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Drug Interaction between Tacrolimus and Everolimus in Experimental Model of Chronic Tacrolimus Nephrotoxicity and Pancreatic Injury

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Background: The effect of everolimus (EVR) on TAC-induced organ injury is undetermined.This study was conducted to investigate the pharmacological interaction between EVR and TAC at the blood and tissue level.
Methods: Male SD rats was oral treatment with TAC (6 mg/kg/day) and EVR (1 or 2 mg/kg/day) for 4 weeks. The effect of EVR on TAC-induced nephrotoxicity and pancreatic islet dysfunction was evaluated by renal and pancreatic function. Concentration of each drug was evaluated in the whole blood and tissue samples from kidney, pancreas and liver using LC/MS/MS. IB of P-glycoprotein (P-gp) and CYP3A4. Expression of 8-OHdG were measured in serum and urine.
Results: The EVR (1 or 2) treatment did not cause severe injury, but Combination treatment with EVR (1 or 2) aggravated TAC-induced toxicity.
In whole blood, higher TAC concentration was detected in the TAC plus EVR (1 or 2) group, and it is increased by dose dependent. EVR concentration was also seems to similar pattern. In kidney, pancreas and liver tissue, a surprising higher TAC concentration was also detected in the TAC+EVR1 or TAC+EVR2 groups in the pancreas (2.4-fold or 2.7-fold), in the kidney (1.4-fold or 1.7-fold) and in the liver (1.5-fold or 2.0-fold), compare to the TAC group. The higher concentration of EVL in kidney, pancreas and liver were also detected in the TAC+EVR1 or TAC+EVR2 groups in the pancreas (1.1.-fold or 1.3-fold), in the kidney (1.3-fold or 1.3-fold) and in the liver (1.4-fold or 2.0-fold), compared with EVR (1 or 2) groups. 8-OHdG excretion in urine and serum were significantly increased in the TAC group compared to the VH group. However, combination administration of EVR (1 or 2) showed much higher level than those of the TAC group. The P-gp level revealed that the TAC or EVR alone treatment groups was higher than that of VH group in pancreas and kidney. Co-treatment of the TAC and EVR was further increased P-gp expression compared to the TAC or EVR alone treatment groups. The CYP3A4 expression was not significantly defferent among the VH, TAC and EVR groups in liver, but Co-treatment of the TAC and EVR was increased CYP3A4 expression compared to the TAC or EVR alone treatment groups.
Conclusion: EVL aggravates TAC-induced organ injury and pharmacologic interaction between EVL and TAC have synergy effect. The reason for drug interaction between two drugs interaction between two drugs is related to the mutual competitive interactions targeting P-gp and CYP3A4.

Key Words: TAC, EVR, Drug interaction, Tacrolimus, Everolimus, Drug interaction