ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2010, p. 2596–2602 Vol. 54, No. 6
0066-4804/10/$12.00 doi:10.1128/AAC.01540-09
Copyright © 2010, American Society for Microbiology. All Rights Reserved.

Pharmacokinetics of Sulfobutylether-Beta-Cyclodextrin and Voriconazole in Patients with End-Stage Renal Failure during Treatment with Two Hemodialysis Systems and Hemodiafiltration▽

Verena Hafner,[1]† David Czock,[1]† Jürgen Burhenne,[1] Klaus-Dieter Riedel,[1] Jürgen Bommer,[2] Gerd Mikus,[1] Christoph Machleidt,[3] Thomas Weinreich,[4] and Walter E. Haefeli[1]*

Department of Clinical Pharmacology and Pharmacoepidemiology, University of Heidelberg, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany[1]; Heimdialyse Heidelberg, Bergheimerstrasse 59, 69115 Heidelberg, Germany[2]; Nephrologisches Zentrum, Wolframstrasse 60-62, 70191 Stuttgart, Germany[3]; and Dialysezentrum Villingen-Schwenningen, Schrambergerstrasse 28, 78054 Villingen-Schwenningen, Germany[4]

Received 30 October 2009/Returned for modification 10 February 2010/Accepted 28 March 2010

Sulfobutylether-beta-cyclodextrin (SBECD), a large cyclic oligosaccharide that is used to solubilize voriconazole (VRC) for intravenous administration, is eliminated mainly by renal excretion. The pharmacokinetics of SBECD and voriconazole in patients undergoing extracorporeal renal replacement therapies are not well defined. We performed a three-period randomized crossover study of 15 patients with end-stage renal failure during 6-hour treatment with Genius dialysis, standard hemodialysis, or hemodiafiltration using a high-flux polysulfone membrane. At the start of renal replacement therapy, the patients received a single 2-h infusion of voriconazole (4 mg per kg of body weight) solubilized with SBECD. SBECD, voriconazole, and voriconazole-*N*-oxide concentrations were quantified in plasma and dialysate samples by high-performance liquid chromatography (HPLC) and by HPLC coupled to tandem mass spectrometry (LC-MS-MS) and analyzed by noncompartmental methods. Nonparametric repeated-measures analysis of variance (ANOVA) was used to analyze differences between treatment phases. SBECD and voriconazole recoveries in dialysate samples were 67% and 10% of the administered doses. SBECD concentrations declined with a half-life ranging from 2.6 ± 0.6 h (Genius dialysis) to 2.4 ± 0.9 h (hemodialysis) and 2.0 ± 0.6 h (hemodiafiltration) ($P < 0.01$ for Genius dialysis versus hemodiafiltration). Prediction of steady-state conditions indicated that even with daily hemodialysis, SBECD will still exceed SBECD exposure of patients with normal renal function by a factor of 6.2. SBECD was effectively eliminated during 6 h of renal replacement therapy by all methods, using high-flux polysulfone membranes, whereas elimination of voriconazole was quantitatively insignificant. The SBECD half-life during renal replacement therapy was nearly normalized, but the average SBECD exposure during repeated administration is expected to be still increased.

Voriconazole (VRC), a triazole broad-spectrum antifungal agent, is used for systemic treatment of severe fungal infections, including invasive aspergillosis and invasive candidiasis (6, 9). For intravenous administration, sulfobutylether-beta-cyclodextrin (SBECD) is used as a solvent. SBECD is a cyclic oligosaccharide composed of 1,4-linked glucopyranose molecules that form a truncated cone with a hydrophilic outer surface and a hydrophobic cavity (10, 15). This structure leads to an inclusion complex with the lipophilic voriconazole in its center (4). SBECD appears to be well tolerated in humans, but in animal studies, vacuolation of epithelial cells of the urinary tract as well as an activation of macrophages in liver and lung was observed after repeated doses of SBECD (5). SBECD is a pharmacologically inert agent. The terminal half-life of SBECD in humans with normal renal function is 1.8 h (1), and the steady-state volume of distribution is approximately 0.2 liter/kg of body weight, which is similar to extracellular fluid volume in humans and evidence of very little penetration into the tissues (17). SBECD is renally excreted (95% of the compound), and its clearance is linearly correlated with creatinine clearance. An increased SBECD exposure has been observed in patients with moderate renal impairment and renal failure (1, 19). Preliminary data from four patients with end-stage renal failure on intermittent hemodialysis indicated an extracorporeal SBECD clearance of 3.3 liters/h and removal of approximately 46% of SBECD during 4 h of hemodialysis (12).

