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Cyclosporine A 신독성 유발 쥐모델에서 nitric oxide 공여체와 cGMP phsophodiesterase 억제제의 비교 효과

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cGMP Phosphodiesterase Inhibitor Ameliorate Renal Injury in a Rat with Cyclosporine A Nephrotoxicity Via Addictive Effect Independent Nitric Oxide Pathway

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Background : Cyclosporine-A (CsA) inhibits the differentiation of T cells by suppressing calcineurin and thus blocks the activation of the IL-2 promotor gene which used for patients with nephrotic syndrome, kidney transplantation. long term CsA use must be limited. The mechanism of CsA induced nephrotoxicity have been suggested vasoconstriction due to the reduction of nitric oxide (NO), and tissue fibrosis caused by the elevation of transforming growth factor (TGF)-beta, vascular endothelial growth factor (VEGF). The NO donor (nitroprusside) and cyclic guanosine monophosphate (cGMP) phosphodiesterase (PDE) inhibitor (Udenafil), active in the NO/cGMP pathway has been reported to ameliorate renal injury.

Methods : The all groups(SD rat, 250 g, male) were provided low salt diet for 28 days. CsA group (N=6) was injected 15 mg/kg cyclosporine-A subcutaneously for 28 days, Nitroprusside group (N=6) was injected 15 mg/kg cyclosporine-A subcutaneously and treated with 5 mg/kg nitroprusside by osmotic pump for 28 days, Udenafil group (N=6) was injected 15 mg/kg cyclosporine-A subcutaneously and treated with 10 mg/kg udenafil orally for 28 days. After the collection of blood for BUN and creatinine on day 28, the remaining kidney was resected surgically and the injury was assessed by H&E staining, immunohistochemical staining for eNOS and VEGF was used to assess degree of renal injury.

Results : The BUN was Control group 21.83 mg/dL, CsA group 162.08 mg/dL, Nitroprusside group 141.63 mg/dL, Udenafil group 111.40 mg/dL. The creatinine was Control group 0.23 mg/dL, CsA group 2.50 mg/dL, Nitroprusside group 2.05 mg/dL, Udenafil group 1.15 mg/dL. Both parameters showed that the Udenafil group have statistically significant decrease compared with CsA group (p=0.041, p=0.004). Nitroprusside group was not showed statistically significant change compared with CsA group (p=0.39, p=0.14). The H&E staining of the Nitroprusside and Udenafil group compared to CsA group showed that the level of loss of the nuclei in the proximal tubules and tubulointerstitial inflammation were significantly decreased. The immunohistochemical staining for eNOS, VEGF showed that stained strongly in the Nitroprussdie and Udenafil group compared to the Control and CsA group.

Conclusion : cGMP phosphodiesterase-5 inhibitor ameliorated kidney injury in a rat model of CsA-induced nephrotoxicity more than NO donor. PDE-5 inhibitor has addictive effect on NO/cGMP pathway independent nitric oxide pathway.

Key Words : Cyclosporine A 신독성, NO, eNOS
Cyclosporine A nephrotoxicity, Nitric oxide, eNOS