

Cardiovascular Topics

Potential renoprotective effects of the angiotensin receptor blocker eprosartan: a review of preliminary renal studies

B. RAYNER, B. JAEGER, C.N. VERBOOM, M. PASCOE

Summary

The importance of the renin–angiotensin–aldosterone system (RAAS) in the pathogenesis of hypertension and in renal disease, particularly in patients with diabetes, has become increasingly evident. Pharmacological blockade of the RAAS offers potential for the therapeutic management of these pathologies. Angiotensin converting enzyme (ACE) inhibitors and angiotensin II (AII) receptor blockers have been shown to exhibit effectiveness in the treatment of hypertension. AII receptor blockers have a renal protective effect owing to their ability to reduce systemic blood and intraglomerular pressures. Eprosartan is a chemically distinct AII blocker, which displays a dual mode of action whereby it blocks both pre- and postsynaptic AT₁ receptors, potentially benefiting patients with hyper-

tension and renal disease. In addition, evidence suggests that eprosartan is well tolerated by both healthy subjects and patients with varying degrees of renal impairment, such that the dose does not need to be modified in patients with mild to moderate renal impairment.

Results from preliminary studies demonstrate that eprosartan doses well below those required for blood pressure control have a pronounced effect on the kidney and do not compromise renal autoregulatory mechanisms. Therefore, eprosartan may have a benefit in the prevention or delay of renal damage in hypertensive patients with renal impairment, although this remains to be determined in a clinical setting.

The renin–angiotensin–aldosterone system (RAAS) is a complex system of enzymes, proteins and peptides that are involved in blood pressure regulation, and fluid and electrolyte balance. Angiotensin II (AII), the major effector hormone, causes arteriolar smooth muscle contraction and stimulation of aldosterone production via the AII receptor AT₁ subtype. The net effect of the activation of the RAAS is to elevate blood pressure and retain sodium. Regulation of the RAAS occurs primarily in the kidney and provides a rapid and efficient mechanism for producing acute changes in blood pressure and fluid and electrolyte balance.¹ Decreases in renal perfusion pressure, increases in renal beta-adrenergic stimulation and sodium depletion are the major stimuli for renal renin release, which results in increased AII. In the kidney, AII plays an important

Divisions of Hypertension and Nephrology, Grootte Schuur Hospital, Cape Town, South Africa

BRIAN RAYNER, M.B., Ch.B., F.C.P. (S.A.), M.Med. (U.C.T.)
MICHAEL PASCOE, M.B., Ch.B., F.C.P. (S.A.)

Solvay Pharmaceuticals, Hans Böckler Allee 20, 30173 Hannover, Germany

BODO JAEGER, M.D., Ph.D.
CEES-NICO VERBOOM, Ph.D.

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role in renal autoregulation, mainly under conditions of reduced renal perfusion. It constricts the efferent arteriole, restoring intraglomerular pressure and glomerular filtration rate.^{2,3}

The RAAS is often inappropriately activated in systemic hypertension and renal disease, and plays a central role in the pathophysiology of these disorders. Generation of AII can occur entirely at the tissue level, for example in diabetes, where glucose directly stimulates AII production solely within the kidney.⁴ The kidney is particularly vulnerable to the effects of the pathophysiological activation of AII through a variety of mechanisms. AII constricts the efferent arteriole, resulting in an increase in glomerular pressure and loss of renal autoregulation. Glomerular hypertension is damaging to the kidney, particularly in the context of diabetes and hypertension, and leads to endothelial damage and progressive glomerulosclerosis. AII also increases glomerular permeability to protein, resulting in proteinuria and influx of macromolecules into the mesangium, and activates transforming growth factor (TGF)- β , resulting in activation of fibroblasts, collagen deposition and scarring.⁵ Activation of the RAAS also plays a role in systemic hypertension, which contributes to renal damage in most forms of renal disease, especially in diabetes.⁶

This review will provide an overview of the pharmacological inhibition of the RAAS and how it provides a potential therapeutic option for treatment of hypertension and renal disease. We will focus on experimental data that demonstrate that the newer AT₁ receptor blockers provide an effective and well-tolerated option for the treatment of hypertensive patients with concomitant renal disease. In addition, the present review explores recent clinical data, which provide an insight into the benefits of antihypertensive agents for the prevention or the delaying of renal disease progression.

