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Letter to the Editor

Fanconi Syndrome Associated with Cidofovir Therapy

Cidofovir is a nucleoside analog with potent activity against cytomegalovirus (CMV); it is 10-fold more potent than ganciclovir in vitro (4). Its phosphorylated metabolite has an intracellular half-life greater than 48 h, and it is estimated that intracellular phosphorylated cidofovir may inhibit CMV replication for 5 to 10 days (1). The proposed maintenance treatment in patients presenting with CMV retinitis, a devastating AIDS-related opportunistic infection, consists of only one intravenous administration every 2 weeks, which is clearly attractive. However, experimental and preclinical studies have shown that cidofovir may induce tubular injuries (3). We report a case of Fanconi syndrome and acute renal failure which occurred in a patient with CMV retinitis while he received cidofovir.

A 55-year-old human immunodeficiency virus-seropositive homosexual male suffered a relapse of CMV retinitis after a long period of intravenous ganciclovir maintenance administration. Serum creatinine was 108 μmol/liter, creatinine clearance was 71 ml/min/1.73 m^2, serum bicarbonate was 22 mmol/liter, serum phosphore was 1.29 mmol/liter, and proteinuria glycosuria was undetectable. His daily treatment consisted of indinavir (800 mg three times a day), stavudine (40 mg twice a day), and sulfamethoxazole (400 mg)-trimethoprim (80 mg).

A first injection of cidofovir (360 mg intravenously, 5 mg/kg of body weight) and a second one a week later were given in association with oral probenecid (4 g/day) and intravenous hydration (2 liters of 0.9% NaCl). A third injection (290 mg) was given without probenecid (stopped for an erythroderma). Before the third injection, serum creatinine clearance was 77 ml/min/1.73 m^2, serum bicarbonate was 19 mmol/liter, and serum phosphore was 0.5 mmol/liter. Acute renal failure associated with Fanconi syndrome without pain or fever was diagnosed 5 days later; serum creatinine was 415 μmol/liter, creatinine clearance was 18 ml/min/1.73 m^2, serum bicarbonate was 15 mmol/liter, serum phosphore was 2 mmol/liter, nonselective proteinuria was 2.7 g/liter, and glycosuria was 7.1 mmol/liter. Renal echography was normal. A kidney biopsy revealed interstitial fibrosis and tubular necrosis affecting primarily the proximal convoluted tubules with partial loss of epithelial cells and denudation of the adjacent basement membranes. Four months later, renal failure remained (creatinine clearance, 33 ml/min/1.73 m^2), with mild glycosuria (4 mmol/liter) and proteinuria (1.2 g/liter).

Cidofovir may induce a nephropathy in humans (2) that is characterized by degeneration and necrosis of the proximal convoluted tubule cells. Prevention of cidofovir nephrotoxicity includes hydration and probenecid treatment. Probenecid decreases the tubular secretion of cidofovir and limits nephrotoxicity in monkeys (3), but its efficacy in humans has not been established. In our patient, tubular injury preceded renal insufficiency. It occurred soon after the initiation of cidofovir treatment despite administration of probenecid with the first two injections. We strongly suggest that proximal tubular function be assessed (consisting at least of glycosuria and acidosis assessment) before each cidofovir administration in addition to the serum creatinine and proteinuria assessment recommended. The occurrence of any tubular toxicity even without alteration in renal function indicates that cidofovir treatment should be stopped. The efficacy of probenecid in our case is unclear; its use with the first injection of cidofovir did not prevent the onset of acidosis and hypophosphoremia, the first symptoms of tubular injury. The third injection of cidofovir without probenecid may have increased the nephrotoxicity of the drug. The possibility that indinavir, which was coadministered in our patient, enhanced cidofovir nephrotoxicity is not excluded. Indinavir nephrotoxicity has been recently reported (5). Finally, the efficacy and side effects of probenecid and indinavir coadministered with cidofovir remain to be determined through prospective studies.

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