KSN 2017 Abstract

KSN-17-O057

Itraconazole ameliorates chlorhexidine gluconate-induced peritoneal fibrosis in mice through regulating Hedgehog signaling pathway

Jin sug KIM[1], Eun ji PARK[1], Su woong JUNG[1], Tae won LEE[1], Chun gyoo IHM[1], Yu ho LEE[2], Sang ho LEE[2], Ju-young MOON[2], Yang gyun KIM[2], *Kyung hwan JEONG[1]

[1]Nephrology, Kyung Hee University Medical Center, Korea,South, [2]Nephrology, Kyung Hee University Hospital at Gangdong, Korea,South

Objectives : Peritoneal fibrosis is a devastating complication of peritoneal dialysis (PD), and one of the important causes that lead to discontinuation of PD. However, the precise mechanism is unclear and specific treatment has not yet been established. Recent evidence suggests that Sonic hedgehog (Shh) signaling pathway is involved in fibrogenesis, and drugs that inhibit this pathway are emerging in the treatment of fibrosis. Itraconazole, an anti-fungal agent, is recently also reported as an inhibitor of Shh signaling pathway. In this study, we investigated whether itraconazole suppressed chlorhexidine gluconate (CG)-induced peritoneal fibrosis in mice.

Methods : Peritoneal fibrosis was induced intraperitoneal (IP) injection of 0.1% CG every other day for 4 weeks, with or without itraconazole treatment (20mg/kg, IP injection on a daily basis). Saline was administered intraperitoneally to the control groups. Male C57BL/6 mice were divided into four groups: saline injection (group 1), saline injection plus itraconazole (group 2), CG injection (group 3), CG injection plus itraconazole (group 4). The effects of itraconazole were evaluated based on peritoneal thickness, immunohistochemical staining, and real-time polymerase chain reaction. The peritoneal thickness was identified by Masson's trichrome staining.

Results : Peritoneal thickening was evident in the group 3 (CG injection), and the thickening was markedly decreased in the group 4 (CG injection plus itraconazole) (59.9 ± 34.9 μm vs. 16.8 ± 9.0 μm, $p < 0.001$). Immunohistochemical staining revealed that IP injection of itraconazole downregulated infiltration of collagen I and Shh in the peritoneal tissue. The mRNA expression of markers for tissue fibrosis including transforming growth factor-β1 (TGF-β1), α-smooth muscle actin (α-SMA), and tumor necrosis factor-α (TNF-α) were increased in the group 3 (CG injection) and were downregulated in the group 4 (CG injection plus itraconazole). Similar results were shown in the markers for Shh signaling pathway. Itraconazole suppressed mRNA expression of Shh, Patched 1 (PTCH1), Smoothened (SMO), and Gli in

peritoneal tissues. Hypoxia inducible factor-1α (HIF-1α) and heat shock protein (HSP), which previously reported as a regulator of Shh, did not suppressed by itraconazole.

Conclusions : Our results suggest that itraconazole ameliorates the peritoneal fibrosis by regulating Shh signaling pathway. Itraconazole can be a potential therapeutic strategy for peritoneal fibrosis in PD.

Keywords : Peritoneal fibrosis, Itraconazole, Hedgehog signaling pathway