

Sirolimus에 의한 당뇨에서 dipeptidyl peptidase IV inhibitor와 metformin의 병합투여에 의한 치료효과

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The Effect of Combined Treatment of Dipeptidyl Peptidase IV Inhibitor and Metformin in Sirolimus-induced Diabetes Mellitus

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Background: The contribution of the immunosuppressant sirolimus (SRL) to the development of post-transplant diabetes mellitus (PTDM) are being increasingly recognized. This study was performed to evaluate whether the combined treatment of dipeptidyl peptidase IV inhibitor (DPP IV inhibitor) with metformin results in lower glycaemia than DPP IV inhibitor or metformin administered alone in SRL-induced diabetes mellitus.

Method: Male Sprague dawley rats were treated initially with SRL (0.3 mg/kg, s.c) for 3 weeks and then started to treated with DPP IV inhibitor (LC15-0444, 5 mg/kg/day, oral gavage) and/or metformin (200 mg/kg/day, oral gavage) for further 3 weeks. Body weight, urine volume, and water intake were measured before sacrifice. The effect of combined treatment of LC15-0444 and metformin was evaluated by intraperitoneal glucose tolerance test (IPGTT), and islet size. Area under the curve for glucose (AUCg) calculated by trapezoidal estimation. Serum insulin level was assessed by comparing basal (0 min.) and 5 min. after intraperitoneal glucose injection. The influence of oxidative stress was evaluated by measuring 8-hydroxy-2'-deoxyguanosine (8-OHDG) level in serum samples.

Results: After 6 weeks, SRL treatment decreased delta body weight. Water intake and urine volume for 24-h was increased compared with vehicle group. SRL treatment significantly increased AUCg from the values obtained during the IPGTT (SRL, 254.2±10 mg/dL.min vs. VH, 166±5 mg/dL.min, p<0.05), but metformin or LC15-0444 treatment group recovered these value compared with the SRL alone (LC15-00444, 220.9±9 mg/dL.min; metformin, 227.9±10 mg/dL.min, p>0.05). Combined treatment with LC15-0444 and metformin has more significantly decreased blood glucose level (180.5±10 mg/dL.min) than LC15-0444 or metformin treatment alone. Consistently, serum insulin level responded by glucose injection showed higher level in combination group than LC15-0444 or metformin treatment alone. However, islet size and serum 8-OHDG level did not significantly changed in combined group compared with single treated group.

Conclusion: Combined treatment with LC15-0444 and metformin showed better glucose tolerance by improving insulin secretion than single therapy. This finding provides the rationale for the use of DPP IV inhibitor in PTDM taking sirolimus and metformin.

Key Words: 이식후 당뇨, 디펩티달 펩티다제4, 메트포르민, 시로리무스
Sirolimus, Sipeptidyl peptidase IV inhibitor, Metformin, Diabetes