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Acute renal failure in a lung transplant patient after therapy with cidofovir

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Sir: A 41-year-old man underwent double lung transplantation 4 months ago because of severe respiratory failure due to cryptogenic lung fibrosis. He received 2 mg tacrolimus b. i. d. and 20 mg prednisolone once a day. The patient was doing well until diarrhea started. IgM-antibodies to cytomegalovirus (CMV) were positive, and a virus load in the blood of 46,200 DNA-copies/ml was demonstrated by quantitative CMV-polymerase chain reaction (PCR). Colonoscopy revealed multiple aphthoid lesions and erosions in the cecum and ileum. CMV-colitis was verified histologically and immunohistochemically, and the patient was treated with ganciclovir (5 mg/kg) for a total of 3 weeks.

As the patient (who had already been hospitalized for over 3 months) wanted to leave the hospital, it was decided that cidofovir be administered (Vistide; Pharmacia & Upjohn), which constitutes an alternative to ganciclovir because of its long half-life, thus allowing infrequent intravenous dosing intervals. Cidofovir (5 mg/kg) was given after hydration with 2 l saline. Probenecid was not available. Although serum creatinine levels had been stable during the preceding 2 weeks, elevated serum creatinine (1.7 mg/dl) was determined on the day of, and prior to, cidofovir treatment. Other laboratory parameters like complete blood cell count, liver function, and inflammatory parameters were normal.

Four days later, the patient developed acute renal failure with anuria. The serum creatinine level was 6 mg/dl, and blood urea nitrogen was 70 mg/dl. Because of fluid retention, it was necessary to start hemodialysis. The patient underwent hemodialysis every other day for 1 week. In spite of dialysis and hemofiltration, creatinine levels remained at 4–5 mg/dl. The determination of CMV-PCR showed an increased virus load up from 46,200 copies/ml at the beginning of cidofovir therapy to 148,000 DNA-copies/ml. Therefore, therapy with ganciclovir (5 mg/kg) was resumed for 18 days, resulting in a rapid decrease of the virus load (1150 copies/ml). Kidney function, however, did not improve over the next 5 weeks, and the patient succumbed to fungal infection.

Cidofovir (HPMPC, Vistide) is a novel nucleotide analogue of deoxycytidine monophosphate with broad in vitro and in vivo activity against a wide variety of DNA viruses, including *Herpesviridae*, human polyomavirus, human papillomavirus, adenovirus, and cytomegalovirus [7]. The mechanism of cidofovir is attributed to its active intracellular metabolite, cidofovir diphosphate (a triphosphate analogue of deoxycytidine), which both inhibits and acts as an alternative substrate for (cytomegalovirus) DNA polymerase [2]. Cidofovir diphosphate persists in cells with an intracellular half-life of 17 h, which permits antiviral efficacy with infrequent dosage (maintenance dose every 2 weeks) [2, 7].

In this case, cidofovir was used for systemic CMV infection. However, after administration of cidofovir, an increase of the virus load from 46,200 copies/ml up to 148,000 DNA-copies/ml in the quantitative CMV-PCR within 1 week was observed. Through renewed treatment with ganciclovir, the patient improved. A second point in this case was the development of acute renal failure. Cidofovir is cleared from the body almost exclusively by the kidneys and is excreted by both glomerular filtration and active tubular secretion [1]. Disadvantages of cidofovir primarily include the risk of adverse drug reactions such as nephrotoxicity, which is likely to occur in up to 50 % of patients [3]. According to the manufacturer, probenecid should be administered with cidofovir to minimize the effect of nephrotoxicity by preventing tubular secretion, because tubular transport has been hypothesized to contribute to an accumulation of drug within proximal tubule cells. Nevertheless, the mechanism of nephrotoxicity is not fully understood.

In patients treated with cidofovir, proteinuria and elevations in creatinine have been reported for 39 % and 24 %, respectively [5, 6]. In addition, renal impairment was observed in some patients after cidofovir administration despite hydration with intravenous normal saline and the administration of oral probenecid to inhibit anion transport [7, 4]. Other adverse effects of cidofovir are neutropenia, seen in 15 % of the individuals treated, and potentially irreversible dose-dependent nephrotoxicity [5, 9] and iritis [8].

References

1. Cundy KC, Petty BG, Flaherty J, Fisher PE, Polis MA, Wachsman M, Lietman PS, Lalezari JP, Hitchcock MJ, Jaffe HS (1995) Clinical pharmacokinetics of cidofovir in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 39: 1247–1252
2. Ho HT, Woods KL, Bronson JJ, De Boeck H, Martin JC, Hitchcock MJ (1992) Intracellular metabolism of the antiherpes agent (S)-1-[3-hydroxy-2-(phosphonylmethoxy)propyl]cytosine. Mol Pharmacol 41: 197–202

3. Kendle JB, Fan-Harvard P (1998) Cidofovir in the treatment of cytomegaloviral disease. Ann Pharmacother 32: 1181–1192
4. Lalezari JP, Drew WL, Glutzer E, James C, Miner D, Flaherty J, Fisher PE, Cundy K, Hannigan J, Martin JC, Jaffe HS (1995) (S)-1-[3-hydroxy-2-(phosphonymethoxy)propyl]cytosine (cidofovir): results of a phase I/II study of a novel antiviral nucleotide analogue. J Infect Dis 171: 788–796
5. Lalezari JP, Stagg RJ, Kuppermann BD, Holland GN, Kramer F, Ives DB, Youle M, Robinson MR, Drew WL, Jaffe HS (1997) Intravenous cidofovir for peripheral cytomegalovirus retinitis in patients with AIDS. A randomized, controlled trial. Ann Intern Med 126: 257–263
6. Lalezari JP, Holland GN, Kramer F, McKinley GF, Kemper CA, Ives DV, Nelson R, Hardy WD, Kuppermann BD, Northfelt DW, Youle M, Johnson M, Lewis RA, Weinberg DV, Simon GL, Wolitz RA, Ruby AE, Stagg RJ, Jaffe HS (1998) Randomized, controlled study of the safety and efficacy of intravenous cidofovir for the treatment of relapsing cytomegalovirus retinitis in patients with AIDS. J Acquir Immune Defic Syndr Hum Retrovirol 17: 339–344
7. Lea AP, Bryson HM (1996) Cidofovir. Drugs 52: 225–230
8. Tseng AL, Mortimer CB, Salit IE (1999) Iritis associated with intravenous cidofovir. Ann Pharmacother 33: 167–171
9. Vittecoq D, Dumitrescu L, Beaufils H, Deray G (1997) Fanconi syndrome associated with cidofovir therapy. Antimicrob Agents Chemother 41: 1846

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