CLINICAL PHARMACOLOGY

ACE INHIBITORS IN DIABETIC NEPHROPATHY

Physiology of the renin angiotensin system

The renin angiotensin system (RAS) is an enzymatic cascade that results in the formation of the vasoactive peptide angiotensin II. The stimulation of this cascade is via the release of renin owing to hypotension, erect posture, salt depletion, beta-adrenergic stimulation and central nervous system excitation.

Angiotensin II is formed by the conversion of angiotensin I by angiotensin-converting enzyme (ACE). Angiotensin II stimulates the release of aldosterone from the adrenal gland. Angiotensin II is important in blood pressure control and sodium and water homeostasis, as well as in cardiovascular function and structure. Aldosterone results in sodium and water retention (Fig. 1). After aldosterone secretion, increases in renal sodium and water retention as well as blood pressure are seen, thereby turning off the stimulus for renin release.

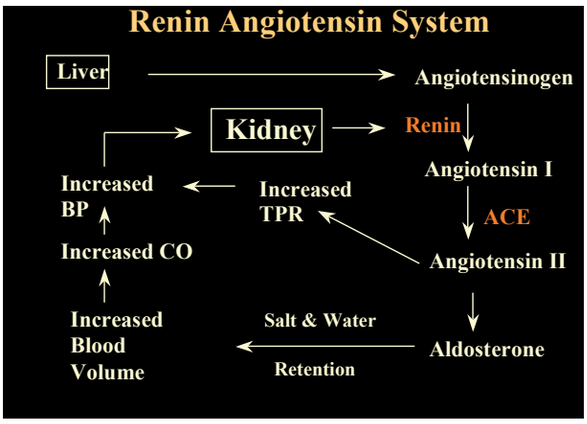

Fig. 1. Renin angiotensin system (ACE = angiotensin-converting enzyme; CO = cardiac output; TPR = total peripheral resistance).

RAS has been implicated in the pathophysiology of hypertension, congestive cardiac failure, diabetic nephropathy and in certain vascular diseases.

Diabetic nephropathy

Approximately 30 - 40% of all diabetics will manifest diabetic nephropathy, which has become the leading cause of end-stage renal disease (ESRD) in industrialised countries. Type 2 diabetics have a lower risk than type 1 diabetics of developing ESRD. However, as they represent more than 85% of the diabetic population, more patients with type 2 than type 1 diabetes ultimately progress to ESRD. Cardiovascular disease is the major cause of death in patients with ESRD worldwide and its frequency is increased further in diabetics.

The most important risk factors for the progression to ESRD in patients with diabetes are hypertension and albuminuria. These are also predictors of poor renal and cardiovascular outcomes in patients with diabetes.

Based on experimental models, haemodynamic changes at the glomerulus exert a major influence on the rate of progression of renal disease. Glomerular hyperfiltration and hypertension lead to progressive glomerulosclerosis and development of overt proteinuria. In addition, glomerular capillary hypertension contributes directly to the function of remaining intact nephrons. Early hyperfiltration is usually followed by persistent microalbuminuria. Proteinuria has been recognised as an independent risk factor for the progression of renal disease. This, combined with an elevated serum creatinine or blood pressure, places individuals at higher risk of renal disease progression.

The presence of systemic hypertension is not required for the development of glomerular hyperfiltration and hypertension, but, when present, amplifies the pathological effects of these changes.

RAS and diabetic nephropathy

RAS is important in the development and progression of both micro- and macrovascular complications of diabetes. Angiotensin II acts unfavourably on the intrarenal arterioles by increasing intraglomerular pressure and permeability, causing macrophage infiltration and leading to the release of transforming growth factor beta. Combination of all these effects leads to proteinuria, glomerulosclerosis, tubulo-interstitial fibrosis and eventual renal failure.

Inhibiting RAS has advantages with regard to renal function that extend beyond lowering blood pressure in the patient with hypertension and diabetes. In the kidneys, inhibition of RAS is associated with relaxation of the efferent arterioles and a reduction in intraglomerular pressure and proteinuria, thereby slowing progression of chronic renal failure. With this in mind, it is easy to understand why the angiotensin-converting enzyme inhibitors (ACEIs) are a rational choice of agent in the management of diabetic nephropathy. This is in addition to the important nutritional methods, low-protein diet and salt restriction, as well as intensive blood glucose control.

ACEIs and diabetic nephropathy – the evidence

ACEIs reduce glomerular capillary pressure and volume, which in animal models of diabetic nephropathy results in preservation of renal function. In a randomised controlled trial of captopril in type 1 diabetics with nephropathy it was found that the progression of renal failure (defined as either doubling of the baseline serum creatinine, death, dialysis, or transplantation) was reduced by nearly 50%. This effect was independent of blood pressure reduction, and of greatest

benefit in those with the poorest baseline kidney function. This pivotal trial showed that ACEIs can slow the progression of renal disease.

A 5-year randomised controlled trial of enalapril in normotensive type 2 diabetics with microalbuminuria reported a reduction of albuminuria and a stabilisation of serum creatinine in the enalapril group compared with the placebo group. A further study of enalapril in type 2 patients reported a 12.5% absolute risk reduction for the enalapril-treated arm in the development of microalbuminuria over the 6-year follow-up.

