Effects of Eprosartan in Chronic Kidney Disease

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Increased activities of the renin system and the sympathetic nervous system are key contributors to the pathogenesis of hypertension in chronic kidney disease patients. Eprosartan is an angiotensin II receptor antagonist, which effectively reduces muscle sympathetic nerve activity (MSNA) in chronic kidney disease patients. J Clin Basic Cardiol 2005; 8: 15–7.

**Key words:** hypertension, chronic kidney disease, sympathetic nervous system, angiotensin II receptor blocker, angiotensin II antagonist

Hypertension is common in chronic kidney disease (CKD) patients [1–4]. Its prevalence varies between 30 % and 100 % depending on the target population, cause of renal disease, and level of renal function. Traditionally this hypertension is viewed as largely volume-dependent. There is clear evidence that CKD is often characterised by an activated renin system and sympathetic nervous system, which contributes to the pathogenesis of renal hypertension, but may also adversely affect prognosis independently of their effect on blood pressure. This could have important implications for the choice of treatment. The purpose of this brief review is to summarise available knowledge on the pathogenesis of renal hypertension with some emphasis on the sympathetic nervous system and secondly to discuss the clinical relevance and the consequences of this knowledge for the choice of treatment.

Pathogenesis

In the pathogenesis of renal hypertension fluid overload and inappropriately enhanced activity of the renin system are established as contributors. It is now increasingly clear that also sympathetic hyperactivity is often present. The application of microneurography for quantifying muscle sympathetic nerve activity (MSNA), which is the centrally originated sympathetic outflow towards the resistance vasculature, greatly enhanced our knowledge. Haemodialysis patients who still have their native kidneys have elevated MSNA [5]. Also hypertensive CKD patients not yet on dialysis have increased MSNA, independent of age [6–10]. Bilaterally nephrectomised patients have MSNA identical to healthy controls, indicating that the signal that commands the brain to increase sympathetic outflow is generated in the affected kidneys [5].

Clinical Relevance

CKD is associated with high cardiovascular morbidity and mortality. There is substantial evidence that sympathetic hyperactivity is also harmful, independent of its effect on blood pressure. In essential hypertension indices of sympathetic activity are related to left ventricular hypertrophy. Also in CKD patients there is a positive relation between noradrenaline and left ventricular dimensions [11], and patients with left ventricular hypertrophy generally have poorer prognosis. Sympathetic activity contributes to the development of other forms of organ damage independent of its effect on blood pressure. It is associated with heart failure, arrhythmias and in experimental conditions with atherogenesis (review in [1–4]). Plasma noradrenaline is an independent predictor for all-cause mortality and cardiovascular events in haemodialysis patients without overt heart failure [12].

There is experimental evidence that catecholamines are involved in the development of kidney damage also independent of their effect on blood pressure (review in [1–4]). These effects include vascular and glomerular injury. Catecholamines induce renal vasoconstriction but also proliferation of smooth muscle cells and adventitial fibroblasts in the vascular wall. Podocyte injury is a pivotal step in the development of glomerulosclerosis. Podocytes have adrenergic but also angiotensin II (Ang II) receptors. Adrenergic blockade has been tested in experimental CKD models. In sub-total nephrectomised rats a low dose of moxonidine but also of α- and β-blockers ameliorates renal damage without affecting blood pressure [1–4]. In normotensive diabetic humans moxonidine reduces albuminuria without affecting blood pressure [1–4].

Treatment

Based on the pathophysiological mechanisms outlined above, it seems logical that treatment should include an ACE inhibitor or an Ang II receptor antagonist, combined with diuretics (or ultrafiltration in case of haemodialysis patients) to maintain normovolaemia. Indeed we have shown that ACE inhibition and Ang II receptor antagonism reduce MSNA [6, 7, 10]. These types of agents also reduce cardiac sympathetic activity in essential hypertension, whereas a calcium channel blocker does not [13].

Experimental data suggest that eprosartan might be able to more effectively lower sympathetic activity than other Ang II receptor antagonists [14, 15]. We evaluated the effect of eprosartan on blood pressure and MSNA in CKD patients (n = 11, creatinine clearance 47 ± 10 ml/min.). MSNA (peroneal nerve), blood pressure, and baroreceptor sensitivity were measured in the absence of antihypertensive drugs (except diuretics), during chronic (6 weeks) eprosartan 600 mg [10]. Normovolaemia was controlled by diuretics and confirmed by extracellular fluid volume measurements. Healthy controls were studied as well (n = 22).

