

## Individual or Combined Effects of Enalapril and Verapamil on the Chronic Cyclosporine Nephrotoxicity in Rats

Sang Koo Lee, M.D., Joo Yeol Park, M.D.<sup>†</sup>, Eun Sil Yu, M.D.\*  
Won Seok Yang, M.D., Soon Bae Kim, M.D., Su Kil Park, M.D.  
and Jung Sik Park, M.D.

*Departments of Internal Medicine, Pathology\* and  
Asan Institute for Life Sciences<sup>†</sup>, University of Ulsan, Seoul, Korea*

Previous studies have demonstrated that enalapril or verapamil seems to attenuate the cyclosporine nephrotoxicity. However, the effect of individual or combined treatment on the osteopontin, TGF- $\beta$ , endothelin-1 and procollagen alpha 1(I) gene expressions, which have been implicated in the pathogenesis of cyclosporine nephrotoxicity, has not been known much. Enalapril(50mg/L in drinking water) and verapamil(0.5mg/kg/day, subcutaneously), alone or in combination, were administered to rats with chronic cyclosporine nephrotoxicity(cyclosporine, 25mg/kg/day, subcutaneously)(each n=5). 5 rats treated with olive oil vehicle were served as normal. After 4 weeks, biochemical parameters were measured and renal cortical mRNA levels were evaluated by Northern blot analysis. Cyclosporine reduced the renal creatinine clearance significantly and induced the renal cortical osteopontin, TGF- $\beta$ , endothelin-1 and procollagen alpha 1(I) gene expressions around  $13.5 \pm 1.3$ ,  $2.4 \pm 0.2$ ,  $1.5 \pm 0.1$ ,  $1.9 \pm 0.1$  folds respectively. Individual treatment with enalapril or verapamil significantly suppressed the cyclosporine-induced osteopontin and TGF- $\beta$  mRNA expression, but not endothelin-1 and procollagen alpha 1(I). Combined treatment also inhibited the osteopontin and TGF- $\beta$  mRNA expression but there was no difference between combined treatment and each individual treatment. In conclusion, enalapril or verapamil significantly blunted the cyclosporine-induced osteopontin and TGF- $\beta$  gene expressions. However, combined treatment did not show any additive effects.