The Heart Outcomes Protection Evaluation (HOPE) study evaluated the effects of ramipril on cardiovascular and renal disease endpoints. This large study (*N* = 9 541) included 3 577 subjects with diabetes (98% type 2). Analysis of the diabetic patients revealed an overall risk reduction of 24% in overt nephropathy in those treated with ramipril over 4 - 5 years. The MICRO-HOPE study demonstrated a 25% risk reduction in cardiovascular endpoints in diabetic patients treated with ramipril, thus further highlighting the importance of blocking RAS in diabetic patients.

The results of a recent meta-analysis confirmed the beneficial effects of ACEI treatment in diabetic nephropathy. Progression to renal failure was reduced by 65% in patients with diabetes and microalbuminuria, and by 40% in patients with overt proteinuria. These results provide robust support for the use of ACEIs in diabetic patients with or without hypertension and microalbuminuria.

In the meta-analysis ACEIs were generally well tolerated, with cough the only adverse event that was significantly increased compared with placebo. It is important to note though that angioedema is a potentially lethal adverse event in patients taking ACEIs. The development of angioedema precludes the future use of an ACEI in the patient. Hyperkalaemia is another potentially life-threatening adverse event of ACEIs, particularly in patients with impaired renal function. A variety of ACEIs and doses have been studied; however, there is no consensus regarding the optimal ACEI and dose.

What about the angiotensin II receptor blockers (ARBs)?

The role of the more expensive ARBs in slowing the progression of renal disease has also been investigated. Randomised placebo-controlled trials of both irbesartan and losartan found that ARBs reduced the risk of progression of renal disease.

ARBs were compared with ACEIs in two studies. The Evaluation of Losartan in the Elderly (ELITE) study compared losartan with captopril in 722 patients (25% diabetics) over 65 years of age with heart failure. The study showed that there was no difference in renal dysfunction between the groups at both baseline and study completion. A recent study compared the renoprotective effects of telmisartan with enalapril in patients with type 2 diabetes presenting with early nephropathy and moderate hypertension. The primary endpoint was a change in glomerular filtration rate after 5 years. The results revealed that telmisartan was not inferior to enalapril in providing long-term renoprotection in patients with type 2 diabetes. These findings suggest that the benefit of slowing the progression of renal disease can be seen with ACEIs as well as ARBs.

Conclusion

RAS has an important role in the development of diabetic nephropathy, its progression as well as cardiovascular outcomes. There is good evidence that the ACEIs should be considered first-line agents in the prevention of the progression of diabetic nephropathy in both type 1 and type 2 diabetics. The more expensive ARBs should be reserved for patients who are ACEI intolerant, e.g. those with severe cough and angioedema (with caution).

IN A NUTSHELL

Diabetic nephropathy is a major cause of morbidity and mortality in diabetics.
RAS plays a crucial role in the development of diabetic nephropathy.
Tight control of blood pressure and glucose plays an essential role in the prevention and management of diabetic nephropathy.
ACEIs should be utilised in all diabetic patients with microalbuminuria who are normotensive, and should be considered in all diabetic patients with hypertension.
ARBs should be reserved for ACEI intolerance.

Further reading

ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? *Ann Intern Med* 2001; **134**: 370-379.

Barnett A. Prevention of loss of renal function over time in patients with diabetic nephropathy. *Am J Med* 2006; **119**: 40-47S.

Barnett A, Bain SC, Bouter P, *et al*. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004; **351**:1952-1961.

De P, Das G, Harley K, Nair H. Dual blockade of renin-angiotensin system in diabetic nephropathy: review of literature and local experience. *S Afr J Diabetes Vasc Dis* 2006; **3**: 85-90.

Hollenburg NK. Diabetes, nephropathy and the renin system. *J Hypertens* 2006; **24** (suppl. 1): S81–S87.

HOPE Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342**: 145-153.

HOPE Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: result of HOPE study and MICRO-HOPE substudy. *Lancet* 2000; **355**: 253-259.

Kshirsagar AV, Joy MS, Hogan SL, Falk RJ, Colindres RE. Effect of ACE inhibitors in diabetic and nondiabetic chronic renal disease: a systematic overview of randomized placebo-controlled trials. *Am J Kidney Dis* 2000; **35**: 695-707.

Lewis EJ, Hunsicker LG, Bain RP. Renoprotective effects of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345**: 851-860.

Lewis EJ, Hunsicker LG, Clarke WR, *et al*. for the Collaborative Study Group. The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. *N Eng J Med* 1993; **329**: 1456-1462.

Pitt B, Segal R, Martinez FA, *et al*. Randomised trial of losartan versus captopril in patients over 65 with heart failure. *Lancet* 1997; **349**: 747-752.

Strippoli GFM, Craig M, Craig JC. Antihypertensive agents for preventing diabetic kidney disease (Review). *The Cochrane Library* 2006, Issue 2 **http://www.thecochranelibrary.com** (accessed 24 August 2005).

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