Voriconazole is extensively metabolized by the hepatic cytochromes CYP2C19, CYP2C9, and CYP3A4 with a terminal elimination half-life ($T_{1/2}$) of approximately 7 h. The main metabolite, voriconazole-*N*-oxide, has only minimal antifungal activity, but its role in voriconazole-associated toxicity is unclear. Extracorporeal voriconazole clearance by hemodialysis is reported as 7.3 liters/h (17) but is considered clinically irrelevant due to the large apparent volume of distribution. Only 2% of a voriconazole dose is excreted unchanged renally. Voriconazole exhibits nonlinear pharmacokinetics, presum-

* Corresponding author. Mailing address: Department of Clinical Pharmacology and Pharmacoepidemiology, University of Heidelberg, Im Neuenheimer Feld 410, D-69120 Heidelberg, Germany. Phone: 49 6221 56 8740. Fax: 49 6221 56 4642. E-mail: walter.emil.haefeli@med.uni-heidelberg.de.

† These two authors made equal contributions to this work.

▽ Published ahead of print on 5 April 2010.

ably due to saturation of metabolism, which can be described by a two-compartment model with saturable elimination (8).

During hemodialysis, solutes are removed by diffusion over a semipermeable membrane, whereas in hemofiltration, removal of solutes is achieved by convective transport over the membrane by ultrafiltration. In intermittent hemodialysis, as used for patients with end-stage renal disease, a low ultrafiltration rate is used to remove excess water from the body (convective transport of solutes is of limited importance here). In intermittent hemodiafiltration, a higher ultrafiltration rate is used, which usually leads to an increase in extracorporeal solute clearance (excessively removed water is replaced in parallel). Genius dialysis is a special kind of hemodialysis with a single batch system where the whole dialysate is contained in one tank (3). Dialysis settings differ between countries. In Germany, dialysis durations of 4 to 5 h and blood flow rates between 200 and 300 ml/min are usually applied, whereas in the United States, dialysis durations of 3 to 4 h and blood flow rates over 300 ml/min are commonly used (13).

SBECD and voriconazole pharmacokinetics in patients with renal failure undergoing different renal replacement therapies are still unknown. The aim of the present study was to determine the pharmacokinetics of SBECD and voriconazole in patients undergoing Genius dialysis, hemodialysis, or hemodiafiltration.

MATERIALS AND METHODS

Study population. Fifteen patients with end-stage renal failure on long-term hemodialysis and with residual urine production of <500 ml/day were enrolled in the study in three hemodialysis centers in Germany (Heimdialyse Heidelberg, dialysis center in Villingen-Schwenningen, and dialysis center in Stuttgart). Exclusion criteria were as follows: age below 18 years; failure to provide written informed consent; concomitant treatment with vinca alkaloids, methadone, HIV protease inhibitors, nonnucleoside reverse transcriptase inhibitors, cyclosporin, tacrolimus, sirolimus, benzodiazepines, terfenadine, astemizole, pimozide, quinidine, ergotamine, dihydroergotamine, rifampin, rifabutin, carbamazepine, phenobarbital and other long-acting barbiturates, efavirenz, ritonavir, phenytoin, or St. John's wort within a period of 4 weeks prior to administration of study treatment; any treatment with a substance potentially requiring dose adjustment of voriconazole (VRC) or the concomitant drug itself within a period of less than five times the respective elimination half-life, or any concomitant drug with the potential to prolong the QT interval corrected for heart rate (QT_c) interval. Further exclusion criteria follow: therapeutic indication for voriconazole; clinically relevant anemia (hemoglobin < 10 g/dl); cardiac arrhythmia or myocardial infarction within the previous 2 years; history of clinically significant drug hypersensitivity to voriconazole, SBECD, or chemically related substances; alcohol abuse; participation in another clinical study during the last 2 months; clinically relevant abnormalities in potassium, calcium, and magnesium plasma concentrations; increase of alanine aminotransferase or aspartate aminotransferase more than three times the upper limit of normal; and pregnancy or lactation. In females of childbearing potential, reliable contraception (Pearl index < 1%) was required (11).

