Single-Dose Pharmacokinetics of Cidofovir in Continuous Venovenous Hemofiltration

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Dosage recommendations for cidofovir are available for renally competent as well as impaired patients; however, there are no data for patients undergoing continuous renal replacement therapy. We determined the single-dose concentration-versus-time profile of cidofovir in a critically ill patient undergoing continuous venovenous hemofiltration (CVVH). One dose of 450 mg cidofovir (5 mg/kg) was administered intravenously due to a proven cytomegalovirus (CMV) infection and failure of first-line antiviral therapy. Additionally, 2 g of probenecid was administered orally 3 h prior to and 1 g was administered 2 h as well as 8 h after completion of the infusion. The concentrations of cidofovir in serum and ultrafiltrate were assessed by high-performance liquid chromatography. The peak serum concentration measured at 60 min postinfusion was 28.01 mg/liter at the arterial port. The trough serum level was 19.33 mg/liter at the arterial port after 24 h. The value of the area under the concentration-versus-time curve from 0 to 24 h was 543.8 mg · h/liter. The total body clearance was 2.46 ml/h/kg, and the elimination half-life time was 53.32 h. The sieving coefficient was 0.138 ± 0.022. Total removal of the drug was 30.99% after 24 h. Because of these data, which give us a rough idea of the concentration profile of cidofovir in patients undergoing CVVH, a toxic accumulation of the drug following repeated doses may be expected. Further trials have to be done to determine the right dosage of cidofovir in patients undergoing CVVH to avoid toxic accumulation of the drug.

Cidofovir [(S)-1-(3-hydroxy-2-(phosphonylmethoxy)propyl)cytosine] (HPMPC) is an acyclic nucleotide analogue with broad-spectrum antiviral activity against herpesviruses (1). Its potency in inhibiting human cytomegalovirus (HCMV) has been shown in conventional in vitro studies (2–4). It is approved for the systemic treatment of HCMV retinitis in patients with AIDS and as a second-line therapy for HCMV infections not responding to ganciclovir or foscarnet (5–8). The drug has also shown clinical efficacy against mucocutaneous infections with acyclovir-resistant herpes simplex virus and human papillomavirus infection in immunocompromised patients (9, 10).

Intracellular cidofovir is phosphorylated to its active form (cidofovir diphosphate) by cellular enzymes (1). In vitro studies suggest that the diphosphorylated form of HPMPC (HPMPCpp) may have a long (approximately 17 h) intracellular half-life (t1/2) (11, 12). It has been hypothesized that a single-bolus dose of HPMPC may result in sufficiently sustained intracellular levels of HPMPCpp achieving a prolonged (5- to 10-day) inhibition of HCMV (13, 14). There is also clinical evidence that a once-per-week dose of cidofovir is sufficient to delay progression of HCMV retinitis in immunocompromised patients (6). Cidofovir is rapidly excreted via the kidneys, with a renal clearance of 149 ml/h/kg and a systemic clearance of 177 ml/h/kg after the administration of a dose of 5 mg/kg, while coadministration of probenecid reduces renal clearance to 96.1 ml/h/kg, in comparison to a reported systemic clearance of 138 ml/h/kg (15). Urine recovery within 24 h was reported to be 85.9% of a 3-mg/kg dose (15). The dose-limiting effect of cidofovir in animals and humans is its nephrotoxicity, characterized by effects on proximal tubular cells (6). This toxicity is alleviated by concomitant administration of probenecid, a known inhibitor of the active tubular secretion of acidic drug molecules and hydration, as may be derived from the reduced 24-h urine recovery of 72.5% (±7.17%) when cidofovir is coadministered with probenecid (15). Dosage recommendations for cidofovir are available for the systemic treatment of CMV retinitis in immunocompromised patients or infection with herpesviruses (1, 6, 9). There are no data available for patients undergoing continuous renal replacement therapy (RRT). This dilemma is aggravated by the fact that due to its toxicity, cidofovir is a second-line therapy option, and thus the combination of patients receiving continuous RRT and cidofovir is extremely rare.

In the presented case, continuous RRT was performed as continuous venovenous hemofiltration (CVVH). CVVH is important in the treatment of intensive care patients suffering from sepsis and systemic inflammatory response syndrome due to its good hemodynamic tolerability. The physicochemical properties of the drug (protein binding, volume of distribution, molecular charge, and molecular weight) and the characteristics of the renal replacement technique used (type of filter, blood flow rate, usage of countercurrent dialysis, ultrafiltration rate, and adsorption of the drug onto the filter) are the determining factors of RRT relating to the elimination of the given drug (16–20).

We determined the concentration-versus-time profile of cidofovir given in a single-bolus dose to a patient undergoing CVVH.