Blood pressure, heart rate, and MSNA were higher in patients than in controls. During eprosartan mean arterial pressure (MAP, 111 ± 9 mmHg to 98 ± 7 mmHg, p < 0.001),
heart rate (71 ± 10 bpm to 65 ± 8 bpm, p < 0.001) and MSNA (35 ± 10 bursts/min to 27 ± 8 bursts/min, p < 0.001) decreased (Fig. 1).

Because blood pressure and MSNA were not normalised, we did an additional set of studies. After the addition of moxonidine (6 weeks) to chronic treatment with eprosartan a further reduction of MAP to 89 ± 7 mmHg (p < 0.05) and of MSNA to 20 ± 10 bursts/min (p < 0.05) occurred. Heart rate did not change. Results were not different anymore from control subjects (MAP 88 ± 9 mmHg and MSNA 20 ± 11 bursts/min). Baroreceptor sensitivity was not affected by the treatment.

**Discussion**

In CKD patients ACE inhibitors and Ang II receptor antagonists are accepted by Guideline Committees in Europe and the USA as first choice therapy [16, 17]. In many cases diuretics should be added to maintain normovolaemia. In CKD patients, whether or not on dialysis, ACE inhibitors appear to be most effective in reducing left ventricular hypertrophy. In various CKD populations ACE inhibitor or Ang II receptor antagonist use is associated with improved survival and reduction of kidney failure progression independently of their effects on blood pressure (see review [1–4]).

Eprosartan is particularly effective in CKD patients [10]. It has a profound antihypertensive effect and it reduces sympathetic hyperactivity (Fig. 1). Interestingly, also heart rate decreases slightly but significantly, suggesting that cardiac sympathetic activity is also reduced. Futhermore, experimental evidence shows that eprosartan is very effective in preserving renal structure and function in various renal injury models as well [18, 19].

None of the tested agents normalise sympathetic hyperactivity in CKD patients, at least MSNA is not normalised [6, 7, 10]. In that respect our finding that addition of moxonidine in CKD patients on chronic treatment with an Ang II antagonist normalised MSNA might be significant [10]. In dialysis patients with dilated cardiomyopathy the addition of carvedilol to the standard therapy regimen reduced cardiovascular morbidity and mortality as compared to placebo [20]. And in another study in CKD patients who were on standard treatment, in most cases including an ACE inhibitor or an Ang II receptor antagonist, kidney function remained stable after addition of moxonidine whereas it progressed after the addition of a calcium channel blocker [21]. All these data support the notion that mechanisms which are affected by ACE inhibitor or Ang II receptor antagonist use are important in determining cardiovascular and renal prognosis in CKD patients and that in selected patients addition of yet another sympatholytic agent might be beneficial.

Registry data indicate that many patients do not receive appropriate treatment. In the USRDS survey only 14 % of patients obtained an ACE inhibitor and 8.5 % a beta-blocker [22]. In a recent study from Germany more than 90 % of a CKD population was on an ACE inhibitor or Ang II receptor antagonist [21]. The second issue of concern is that when patients receive appropriate medication, treatment targets should be reached. In a recent American survey in more than 3000 CKD patients (creatinine clearance < 60 ml/min/1.73 m²) only 37 % had a blood pressure < 130/80 mmHg [23]. In a random sample of our own outpatients clinic CKD population (n = 200, creatinine clearance < 70 ml/min/1.73 m²) 45 % had a blood pressure level of ≤ 130/80 mmHg (unpublished data). This and other data indicating that treatment targets are not reached in many cases induced us to initiate a large scale program to improve the quality of treatment in CKD patients [24].

**Conclusion**

Apart from volume overload, increased activities of the renin system and the sympathetic nervous system contribute importantly to the pathogenesis of hypertension in CKD patients. There is substantial evidence that the renin system and the sympathetic nervous system also adversely affect cardiovascular risk independently of their effect in blood pressure. As a consequence, treatment should include inhibition of these pressor systems together with correction of volume status. Eprosartan, which is an Ang II receptor antagonist, effectively reduces sympathetic hyperactivity. It is an appropriate choice for use in these patients.

**References:**

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