Study design and procedures. We performed a three-period, randomized, crossover study. The patients received 6 h of standard hemodialysis, hemodialysis with the Genius system, or hemodiafiltration instead of their usual renal replacement therapy, with a wash-out phase of 14 days between study days. At the start of renal replacement therapy, the patients received a single 2-h infusion of 4 mg of voriconazole (Vfend; Pfizer, Berlin, Germany) per kg of body weight. After reconstitution with water for injection, the product nominally contained 10 mg/ml voriconazole and 160 mg/ml SBECD. In order to obtain accurate doses, the concentrations of voriconazole and SBECD were measured in 3 vials showing actual voriconazole values of 10.75, 9.11, and 10.86 mg/ml (mean, 10.24 mg/ml) and SBECD values of 232, 212, and 216 mg/ml (mean, 220 mg/ml). Concomitant medication was kept constant, especially during study days, where possible. The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg, and the study was conducted in accordance with the Declaration of Helsinki, the guidelines for good clinical practice, and the specific legal requirements in Germany.

Blood and dialysate sampling. Before study drug administration, blood samples for safety laboratory screening were taken (hemoglobin; hematocrit; complete blood count; and the levels or values of sodium, potassium, calcium, creatinine, urea, uric acid, glucose, creatine kinase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin, total protein, albumin, triglycerides, total cholesterol, partial thromboplastin time, and international normalized ratio in serum or plasma). Venous blood samples for quantification of SBECD, voriconazole, and voriconazole-*N*-oxide were taken immediately before and 1, 2, 3, 4, 6, and 6.5 h after the start of intravenous voriconazole administration. All blood samples were taken from a peripheral vein or a central or peripheral intravenous catheter other than the voriconazole administration site. Two additional blood samples from the afferent and efferent blood lines where blood flows into and out of the dialyzer were taken 2 and 3 h after the start of drug administration. In the case of hemodialysis with the Genius system, dialysate samples were taken immediately at the start of dialysis and at 1, 2, 3, 4, 5, and 6 h after the start of drug administration. For hemodialysis and hemodiafiltration, the complete dialysate or ultrafiltrate was collected in a separate tank (high-density polyethylene; Schäfer Shop, Betzdorf/Sieg, Germany). At the end of the hemodialysis session, the collected dialysate/ultrafiltrate was weighed in order to quantify the collected volume (assuming a dialysate density of 1 g/cm^2) and stirred, and 5 samples were taken for quantification of SBECD and voriconazole. Blood samples were centrifuged, and plasma and dialysate samples were frozen at −20°C until analysis.

Renal replacement therapies. Hemodialysis with the Genius system was performed using a Genius 90 apparatus (Fresenius, Germany) and a high-flux polysulfone dialyzer with a membrane surface of 1.4 m^2 (FX 60 S; Fresenius, Germany). Hemodialysis and hemodiafiltration were performed using a Fresenius 4008 apparatus (Fresenius Medical Care, Germany) and the same dialyzer. The blood flow rate was set at 250 ml/min in all three systems and kept constant during the 6-h session. The dialysate flow rates were set at 250, 500, and 500 ml/min for Genius dialysis, hemodialysis, and hemodiafiltration, respectively. The ultrafiltration rate was determined by clinical needs and was kept constant during the dialysis session whenever possible. In the case of hemodiafiltration, the ultrafiltration rate was increased by 50 ml/min and the substitution fluid was administered in postdilution mode. The following parameters were documented for the three methods: cumulative blood volume every hour and ultrafiltrate volume for Genius dialysis; cumulative ultrafiltrate volume and cumulative blood volume every hour for hemodialysis; and cumulative blood volume, infusion volume every hour, and ultrafiltrate volume for hemodiafiltration. From these values, effective flow rates were calculated and used for pharmacokinetic calculations where appropriate.

