Emerging Therapeutic Intervention with Angiotensin II Antagonists in Nephrology

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Loss of renal function leads to further loss of renal function, suggesting that after a certain point, reduction in functioning nephron number causes failure of the remaining units. Disorders associated with mild but permanent nephron injury often progress to end-stage renal failure even when the underlying disease resolved spontaneously or is treated successfully. Systemic hypertension can be both cause and consequence of renal injury and can accelcrate renal disease. Recent data suggest that glomerular capillary hyperperfusion and hypertension initiate glomerular structural and functional injury.

The most prominent clinical example of glomerular hypertension in the absence of systemic hypertension in diabetes mellitus. In diabetic rats the metabolic derangement is accompanied by single nephron hyperfiltration caused by glomerular capillary hyperperfusion and hypertension. Treatments that limit these hemodynamic abnormalities retard the development of structural and funetional injury. These include dietary protein restrietion and reduction in systemic arterial pressure. Interventions that control systemic hypertension, however, do not always control glomerular capillary hypertension. In rats, an antihypertensive regimen of vasodilators normalized systemic pressure but failed to lower glomerular capillary pressure in the remnant kidney and did not prevent the development of proteinuria or glomerular sclerosis. Administration of an angiotensin converting enzymc(ACE) inhibitor, however, resulted in control of systemic and glomerular hypertension and limited proteinuria and glomerular sclerosis. Several large clinical trials have now strongly confirmed these renoprotective properites of ACE inhibitors.

However, there can be problems associated with ACE inhibition. The precursor to the RAS is angiotensinogen, a large peptide made in the liver, which is converted into a 10-amino acid peptide, angiotensin I, by renin. Angiotensin 1 is then converted into an eightamino acid peptide, angiotensin II, by ACE. If patients are taking ACE inhibitor therapy and angiotensin II is still detected in the blood, angiotensin II must be converted from angiotensin I through other

pathways. This provided the rationale for searching for a molecule that blocks angiotensin II from binding to its receptor as another way to inhibit the RAS.

Losartan is the first orally active, highly specific angiotensin II subtype I (AT1) receptor antagonist that effectively blocks angiotensin II binding, thereby preventing its physilogic effects.

ACE not only converts angiotensin I to physiologically active angiotensin II, but also degrades kinins and, when ACE is inhibited, kinins accumulate; this may be responsible of the cough experienced by some patients on ACE inhibitors. Therefore, a potential advantage of blocking the receptor rather than ACE is that kinins do not aceumulate and cough does not occur. In Caucasians on ACE inhibitor therapy, debilitating cough leading to discontinuation of therapy is experienced in 8-15% of patients. However, among Asians, this is variably estimated as high as 50%.

Angiotensin antagonists are also renoprotective in animals. In rat models of chronic renal failure, angiotensin antagonists are apparently as effective as ACE inhibitors in terms of reducing hypertension, restoration of glomerular pressure from high to normal, antiproteinuria, and prevention of glomerulosclerosis. If losartan treatment is given to diabetic rats which are then compared with untreated diabetic rats and those receiving ACE inhibitors, losartan demonstrates a favorable effect on glomeruloseclerosis equivalent to that achieved by the ACE inhibitor.

Several small clinical studies have now been performed with angiotensin antagonists. In one study, 12 patients with proteinuria due to non-diabetic renal diseases were given losartan 50mg for four wecks, then 100mg for four weeks; a dose-dependent decrease in urinary protein excretion was seen in the absence of a further fall in blood pressure and, no change in GER. After cessation of losartan and a wash-out period, patients were given 10mg enalapril for four weeks, then 20mg for four weeks. A mirror-image effect was seen with losartan and enalapril therapy on blood pressure, proteinuria and GFR.

A recent trial of losartan in 75 patients with underlying renal insufficiency was performed. After 12 weeks of losartan, there was no change in GFR from baseline; losartan apparently does not adversely affect renal function even in those with low baseline values of GFR.

The ELITE(Evaluation of Losartan in the Elderly) trial published recently in the Lancet looked at whether losartan affects serum creatinine in elderly patients with heart failure(NYHA class II-IV). Patients were randomized to receive losartan or captopril, with about 350 patients in each group; the event rate for the primary end-point was exactly the same, namely that both drugs increased serum creatinine by 0.3mg/dl or more in 10% of patients. Surprisingly, in the

losartan patients there were significantly fewer deaths and hospitalizations for heart failure than in the captopril group after about one year, which caused ecssation of the trial. An ELITE II trial is now underway which is focused on the end-points of death and hospitalization from heart failure.

A randomized, double-blind, placebo-controlled study of losartan is alos underway in NIDDM patients with advanced nephropathy. The objective of this RENAAL(Reduction in End-points with the Angiotensin II antagonist, Losartan) study is to determine whether losartan plus any additional conventional antihypertensive drugs can effectively reduce the risk of reaching the mortality or end-state renal failure end-points, compared with placebo and conventional antihypertensives. Secondary aims are to study the effects of losartan on proteinuria, safety, tolerability, cost nd the need for hospitalization. Patients are being recruited from sites world-wide. Almost 1,200 patients have been enrolled to date, and the target is 1,500.

Never again should a patients with chronic nephropathy fail to be evaluated for an ACE inhibitor, due to their proven renoprotective effects. Convincing evidence is awaited from ongoing clinical trials concerning the potential nephroprotective effects of angiotensin II antagonists, especially in NIDDM. Fifty percent of diabeties should no longer reach end-stage renal failure and there is now hope for patients with other forms of chronic renal disease. The ultimate goal is to obviate the need for renal dialysis or transplantation.