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Patient. The cidofovir plasma levels in a male anuric intensive care patient with double lung transplantation and proven CMV retinitis not responding to first-line treatment were measured. The following demographic parameters were assessed: age, 54 years; weight, 90 kg; height, 170 cm; and APACHE score, 33. The serum creatinine level was 286 mol/liter prior to CVVH. Hemodialysis was not employed. Concomitant drug therapy consisted mainly of intravenous (i.v.) cefotaxime, anticoagulation with heparin, and morphine derivatives. The patient did not receive albumin substitution. Additional antimicrobial therapy and anticytotoxic therapy were permitted. All drugs were administered as clinically indicated by the attending physician. The patient neither was hypersensitive to cidofovir nor showed other intolerance to this substance.

CVVH. CVVH was performed as described previously using a polyethylene sulfone hemofilter with a membrane surface of 1.2 m² (Aqua Max HF 12; Fresenius, Germany) (21–24). A roller pump (Brady, Vienna, Austria) in connection with an automatic balancing system (Equallowe, Amicon, Ireland) was chosen for CVVH. The dialysis membranes were functional during the whole blood sampling period. The filters were not exchanged during the sampling time. The standard blood flow rate was 180 ml/min; rates were adjusted according to clinical need. The ultrafiltration rate was 25 ml/min. A bicarbonate-based crystalloid solution was infused as substitution fluid into the venous line (postdilution) at a rate that depended on balanced fluid therapy.

Drug administration and sampling. The patient received one dose of 450 mg cidofovir (Pfizer Enterprises, Luxembourg), equivalent to a dose of 5 mg/kg, dissolved in 100 ml of physiological saline solution and infused over a period of 60 min into a central venous catheter different from the venous catheter used for CVVH. The intended dosing interval between cidofovir doses was 1 week.

In addition to cidofovir, 2 g of probenecid was given orally 3 h prior to and another 1 g was given 2 h as well as 8 h after completion of the infusion.

Blood samples were drawn from the arterial (input) and venous (output) lines of the extracorporeal circuit before and 15, 30, 60, 120, 240, 360, 720, and 1,440 min after the start of the infusion. Ultrafiltration samples were collected from the outlet of the ultrafiltrate compartment of the hemofilter at corresponding times. All samples were plasma separated immediately and stored at −80°C until analysis.

Drug assay. The concentration of cidofovir in serum and ultrafiltrate was assessed by high-performance liquid chromatography (HPLC) as described previously with minor modifications (25). Briefly, after the addition of 300 µl of an acetic acid-acetonitrile-water solution (1:80:19, vol/vol) to 100 µl of serum or ultrafiltrate, the resulting mixture was vortex mixed, followed by centrifugation at 15,000 × g for 5 min. The supernatant (300 µl) was transferred into screw-cap polypropylene centrifugation tubes, and 100 µl of a phenacyl bromide solution (2.5 mmol/liter in acetonitrile; Sigma, Munich, Germany) was added to each tube. The tubes were sealed and incubated for 45 min at 80°C. After incubation, the samples were evaporated to dryness under a stream of nitrogen and the residues reconstituted in 500 µl of water. The constituted samples were briefly vortex mixed, centrifuged for 5 min (15,000 × g), and transferred into autosampler vials for HPLC analysis. The chromatographic assay included a Merck "La Chrom" system (Merck, Darmstadt, Germany) equipped with an L-7250 injector, an L-7100 pump, an L-7300 column oven (set at 45°C), a D-7000 interface, and an L-7480 fluorosence detector (excitation, 305 nm; emission, 270 nm). Separation of cidofovir from endogenous compounds in plasma and ultrafiltrate was achieved by an isocratic ion pair reversed-phase HPLC method using a Hypersil BDS C18 column (5 µm, 250 by 4.6 mm [inner diameter]; Astmoor, England) preceded by a Hypersil BDS C18 precolumn (5 µm, 10 by 4.6 mm [inner diameter]). The mobile phase consisted of docetyltrimethylammonium phosphate (Aldrich, Munich, Germany) (6 mM) and phosphoric acid (12 mM) in acetonitrile-water (30:70, vol/vol). Linear calibration curves were determined from the peak areas of cidofovir with respect to the external standard by spiking drug-free serum and ultrafiltrate with standard solutions of cidofovir (final concentration ranging from 0.5 µg to 200 µg/ml). The detection limit, defined as a signal-to-noise ratio of 3, was 2.5 ng/ml.

Pharmacokinetic analysis. The methods used for pharmacokinetic analysis with commercially available software (Kinetics 3.0; Innaphase, Philadelphia, PA, USA) have been described previously (26, 27). The area under the concentration-time curve (AUC) was determined by noncompartmental analysis using the trapezoidal rule. The elimination half-life was calculated as t1/2 = ln(2)/kel, where kel is the slope of the decreasing part of the concentration-time curve. The clearance (CL) was determined as dose/AUC. The volume of distribution (V) was calculated as V = CL/kliv.

