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Paricalcitol Enhances Antifibrotic Effect of Aliskiren in Obstructive Nephropathy

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Background: Besides the effect on blood pressure, previous experiments have reported the renoprotective effect of aliskiren, a direct rennin inhibitor, against unilateral ureteral obstruction (UUO)-induced renal fibrosis and inflammation. Paricalcitol, a vitamin D activator, has also been shown to attenuate renal inflammation and interstitial fibrosis. The aim of this study was to assess any potential additive effects of a therapy combining aliskiren with paricalcitol on reducing renal fibrosis.

Methods: C57BL6/J mice were treated individually with aliskiren or paricalcitol or their combinations until 7 days after initiation of UUO.

Results: In obstructed kidneys of UUO mice, monotherapy with aliskiren or paricalcitol significantly attenuated interstitial fibrosis, collagen deposition and α-smooth muscle actin compared to vehicle-treated UUO control. Levels of renal Nox1 and Nox4 were significantly attenuated with either aliskiren or paricalcitol. The therapy combining aliskiren with paricalcitol showed additive efficacy in inhibition of these parameters. Increased levels of phospho-ERK and phosphor-p38 MAPK in UUO kidneys were also significantly reduced by either aliskiren or paricalcitol treatment alone or in their combinations. Aliskiren seemed to be more potent than paricalcitol in suppressing angiotensin II type 1 receptor expression in obstructed kidneys. Although aliskiren significantly augmented renin expression in UUO kidneys, paricalcitol decreased intrarenal renin expression, and combination therapy with both effectively blocked the renin expression induced by aliskiren. Monotherapy with either aliskiren or paricalcitol significantly reduced the expression of (pro)renin receptor in UUO kidneys and a combination of both resulted in a further reduction of the renal expression of (pro)renin receptor.

Conclusion: These results suggest that combination therapy with aliskiren and paricalcitol has a better effect in inhibiting UUO-induced renal fibrosis. This mechanistic basis for this synergy may be attributed to a more profound inhibition of intrarenal activity of renin angiotensin system.

Keywords: Aliskiren, Kidney Fibrosis, Paricalcitol, Renin, Vitamin D