ACE Inhibitor and Angiotensin II Antagonist Combination Treatment

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GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **There is currently insufficient evidence that angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor antagonists are of additive specific benefit in diabetic nephropathy, beyond additional antihypertensive benefit.**
- **Although dual blockade is not yet established as a first-line treatment for all patients with diabetic nephropathy, it may be helpful in reaching treatment goals for blood pressure (BP) and albuminuria in individual patients.**
- **Both ACEIs and angiotensin receptor blockers (ARBs) should be suspended in situations where water and sodium depletion is present, e.g. in gastroenteritis.**
- **Studies demonstrate that dual blockade causes hypotension in 5% of patients, hyperkalaemia in 3%, and an increase in creatinine in 8% (Jacobsen 2003).**

Background

Blockade of the renin angiotensin system (RAS) is a major therapeutic tool in the prevention of diabetic nephropathy evolution. Relative benefit of the use of ACEIs, angiotensin receptor antagonists ARAs and their combination remains unclear. This section reviews data on dual RAS blockade in diabetic nephropathy.

Search strategy

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, A II receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.

Date of search: 16 December 2003.

What is the evidence?

There is as yet insufficient data documenting additional specific benefit from adding AII antagonist to ACEI treatment for protection against progression of diabetic nephropathy.

The effect of dual blockade of the RAS in patients with diabetes has been investigated only in short-term studies using surrogate endpoints for progression of diabetic nephropathy, i.e. antiproteinuric effects.

Studies have often used submaximal doses of the single agents, and the combination regimens have been more potently antihypertensive than the single drugs.

Type 2 diabetes
The CALM study (Mogensen et al 2000), a prospective, randomised, double-blind study of 199 microalbuminuric hypertensive Type 2 diabetic patients, documented better BP control (BP reduced a further 10/6 mmHg) with the combination of lisinopril 20 mg and candesartan 16 mg, compared to the same doses of either single agent. No significant changes in microalbuminuria or glomerular filtration rate (GFR) were detectable over 24 weeks.

Rossing et al (2002) reported a randomised, double-blind, crossover study of combination therapy in 18 Type 2 diabetics with overt nephropathy and blood pressure > 135/85 mmHg despite antihypertensive therapy including recommended doses of ACE inhibitors. Candesartan 8 mg once daily or placebo were each added for 2 months, in random order.

Addition of candesartan reduced albuminuria by 25% (95%CI: 2–58, p = 0.04), 24–h systolic blood pressure (SBP) by 10 mmHg (95%CI: 2–18, p = 0.02) and GFR by 5 mL/min/ 1.73 m^2 (95%CI: 0.1-9, p = 0.045). The GFR reduction was reversible on stopping candesartan. Significant variability in individual response to treatment was noted.

Type 1 diabetes
Jacobsen et al (2002, 2003) reported several small randomized controlled double-blind, crossover studies in Type 1 diabetic patients with nephropathy and GFR > 30 mL/min.

Summary of the evidence

Table 1 Characteristics of main studies

Study ID (author,year)	N	Randomization	Continuing therapy	Albuminuria	ABP*	GFR
Jacobsen et al, 2003	18	8-week periods of placebo/ 80 mg valsartan/ 20 mg benzepril/ combination	Loop diuretics	Albuminuria was reduced by all 3 active treatments, by 65% with either single agent, and by 80% with combination.	144/79 on placebo, 129/73 on either single agent, and 122/66 on dual blockade.	Combination therapy induced a reversible decrease in GFR of 12%.
Jacobsen et al, 2002	21	Placebo / irbesartan 300 mg	Previous antihypertensives Including ACEI	37% reduction (20–49, P < 0.001)	SBP NS DBP reduced 5mmHg (1–9, P = 0.01)	No change (K increase required intervention in 2 Patients, mean 4.3–4.6)
Jacobsen et al, 2003	24	Placebo / irbesartan 300 mg	Enalapril 40 mg	25% reduction (15–34, P < 0.001)	reduced 8/4 mmHg (4–12/2–7, P < 0.005)	No change (K unchanged)

*ABP – arterial blood pressure.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

References

Jacobsen P, Anderson S, Jensen BR et al. Additive effect of ACE inhibition and angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephroathy. J Am Soc Nephrol 2003; 14: 992–99.

Jacobsen P, Andersen S, Rossing K et al. Dual blockade of the renin-angiotensin system in type 1 patients with diabetic nephropathy. Nephrol Dial Transplant 2002; 17: 1019–24.

Jacobsen P, Andersen S, Rossing K et al. Dual blockade of the renin-angiotensin system versus maximal recommended dose of ACE inhibition in diabetic nephropathy. Kidney Int 2003; 63: 1874–80.

Mogensen CE, Neldam S, Tikkanen I et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ 2000; 321: 1440–44.

Rossing K, Christensen PK, Jensen BR et al. Dual blockade of the renin-angiotensin system in diabetic nephropathy: A randomized double-blind crossover study Diabetes Care 2002; 25: 95–100.