A one-compartment model with linear elimination was best to describe the i.v. concentration-time data for cidofovir. This model was used to predict the individual concentrations in the patient for 5 mg/m², 4 mg/m², and 3 mg/m² for time points 0, 0.25, 0.5, 1, 2, 4, 6, 12, 24, 48, 72, 96, 120, 144, and 168 h. The concentrations were calculated with the following equations using kel, V, and Cl from the noncompartmental analysis: C(t) = (dose/Tinf)(1/kelV)(1 − e−kelTinf) for time points that are ≤ Tinf (infusion duration) and C(t) = (dose/Tinf)(1/kelV)(1 − e−kelTinf)[e−kel(Tinf − t)] for time points that are > Tinf.

Statistical analysis was performed using a commercially available computer program (Statistica; StatSoft Inc., Tulsa, OK, USA). The clearance of cidofovir (CLe) was determined according to the "hemofiltration" formula CLe = (UFR × CUF)/Ca, where UFR is the ultrafiltration rate and Ca and CUF are the ultrafiltrate and arterial (dialyzer inlet) serum cidofovir concentrations, respectively (27). The sieving coefficient (S) was calculated as S = Udíl/Ca. Total removal (Re) of the drug during hemofiltration was calculated as Re = (Cmax − Cmin)/Cmax × 100, where Cmax and Cmin are the arterial serum drug concentrations at the peak (60 min after the start of the drug infusion) and at the trough of the first dosing interval, respectively.

RESULTS

The peak serum concentration measured at 60 min postinfusion was 28.01 mg/liter at the arterial port. The trough serum level was 19.33 mg/liter at the arterial port after 24 h. The serum half-life was 53.32 h. The area under the concentration-versus-time curve from 0 to 24 h was 543.8 mg · h/liter.

The sieving coefficient was 0.138 (±0.022). Total removal of the drug was 30.99%. The calculated clearance of cidofovir was 2.46 ml/h/kg. The hemofiltration clearance (CLe) was 2.5 (±0.36) ml/h/kg.

The time-versus-concentration profiles of cidofovir in the arterial,
venous, and ultrafiltrate circulation are shown in Fig. 1. The predicted concentration-time profiles for 5 mg/m², 4 mg/m², and 3 mg/m² are illustrated in Fig. 2.

**DISCUSSION**

Dosage recommendations for cidofovir are available for the systemic treatment of CMV retinitis in immunocompromised patients (6–9) or infection with herpesviruses (1). Pharmacokinetics in patients with continuous ambulatory peritoneal dialysis and chronic hemodialysis have been published before (28); however, there are no data available for patients undergoing continuous RRT. The aim of the present report was to evaluate the pharmacokinetics of cidofovir in a critically ill patient with renal failure undergoing continuous renal replacement therapy.

The patient tolerated the intravenous infusion of 450 mg of cidofovir without apparent side effects. The peak (28.01 mg/liter [observed peak, arterial]) versus 19.6 (±7.18) mg/liter [peak serum concentration described in the literature for weekly dosing of 5 mg/kg in renally competent patients] and trough serum concentrations were higher than those in renally competent subjects (15, 29). The serum half-life (measured at the arterial port) was 53.32 h. This is higher than the half-life found in renally competent individuals, which is 2.17 (±0.46) h (15).

The calculated clearance was 2.46 ml/h/kg, whereas the reported clearance in renally competent patients is 138 (±36.2) ml/h/kg (15). After a 24-h hemofiltration process, only about 30% of the substance was removed, while in renally competent subjects 72.5% (±7.17%) is excreted. Extrapolated over 1 week, a trough level before the next dose of approximately 3 mg/liter has to be expected when administering a dose of 5 mg/kg. Although these data were assessed from only one subject, they provide a rough idea of the concentration profile of cidofovir in patients undergoing CVVH. A toxic accumulation of the drug following repeated doses should be expected when following the standard dosing regimen.

Derived from a one-compartment model simulation of expected plasma concentrations following different dosage regimens, a dose of 4 mg/kg would yield a peak level of 20.98 mg/kg, mimicking peak levels described previously for renally competent patients (15). Since cidofovir is intracellularly, a high peak level seems desirable. However, a swift reduction of the serum level as can be seen in renally competent patients would help to alleviate toxicity. Simulations based on a dose of 4 mg/kg predict a slow decline of serum levels to concentrations of 2.38 mg/ml after 1 week and 0.27 mg/ml after 2 weeks (without further cidofovir administration) during CVVH. Following dosing regimens in renally competent individuals, a second dose of cidofovir might be necessary after the first week and every 2 weeks after this point to allow for continuously elevated intracellular cidofovir concentrations.

Based on the (albeit limited) data, we recommend a dosage of between 3 and 4 mg/kg of body weight once per week initially (during the first 2 weeks) followed by a biweekly interval as a compromise between efficacy and toxicity in patients undergoing CVVH. An increased dosing interval may reduce trough levels but might also reduce efficacy due to reduced intracellular enrichment. Further trials have to be performed to determine the correct dosage of cidofovir in patients undergoing CVVH to avoid toxic accumulation of the drug.

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