 8), diuretics (n = 9, furosemide, median dosage 80 mg/day, range 40–160 mg) and vitamin D (n = 1) were not changed during the study.

Patients had increased MSNA, were hypertensive and had high PRA. Data on age and BMI-matched controls (n = 10) measured in identical study conditions are MSNA 27 ± 5 bursts/min, mean arterial blood pressure 99 ± 5 mmHg and PRA 292 (53–625) ng/mL/h.

After 6 weeks treatment with aliskiren, arterial blood pressure decreased in all patients (Table 1), whereas heart rate remained unchanged (Table 1). MSNA also decreased in all patients: from 36 ± 8 bursts/min to 26 ± 8 bursts/min (P = 0.01) (Figure 2, Table 1). PRA decreased significantly in patients during aliskiren treatment from 1214 ng/mL/h (745–1862) to 267 ng/mL/h (186–305) (P = 0.01).

MSNA changed in patients treated with aliskiren (−9.6 bursts/min with 95% confidence interval (CI) −4.0 to −15.0; P-value = 0.003) but not in controls (−0.7 bursts/min 95% CI −2.2 to 4.0; P-value = 0.6). The mean difference in change between aliskiren group and the control group was −8.9 with 95% CI of −15 to −3; P = 0.005.

The change in MSNA during aliskiren was not different from that obtained during ACEi or ARB during previous studies, when MSNA decreased from 33 ± 11 to 25 ± 9 (P > 0.5 for comparison of change in MSNA in the present study versus previous studies) [7]. The change in MSNA induced by aliskiren correlated with the change in mean arterial pressure (r = 0.7, P = 0.02). Body weight and laboratory variables remained stable throughout the study (Table 2). Urinary sodium excretion during the 24 h before the measurements did not differ between the two study days. No patient claimed to experience any side effects of aliskiren or discontinued aliskiren treatment for any reasons.

Discussion

To the best of our knowledge, we are the first to show that aliskiren reduces sympathetic hyperactivity, quantified by MSNA, in hypertensive CKD patients.

The reduction in sympathetic activity occurs despite of the fact that blood pressure was reduced. Furthermore, heart rate showed no change despite of the drop in blood pressure. In this respect, the present data confirm our earlier results with ACEi and ARB [2, 5–8]. This means that baroreceptor resetting has occurred. It further suggests that agents which inhibit the activity of the renin-angiotensin system interfere in the pathogenesis in sympathetic hyperactivity in CKD patients [4]. This is in contrast to amlodipine. We have previously
shown that this agent effectively lowers blood pressure in CKD patients, but it increases sympathetic activity [6].

It is important to mention that 9 of the 10 patients were also on diuretics. Diuretics increase the activity of the renin-angiotensin system. It seems likely that they also affect the sympatholytic efficacy of aliskiren. In previous studies, we quantified extracellular fluid status by measuring bromide distribution, because we have shown that MSNA and PRA change reciprocally with fluid status, both in healthy controls and in CKD patients [2]. Bromide was not available anymore. Information on fluid status could be of importance for two reasons, firstly to show that baseline MSNA was indeed different from controls and secondly to show that the observed change in MSNA was caused by aliskiren and not (partially) by change in fluid status. The first issue is not the primary aim of this study and therefore not addressed and discussed in this paper. However, MSNA was very comparable to results of previous studies when we quantified fluid status. With respect to the second issue, it is important to realize that patients were on both occasions clinically normovolaemic and diuretics were not changed. Body weight remained unchanged, making it very unlikely that fluid status showed any relevant change during the course of the study. Also, urinary sodium excretion did not differ. Therefore, it seems safe to conclude that there was no major difference in fluid status between the two study sessions allowing us to conclude that indeed aliskiren reduces sympathetic hyperactivity in hypertensive CKD patients. In the previous studies, we quantified the effect of ACEi and ARB using a similar protocol [7]. The present results seem to indicate that sympatholytic effects of the different compounds do not show important differences. A more precise comparison can only be done by directly comparing the various compounds within the same patients. All together, the data suggest that aliskiren lowers MSNA. This effect is comparable to ACEi and ARB. Because there is substantial evidence that sympathetic hyperactivity is detrimental to health, this effect is likely to be of clinical relevance [3, 11, 12, 14, 15].

The present study also shows that aliskiren reduces blood pressure in hypertensive CKD patients. Again, it is important to remember that most patients were on diuretic therapy, which most likely (substantially) affects the antihypertensive efficacy. The effect of aliskiren on PRA is different from that of ACEi and ARB. In fact, this was expected, as the level of interference of aliskiren into the renin-angiotensin cascade is different from that of ACEi and ARB. The fact that all these agents reduce sympathetic activity and blood pressure provides support to the idea that these effects are related to AngII reduction and not to the renin inhibition per se.