Quantification of SBECD in plasma and dialysate samples. Reference-grade Captisol (SBECD sodium salt; batch number CY-03A-02053) with an average degree of substitution of 6.6 was supplied by CyDex Inc. (Overland Park, KS) and used as an analytical reference compound. Analytical procedures were established and validated as previously described (2, 4). In brief, plasma and dialysate samples (500 μl) were diluted with 0.2 M sodium phosphate buffer (1.5 ml; pH 7.0) and vortexed. The buffered samples were loaded onto conditioned Bond Elut-CH columns (100 mg; 1 ml) (Varian, Darmstadt, Germany) and washed with sodium phosphate buffer (950 μl; pH 7.0) before being eluted with a methanol-water mixture (30/70 [vol/vol]; 500 μl). The extraction procedures were processed automatically by a roboter system (Agilent, Waldbronn, Germany). The resulting extracts were evaporated to dryness in a stream of nitrogen (40°C), reconstituted with methanol-water (1/9 [vol/vol]; 150 μl), and analyzed by high-performance liquid chromatography (HPLC) (HP 1050 system; Agilent, Waldbronn, Germany). Size exclusion chromatography on a BioSep-SEC-S 3000 column (300-mm length, 7.8-mm diameter; 5 μm; Phenomenex, Aschaffenburg, Germany) was performed at 40°C. The isocratic mobile phase consisted of 0.1 mM 1-naphthol in methanol–0.2 M potassium nitrate (1/9 [vol/vol]) at a flow rate of 1 ml/min. Reconstituted samples were injected (100 μl), and fluorescence detection was performed at 290 nm (excitation) and 290 nm (emission). The lower limit of quantification was 4.0 μg/ml with a linear calibration range between 4 μg/ml and 540 μg/ml. The correlation coefficients (r^2) were always >0.99.

The accuracy and precision for SBECD in plasma and dialysate samples were always within 100% ± 15%, and the standard deviation was <15%. The accuracy and precision for voriconazole and voriconazole-*N*-oxide in plasma and dialysate samples were always within 100% ± 15%, and the standard deviation was <15%.

This analytical assay was validated according to the U.S. Food and Drug Administration guidelines (18) and fulfilled all quality demands for stability, recovery, accuracy, and precision.

Quantification of voriconazole and voriconazole-*N*-oxide in plasma and dialysate samples. Voriconazole (UK-109,496) and the internal standard, a structural analogue of voriconazole (UK-115,794), were kindly provided by Pfizer Inc.

