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Angiotensin Converting Enzyme Inhibition Aggravates Renal Interstitial Injury Resulting from Partial Unilateral Ureteral Obstruction in the Neonatal Rat

Kee Hwan Yoo

Department of Pediatrics Korea University Guro Hospital, Seoul, Korea

Purpose : Obstructive nephropathy remains a major cause of renal insufficiency in infants and children. Angiotensin plays an important regulatory role in renal development, inducing development of the renal pelvis and ureteral peristalsis and affecting the renal expression of important growth factors. The activity of the intrarenal renin-angiotensin system (RAS) is increased during early development and is further enhanced throughout the period of unilateral ureteral obstruction (UUO). ACE inhibitors are increasingly utilized in children with progressive renal disease.

Methods : Because angiotensin is necessary for normal renal development, we examined the effects of ACE inhibition both during and immediately following the period of postnatal nephrogenesis in the neonatal rat subjected to sham operation, partial or complete unilateral ureteral obstruction (UUO) under general anesthesia within the first 48 hours of life. Rats in Group I received enalapril 30 mg/kg body weight (or vehicle) daily for the first 10 days, while in Group II, the 10 days of treatment began 10 days after surgery. Kidneys were harvested at day 21 and analyzed for apoptosis (TUNEL), interstitial macrophages (ED-1 immunohistochemistry), myofibroblasts (α-smooth muscle actin), and collagen (Sirius red).

Results : Compared to vehicle, enalapril treatment increased macrophage and myofibroblast infiltration in sham-operated kidneys in Group I ($p<0.05$). In Group I, ipsilateral partial or complete UUO increased macrophage and myofibroblast infiltration 3 to 10-fold compared to sham-operation ($p<0.05$), and there was no additional effect of enalapril administration. In contrast, in Group II, enalapril increased macrophage, myofibroblast infiltration, and interstitial fibrosis ($p<0.05$) 2 to 4-fold in partially obstructed kidneys, but did not further increase values in complete UUO.

Conclusion : These findings indicate that ACE inhibition has deleterious effects both during and immediately after nephrogenesis. During nephrogenesis, effects are greatest in normal kidneys, while during nephron maturation effects are greatest in kidneys with partial UUO. Complete UUO maximizes injury in the affected kidney, and angiotensin inhibition results in no additional benefit or harm.