Cochrane Corner

Are ACE inhibitors effective in preventing microalbuminuria and the progression of early diabetic renal disease to end-stage renal failure?

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Microalbuminuria

A patient is said to have overt proteinuria if urine tests show more than 300mg/l of albuminuria. Sensitive assays have shown that levels of albuminuria too low to be detected by conventional dipstick urinalysis can be present for months or years before reaching the 300mg/l level. This phenomenon is termed microalbuminuria and is defined as an excretion rate of 30 to 300mg/day.

Diabetic Nephropathy

About 20-35% of diabetic patients develop persistent proteinuria, a decline in glomerular filtration rate, and increased arterial blood pressure, which collectively constitute the clinical syndrome of diabetic nephropathy. The presence of nephropathy is closely associated with the increased morbidity and mortality in insulin dependent diabetes mellitus. Albuminuric diabetics may be 20 times more likely to die of cardiovascular disease than are non-albuminuric diabetics.

Prediction of Nephropathy

Nephropathy is predicted by the presence of microalbuminuria in both insulin dependent and non-insulin dependent diabetes. It may be that angiotensin converting enzyme inhibitors contribute to a slowing of progression by contributing an antiproteinuric effect not necessarily related to the effects of systemic blood pressure.

The review

This review examined randomised controlled trials of angiotensin converting enzyme inhibitors versus placebo, lasting for at least one year in normotensive diabetic patients with microalbuminuria or overt albuminuria. Thirteen studies were found: six using enalapril (10-20 mg /day), six using captopril (50-100mg/day) and one using lisinopril. Normotension was defined from 140/90 to 160/95. The age of onset of diabetes was always less than 41 years.

Both insulin dependent and non-insulin-dependent diabetes mellitus patients are included in randomised controlled trials usually of captopril (25 to 100 mg/day) or enalapril (5 to 20 mg/day). Most patients initially had microalbuminuria but some had overt albuminuria. Baseline albumin excretion rates that had been measured in mg per day averaged 134 and 129 for treatment and control.

End of study data

Mean arterial pressure rose little for the angiotensin converting enzyme inhibitor group (96.7 to 97.0 mmHg) and not as much as for the controls (95 to 101 mmHg). Thus overall a significantly greater antihypertensive effect was experienced by initially normotensive patients in the angiotensin converting enzyme inhibitor than in the placebo group.

The proposed beneficial effect of ACE inhibitors in renal disease is predicated on their ability to predominately alter efferent arteriolar

tone and consequently decrease intraglomerular pressure independent of their effect on systemic blood pressure.

The purpose of treating microalbuminuric diabetic patients with angiotensin converting enzyme inhibitors is not to reduce albumin excretion rate or to prevent its progression per se, but to prevent a future decline in glomerular filtration rate which otherwise would be expected in the majority of these patients and lead to end-stage renal failure and cardiovascular death.

In the natural history of diabetes the decline in glomerular filtration rate usually occurs with the development of overt proteinuria. Albuminuria, like hypertension, is defined with reference to an underlying continuous variable.

Microalbuminuria was defined as 30 to 300 mg/day, usually found in at least two out of three determinations. None of the studies lasted long enough to establish a relationship with end-stage renal failure, but after an open follow-up extension of their study Ravid et al (Ravid 1996) concluded that treatment with enalapril resulted in an absolute risk reduction of 42% for nephropathy to develop during seven years (95% confidence interval 15% to 69%; $p < 0.001$)

Implications for practice

Inhibition of angiotensin converting enzyme can arrest and even reduce the albumin excretion rate in microalbuminuric normotensive diabetics.

This is accompanied by some reduction or prevention of increase in systemic blood pressure and it is not possible to be certain that reduction of albumin excretion rate is due to a separate renal effect.

There appear to be no substantial side effects.

A direct link with postponement of end-stage renal failure has not been demonstrated.

References

References available from B Arroll or the Cochrane Library.

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