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Effect of Cilastatin on contrast-induced nephropathy

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Objectives: Contrast-induced nephropathy (CIN) is a major cause of hospital-acquired acute kidney injury. The mechanism of CIN has not been clearly revealed. P-glycoprotein (P-gp) is an important way to extrude drugs from cells. It is reported that cilastatin attenuates drug-induced nephrotoxicity. In this study, we investigated whether cilastatin regulates P-gp expression and whether the P-gp regulation of cilastatin would prevent CIN in an *in vitro* model.

Methods:

We did 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 and male New Zealand White rabbits.

Results: Contrast showed a dose-dependent toxicity in the HK-2 cells and cilastatin attenuated CIN. Contrast-mediated apoptosis was confirmed by the increase in the caspase 3/7 activity and Bax/Bcl-2 ratio. Contrast suppressed the P-gp expression/function. Cilastatin attenuated contrast-induced apoptosis and P-gp suppression. The role of P-gp in the protection mechanism of cilastatin was proved by a calcein AM test and also confirmed by the non- protective effect of cilastatin in P-gp knockdown HK-2 cell compared to wild-type HK-2 cells. *In vivo*, contrast [16-hr dehydration + indomethacin (10 mg/kg) + Nω-nitro-L-arginine methyl ester (L-NAME) (10 mg/kg) + Iopamidol (2.9 g iodine/kg body weight)] caused acute kidney injury in mice. Cilastatin (150 mg/kg) attenuated contrast-induced tubular damage and apoptosis. To exclude the drug effect in the mice-model results, contrast (10 g/kg dose single intravenous injection in rabbits) caused CIN, but cilastatin (70 mg/kg) attenuated CIN.

Conclusions: Our study showed that one mechanism of CIN might be involved with suppressing P-gp, and cilastatin attenuated CIN by P-gp.