Pharmacological inhibition of the RAAS

Pharmacological blockade of the RAAS offers the potential for therapeutic management of several pathologies including hypertension, heart failure, diabetic nephropathy and hypertensive nephrosclerosis. As patients with hypertension may also have impaired renal function, the treatment of this patient population is clinically important.³

Both angiotensin converting enzyme (ACE) inhibitors and AII receptor subtype AT₁ blockers have been shown to be effective in the treatment of hypertension, although their mechanisms of action differ. ACE inhibitors block the conversion of AI to AII, and thus reduce the influence of AII at the AT₁ receptor. However, they may not completely suppress the action of AII because it can be produced by non-ACE pathways. ACE inhibitors have been shown to exert a renal protective effect by limiting the haemodynamic changes associated with various stages of progressive renal disease.⁷ These renal effects may derive from their

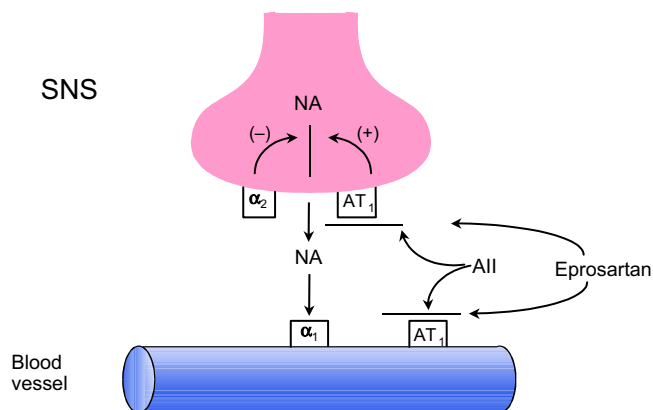


Fig. 1. The sympathetic neuroeffector junction. NA = noradrenaline; α_1 = α_1 adrenoreceptors; α_2 = α_2 adrenoreceptors; AII = Angiotensin II; AT₁ = Angiotensin II receptor type I receptor. Figure reproduced with permission from Brooks DP, Ohlstein EH, Ruffolo RR. Pharmacology of eprosartan, an angiotensin II receptor antagonist: exploring hypotheses from clinical data. *Am Heart J* 1999, 138 (3 Pt 2): 246–251.

ability to lower systemic blood pressure and preferentially dilate efferent arterioles, thereby reducing intraglomerular pressure. In contrast to ACE inhibitors, AII receptor blockers bind to the AT₁ receptor in a highly selective manner, thus interrupting the RAAS at the target organ receptor level. This will, therefore, block the action of AII, whether its production is via ACE or non-ACE pathways. There are a number of agents within the class of AII receptor blockers, which differ in terms of chemical structure and receptor binding characteristics.

Eprosartan is unique in that it is the only non-biphenyl, non-tetrazole AII receptor blocker. It is highly selective for the AT₁ receptor subtype where it binds competitively. In addition, eprosartan has a dual mode of action whereby it blocks both the effect of AII on the blood vessel at the postsynaptic receptor and the positive feedback of AII in the sympathetic nerve ending at the presynaptic receptor (Fig. 1). AII enhances sympathetic nervous system (SNS) function by increasing noradrenaline release through activation of presynaptic AT₁ receptors located on sympathetic nerve terminals, leading to enhanced vasoconstriction. Preliminary experiments have shown that the dose of eprosartan required to block the SNS pathway is higher than that needed to block the RAAS pathway, and that eprosartan reduces SNS activity to a significantly greater degree than valsartan, candesartan and embusartan. Therefore, inhibition of sympathetic outflow by AT₁ receptor blockers is a class effect, with eprosartan being more effective than other agents in this class, at least in the *in vivo* pithed rat experiments.⁸ This dual mode of action may offer potential advantages in patients with hypertension and renal disease, as sympathetic activation is a key component in the genesis of hypertension in renal disease.⁹ Here, we will review the efficacy and safety of eprosartan, its effect on renal haemodynamics and preliminary data of the benefits of AII receptor blockers for patients with renal impairment.

Clinical efficacy of eprosartan

Eprosartan, at a dose of 600 mg once daily, has been shown to be effective in the treatment of hypertension and is generally well tolerated, with a placebo-like side-effect profile.¹⁰ Eprosartan provides clinically significant reductions in both systolic and diastolic blood pressure in patients with all grades of hypertension, irrespective of their age or gender.¹¹⁻¹⁶

Although eprosartan has been shown to be efficacious in reducing blood pressure, some patients may require additional antihypertensive therapy to achieve blood pressure targets.¹⁷ Indeed, evidence from recent studies suggests that hypertensive patients, especially those with renal disease, should have their blood pressure intensively lowered;¹⁸ adding an additional drug from a different class is generally a preferred approach. Eprosartan in combination with the thiazide diuretic, hydrochlorothiazide (HCTZ), has been shown to further reduce blood pressure than eprosartan alone.^{12,19} In addition, when eprosartan is given either alone or in combination with HCTZ, it is generally well tolerated and has a favourable side-effect profile.¹⁰ Studies have confirmed that eprosartan can be safely used in combination with other drugs as its metabolism does not involve the cytochrome P450 enzyme system.²⁰⁻²²

