

Renoprotective Effect of Dual Blockade of Renin-angiotensin System by the Combination of ACE inhibitor and ATII Receptor Antagonist in Type II Diabetic Nephropathy Patients with Overt Proteinuria

인하대학교 의과대학 내과학교실, 인하대학교 의학연구소

송준호 · 이선영 · 박근호 · 이승우 · 김문재

Purpose : We evaluated the renoprotective effects of the dual blockade of rennin-angiotensin system (RAS) by the combination of ACE inhibitor (ACEi) and angiotensin II receptor blocker (ARB) as reflected by reduction of proteinuria and renal TGF- β production.

Methods : A total of 21 patients with type II diabetes with 24-hour protein excretion rate more than 3.0 gm/day and previously having been received single dose of 5 mg of ramipril enrolled to double blinded prospective crossover study with 3 periods; (1) double dose (DD) of 10 mg ramipril, (2) the combination of 5mg ramipril and 8mg candesartan, and (3) DD of 16 mg of candesartan, each for 12 weeks.

Results : Baseline data were as follows; F:M=10:12, age 58 ± 8 years, duration of diabetes 8 ± 2 years, Cr 2.9 ± 1.2 mg/dL, 24-hr urinary protein excretion rate (UPER) 5.5 ± 2.2 g/day, and urinary TGF- β 1 level 37.0 ± 22.8 pg/mg creatinine. BP was maintained as same as baseline for study periods, if necessary, by the adjunction of antihypertensives other than ACEi and ARB. 24-hr UPER was significantly reduced by the combination as compared to in baseline and by DD ramipril ($p < 0.05$). Mean % reduction in 24-hr UPER from baseline were $-4.1 \pm 12.9\%$, -11.0 ± 19.4 , and $-7.6 \pm 20.4\%$ by DD ramipril, the combination, and DD candesartan respectively. The % reduction was significantly large by the combination as compared to by DD ramipril (mean difference 6.9 ± 12.2 ; 95%CI 1.3-12.4; $p < 0.05$). Urinary TGF- β 1 level was significantly reduced by the combination as compared in baseline and by DD ramipril. DD candesartan also reduced urinary TGF- β 1 level as compared to baseline but not to DD ramipril. Mean % reduction from baseline were -4.2 ± 23.0 , -26.7 ± 27.8 , $-18.7 \pm 31.8\%$ by DD ramipril, the combination, and DD candesartan respectively. The % reduction was significantly large by the combination as compared to by DD ramipril (22.6 \pm 32.2; 95%CI 7.9-37.2; $p < 0.05$). The changes of 24-hr UPER and TGF- β 1 level showed no relation with that of BP. No significant changes were detected in the renal function during the study period.

Conclusion : The combination therapy showed benefits in reduction of proteinuria and renal TGF-beta production as compared to double dose of single ACEi or ARB therap in dependent of blood pressure-reducing effect. The switching from ramipril to candesartan also reduced TGF- β but the benefit was modest. The data suggest the combination of ACEi and ARB may provide additional renoprotection by reducing proteinuria and TGF- β production and can be used as a supportive measure for the control of proteinuria in overt diabetic nephropathy.