Possible limitations of our study include the fact that it was not blinded and placebo controlled. However, we quantified the within-subject variability of the MSNA signal in other CKD patients without any change in medication with a 6-week interval. We agree with literature data that the within-subject variability of the MSNA signal is limited [16]. The decrease in MSNA during aliskiren was much greater than the a priori variability of the MSNA signal, which we found in CKD patients, suggesting a real effect of aliskiren. A further limitation is that we only used a fixed dosage. Also, in our previous studies, a fixed dosage of ACEi or ARB was applied. We cannot exclude the possibility that by using other (i.e. higher) dosages, effects on MSNA and blood pressure would be different. We did not compare within the same subjects aliskiren with other inhibitors of the renin-angiotensin system. When comparing with our previous data, the present results seem to indicate that effects of the different compounds are comparable. Furthermore, the study was conducted with a limited number of patients with variable kidney diagnosis. This makes it impossible to analyse whether the efficacy of the agent is related to kidney diagnosis. In our previous analysis of the effects of ACEi and ARBs, we were unable to identify such a relationship [5]. It is important to realize that sympathetic hyperactivity is a feature of kidney injury and not kidney

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Untreated</th>
<th>During aliskiren treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>cGFR (mL/min/1.73 m²)</td>
<td>57 ± 22</td>
<td>58 ± 22</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>54 ± 21</td>
<td>54 ± 21</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>83 ± 15</td>
<td>83 ± 14</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>14.2 ± 1.6</td>
<td>14.3 ± 1.4</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>139 ± 4</td>
<td>138 ± 5</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.9 ± 0.5</td>
<td>3.8 ± 0.5</td>
</tr>
<tr>
<td>Urinary sodium (mmol/24 h)</td>
<td>123 ± 70</td>
<td>126 ± 68</td>
</tr>
<tr>
<td>Total protein in urine (g/24 h)</td>
<td>1.4 ± 0.5</td>
<td>0.6 ± 0.2</td>
</tr>
</tbody>
</table>

*Biochemical values are assessed in plasma, unless indicated otherwise. Untreated indicates: when taken off ACEi or ARB for at least 4 weeks. During aliskiren treatment indicates: when on aliskiren 300 mg for at least 6 weeks. Values are mean ± SD; P > 0.05 for all above-mentioned parameters. To convert haemoglobin from g/dL to mmol/L multiply by 0.62.

**Table 1.** Effects of aliskiren on blood pressure, MSNA and PRA as compared to effects of a control CKD group

<table>
<thead>
<tr>
<th></th>
<th>Aliskiren study group</th>
<th>Control group</th>
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<tbody>
<tr>
<td>Parameters</td>
<td>Baseline aliskiren</td>
<td>First session</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44 ± 11</td>
<td>43 ± 9</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>80%</td>
<td>60%</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>147 ± 10</td>
<td>120 ± 8b</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>96 ± 7</td>
<td>83 ± 7b</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>112 ± 8</td>
<td>96 ± 7b</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64 ± 8</td>
<td>69 ± 7</td>
</tr>
<tr>
<td>MSNA (bursts/100 heart beats)</td>
<td>36 ± 8</td>
<td>26 ± 8b</td>
</tr>
<tr>
<td>MSNA (bursts/min)</td>
<td>56 ± 9</td>
<td>37 ± 14a</td>
</tr>
</tbody>
</table>

*Arterial blood pressures represent values obtained in the supine position. Aliskiren study group: data represent results of when the patients were not on a blocker of renin-angiotensin system (baseline) and when on treatment for at least 6 weeks with aliskiren 300 mg (n = 10). Control group: first and second session indicate two measurements in the same CKD patients without any changes in medication after 6 weeks; n = 10. Data are mean ± SD. 

bP < 0.01 compared to baseline within the group.
failure. However, it is uncertain whether the present results can be generalized to all CKD patients.

In conclusion, aliskiren lowers MSNA in hypertensive Stages 2–4 CKD patients. Results seem comparable to those obtained with ACEi and ARB. Given the interest in the effects on various clinical variables of the addition of aliskiren to ACEi or ARB, it might be interesting to study whether the addition of this compound to chronic treatment with ACEi or ARB would result in further reduction of MSNA. Indeed, we have previously shown that ACEi and ARB reduce but does not normalize MSNA in CKD patients [7] and that it was normalized when another sympatholytic agent was added [8]. The study gives further support to the notion that the renin-angiotensin system and the sympathetic nervous system affect each other. Direct comparison will be necessary to formally compare efficacy of aliskiren versus ACEi or ARB. The present data can be used for sample size estimation but seem to suggest that possible differences will be limited.

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Conflict of interest statement. P.J.B. has received consulting fees from Novartis Pharmaceuticals.

References


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