Renal handling of eprosartan

AII receptor blockers undergo significant non-renal clearance, with the renal clearance of eprosartan being only 30% of total body clearance, and the remainder being hepatic as the unchanged compound.²¹ The renal handling of eprosartan has been studied in a cohort of patients characterised by different levels of renal impairment.²¹ Patients with normal renal function and mild renal failure had similar maximum plasma concentrations (C_{max}) and area-under-the-curve (AUC) values (Table I). Those with moderate renal impairment had 30% higher values and those with severe renal impairment had 60% higher values.²¹

TABLE I. PHARMACOKINETICS OF EPROSARTAN AFTER ADMINISTRATION OF EPROSARTAN IN HEALTHY SUBJECTS AND PATIENTS WITH VARIOUS DEGREES OF RENAL IMPAIRMENT.²¹

Parameter	Healthy	Mild renal impairment	Moderate renal impairment	Severe renal impairment
AUC ₀₋₁₂ (ng/hr/ml)	2961	2239	3711	4597
C _{max} (ng/ml)	590	536	795	888
CL _r (ml/min)	39.2	45.6	23.1	2.2
% fraction unbound (<i>ex vivo</i>)	1.4	1.6	1.6	2.7

AUC₀₋₁₂ = area under the curve from 0-12 hours; C_{max} = maximum concentration; CL_r = renal clearance

Therefore, eprosartan is generally safe and well tolerated by both healthy subjects and patients with varying degrees of renal impairment. There was a trend for decreased renal clearance and increased plasma concentrations of eprosartan with increasing severity of renal failure, but despite these changes, the dose of eprosartan does not need to be modified in patients with mild to moderate renal impairment. It is recommended, however, that the dose does not exceed 600 mg in patients with moderate to severe renal impairment. In addition, unlike ACE inhibitors, AII receptor blockers do not significantly accumulate after repeated dosing in patients with renal insufficiency.²³

Renal haemodynamic effects of eprosartan

The effect of AII receptor blockers on the kidney also involves investigation of their effects on glomerular filtration rate (GFR) and renal plasma flow (RPF). Blockade of AII at the receptor level leads to renal haemodynamic changes analogous to those with ACE inhibitors (i.e. decreased filtration fraction, reduced intraglomerular pressure and increased sodium excretion). The renal haemodynamics of eprosartan at various doses have therefore been compared in healthy subjects and in patients with hypertension and renal impairment.

Healthy subjects

In a study of healthy subjects given a low-salt diet to activate the RAAS, eprosartan doses well below those required for blood pressure control had a pronounced effect on the kidney, with a 100-mg dose producing a maximal renal vasodilator response of 135 ± 19.7 ml/min/1.73m². When the eprosartan dose was increased to 400 mg there was only a modest additional increase to 147 ± 57 ml/min/1.73m².²⁴ By contrast, there was a highly significant dose-related fall in blood pressure, with no indication of a maximal response at 400 mg. Indeed the eprosartan dosage for blood pressure control is 600 mg, showing that there are clear differences in the relation of dose to renal vascular response.

A further study investigated the effects of ACE inhibitors, AII receptor blockers and renin inhibitors on renal blood flow in healthy subjects given a low-salt diet to activate the RAAS.²⁵ AII receptor blockers and renin inhibitors produced renal vascular responses that were greater than the responses to ACE inhibitors.²⁵ From the ratios of blood flow, it was calculated that approximately two-thirds of AII formation was ACE-dependent and one-third was generated by alternate pathways in the healthy human kidney under conditions of low salt intake.²⁵

The interaction between eprosartan and AII has also been examined in healthy volunteers who were given a high-salt diet to suppress the RAAS. This study showed that eprosar-

tan (350 mg) completely reversed the renal vasoconstriction induced by AII at a level sufficient to induce substantial renal vasoconstriction.²⁶ In addition, when eprosartan was given alone, in the absence of exogenous AII, there was a significant vasodilator response, although this was less marked than previous studies using eprosartan 200 mg in healthy subjects on a low-salt diet.²⁴ By contrast, ACE inhibitors did not induce a similar renal vasodilator response when the renin system was suppressed by a high-salt diet, suggesting that 60–70% of Ang II is generated via non-ACE pathways under these conditions.²⁷

Although a low-salt diet may be considered to be artificial, with healthy human beings generally having a higher salt intake, the low-salt model has several advantages. Activation of the RAAS makes it possible to define a relationship between the dose of the blocking agent and the renal vasodilator response.²⁴ The renal vascular response to pharmacological inhibition of the RAAS in normotensive subjects taking a low-salt diet resembles both the response in some patients with hypertension and that in patients with diabetes. In this latter group, it is thought that the disease process might activate the renal renin system.²⁴ Therefore, this model might predict more effectively the renal response to pharmacological interruption of the renin system in disease.

