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Cilastatin attenuates vancomycin-induced nephrotoxicity via P-glycoprotein

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Objectives : Oxidative stress is one of the main pathogenic mechanisms in vancomycin-induced nephrotoxicity (VIN). Some studies suggest proximal renal tubular cell necrosis by vancomycin accumulation as a mechanism of nephrotoxicity, and other studies demonstrate that cilastatin has protective effects against drug-induced nephrotoxicity. We investigated whether cilastatin regulates P-gp expression and whether cilastation prevents VIN.

Methods : We conducted an in vitro study using an immortalized proximal tubule epithelial cell line from a normal adult human kidney (HK-2) and an in vivo study using male C57BL/6J mice.

Results : Vancomycin showed dose-dependent toxicity in the HK-2 cells, and cilastatin attenuated VIN. Vancomycin provoked the reactive oxygen species in a dose-dependent pattern on DCF-DA. Caspase 3/7 activity showed a dose-dependent increase at 6 hours. We confirmed apoptosis by Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay at 24 hr (vancomcyin 2 mM). Cilastatin attenuated vancomycin-induced ROS production and apoptosis, and it also attenuated vancomycin-induced p-gp suppression. In vivo, vancomycin (400mg/kg, 600 mg/kg IP, 7 days) induced acute kidney injury, as demonstrated by elevated blood urea nitrogen and creatinine. Histological examination of the sections indicated greater tubular damage in the vancomycin-treated kidney compared with the control. TUNEL-positive cells decreased significantly in the mouse kidney with cilastatin and vancomycin. Bax levels were significantly increased in the vancomycin-treated kidney. Cilastatin 300mg/kg treatment significantly decreased the vancomycin concentrations in the blood and kidney.

Conclusions : Our study showed that vancomycin-induced nephrotoxicity might be involved in suppressing P-gp function, and cilastatin attenuated VIN.

Keywords : Vancomycin; Cilastatin; Proximal tubule cells; Acute Kidney Injury