It has been reported in patients with type 1 diabetes that moderate hyperglycaemia leads to an increase in plasma renin activity and renal vasoconstriction.²⁸ In a study of healthy subjects, activation of the intrarenal RAAS induced by hyperglycaemia has been shown to increase the renal vasodilator response to the ACE inhibitor, captopril.²⁹ Furthermore, the effects of eprosartan on RPF and GFR in healthy subjects on a high-salt diet in normoglycaemic and hyperglycaemic states were investigated.³⁰ There was an increase in RPF in response to hyperglycaemia, which further increased when eprosartan was given during the period of hyperglycaemia. However, eprosartan did not affect RPF in normoglycaemic patients. In addition, GFR was not affected by either normoglycaemic or hyperglycaemic states. Neither plasma renin activity nor plasma AII concentration changed during hyperglycaemia, suggesting that the enhanced vasodilator effect occurred within the kidney.³⁰ These studies provide some insight into the potential role of alteration in renal haemodynamics by hyperglycaemia in the pathogenesis of diabetic renal disease. Therefore, eprosartan may provide significant benefit in diabetic patients with hypertension.

Patients with renal impairment

Studies have shown that in patients with renal impairment, RPF is maintained following the administration of eprosartan, with no changes in GFR being observed.^{24,31} These studies suggest that eprosartan does not compromise renal autoregulatory mechanisms and may provide benefits in the treatment of hypertensive patients with renal impairment.

Benefit of AII receptor blockers in patients with renal disease and diabetes

It is known that cardiovascular and renal diseases in diabetic patients are due to atherosclerosis in both small and large blood vessels. Microalbuminuria is an early sign of diabetic nephropathy and provides evidence of early renal damage. If microalbuminuria is left untreated, it progresses to overt proteinuria and invariably leads to end-stage renal disease, resulting in the need for dialysis or transplantation.

Effective blood pressure reduction in patients with type 2 diabetes and diabetic nephropathy is known to delay the progression of diabetic nephropathy, to delay the onset of renal failure and to improve survival.³² Therefore, as hypertension is a risk factor for end-stage renal disease, there is consensus that blood pressure management is an important aspect of care in patients with chronic renal insufficiency.³³

The renoprotective effect of ACE inhibitors has been demonstrated in a number of studies. One particular study compared the ACE inhibitor ramipril with the calcium channel blocker amlodipine in hypertensive African-Americans with renal impairment. This study was discontinued early due to the fact that there was a slower decline in GFR with ramipril compared with amlodipine.³⁴ This differential effect was independent of the blood pressure levels reached. Furthermore, it appears that dihydropyridine calcium channel blockers should be used cautiously in the presence of mild to moderate renal impairment.³⁵

Further studies have compared the effect of AII receptor blockers with an ACE inhibitor in patients with renal disease. One study has shown that both ACE inhibitors and AII receptor blockers reduce microalbuminuria in patients with diabetic and nondiabetic nephropathy.³⁶ Another study compared the effect of treatment with valsartan, captopril or placebo on renal function in patients with type 2 diabetes and nephropathy. Both valsartan and captopril significantly decreased the albumin excretion rate compared with placebo.³⁷ These studies suggest that AII receptor blockers are at least as effective as ACE inhibitors in patients with renal disease or those who are at high risk of renal disease, such as those with diabetes.

More recently, the Irbesartan Microalbuminuria study (IRMA-2) and the Microalbuminuria Reduction with Valsartan study (MARVAL) were conducted in patients with type 2 diabetes with microalbuminuria or early-stage renal disease. Results from the IRMA-2 study demonstrated that irbesartan is effective in delaying the progression of microalbuminuria, and that this protection is independent of the reduction in blood pressure.³⁸ Results from the MARVAL study suggest that valsartan offers added protection against renal disease because it directly slows the progression of microalbuminuria.³⁹

Other studies in more advanced stages of diabetic nephropathy have demonstrated that AII receptor blockers are effective in protecting against the progression of nephropathy. The Irbesartan Diabetic Nephropathy Trial

(IDNT) demonstrated the renoprotection of irbesartan independent of the reduction in blood pressure.⁴⁰ In addition, results from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, using the AII receptor blocker losartan, demonstrated similar renoprotective effects in patients with type 2 diabetes and nephropathy.⁴¹ Based on these pharmacological, experimental and early clinical findings, AII receptor blockers represent a promising strategy for hypertensive patients with renal disease.

Conclusions

AII receptor blockers have been shown to have a beneficial effect in both lowering blood pressure and limiting renal haemodynamic changes. In addition, AII receptor blockers provide more effective and complete inhibition of angiotensin II than is provided by ACE inhibitors. Results from preliminary studies suggest that eprosartan may have a benefit in the prevention or delay of renal damage in hypertensive patients with renal impairment. However, it remains to be determined whether the renoprotective action of eprosartan can be translated into a clinical setting.

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