(New York, NY) and used as analytical reference compounds. Voriconazole and voriconazole-*N*-oxide dialysate and plasma concentrations were determined after protein precipitation with acetonitrile and HPLC coupled to tandem mass spectrometry (LC-MS-MS). In brief, plasma and dialysate samples (100 μl) were pipetted into 400 μl acetonitrile containing the internal standard. After vortexing (30 s) and centrifugation (16,000 × *g*, 10 min), supernatant (300 μl) was pipetted into 300 μl of pure water. Aliquots (10 μl) were injected into the LC system (Shimadzu, Duisburg, Germany) consisting of an SIL-10ADvP autosampler, an LC-10ADvP gradient pump, and a Thermosphere TS-130 (Phenomenex, Aschaffenburg, Germany) column oven. The separation was performed using a reversed-phase C_{18} column (Synergy; 4 μm Polar-RP 80A; 150-mm length, 2-mm diameter; Phenomenex, Aschaffenburg, Germany) at 40°C. The eluent consisted of 5 mM ammonium acetate containing 0.1% acetic acid (60%) and acetonitrile (40%) at a flow rate of 0.35 ml/min. For detection, an API 365 tandem mass spectrometer (Applied Biosystems, Darmstadt, Germany) was operated in multiple-reaction monitoring mode. The eluent was directly introduced into the turbo ion spray interface. MS-MS transitions monitored in the negative-ion mode were m/z 408.0 → m/z 222.0 for voriconazole, m/z 364.0 → m/z 140.9 for voriconazole-*N*-oxide, and m/z 406.0 → m/z 220.0 for the internal standard. Calibration curves (30 to 5,000 ng/ml) were calculated from peak area ratios using weighted linear least-squares regression. The lower limit of quantification was 30 ng/ml. The correlation coefficients were always greater than 0.99. The accuracy and precision for voriconazole and voriconazole-*N*-oxide in plasma and dialysate samples were always within 100% ± 15%, and the standard deviation was <15%. This analytical assay was validated according to the U.S. Food and Drug Administration guidelines (18) and fulfilled all quality demands for stability, recovery, accuracy, and precision.

Pharmacokinetic analysis. The pharmacokinetics of SBECD, voriconazole, and voriconazole-*N*-oxide were analyzed using noncompartmental methods. The terminal elimination half-life ($T_{1/2}$) was calculated as $T_{1/2} = \ln(2)/\lambda_z$, where λ_z represents the slope of the terminal part of the plasma drug concentration-time curve up to 6 h as obtained by log linear regression. The area under the curve from 0 to 6 h (AUC_{0-6}) was calculated by the linear trapezoidal rule. The area under the plasma drug concentration-time curve from hour 6 to infinity ($AUC_{6-\infty}$) (assuming continued renal replacement therapy with constant efficacy) was calculated as $AUC_{6-\infty} = C_6/\lambda_z$, where C_6 is the concentration after 6 h. The area under the plasma drug concentration-time curve from hour 0 to infinity was calculated as $AUC_{0-\infty} = AUC_{0-6} + AUC_{6-\infty}$. The total systemic clearance (CL_{tot}) (which results from both residual elimination capacity of the patient and renal replacement therapy) was calculated as $CL_{tot} = D/AUC_{0-\infty}$, where D is the administered dose. For SBECD, the measured dose was used for calculation of SBECD pharmacokinetics, whereas for voriconazole, the nominal dose was used.

The apparent terminal volume of distribution (V_z) was calculated as $V_z = CL_{tot}/\lambda_z$. The clearance by extracorporeal renal replacement therapy (CL_{extra}) itself was calculated by two methods as follows. (i) CL_{extra} was calculated by dividing the amount recovered in the dialysate ($A_{dialysate}$) (as quantified in the dialysate/ultrafiltrate) by the AUC during renal replacement therapy as $CL_{extra,dialysate\text{-}based} = A_{dialysate}/AUC_{0-6}$. (ii) CL_{extra} was calculated using the plasma drug concentrations from the blood lines before and after the dialyzer. This clearance is based on the amount of drug entering the filter minus the amount leaving the filter evaluated by plasma prefilter (C_A) and postfilter (C_V) concentrations, individual plasma flow rate, and ultrafiltration rate. Thus, CL_{extra} was calculated as $CL_{extra,plasma\text{-}based} = [C_A \cdot Q_{plasma,in} - C_V \cdot (Q_{plasma,in} - Q_{UF})]/C_A$, with $Q_{plasma,in}$ being the plasma flow as calculated from blood flow and hematocrit [$Q_{plasma,in} = Q_{blood}(1 - hct)$] where hct is the hematocrit and Q_{UF} is the ultrafiltration rate. In addition, the total amount eliminated during renal replacement therapy (A_{total}), which is due to residual elimination capacity of the patient and renal replacement therapy, was estimated based on plasma values as $A_{total} = CL_{tot} \times AUC_{0-6}$ and expressed as percentage of the administered dose. The rebound in concentrations after the end of renal replacement therapy was calculated from the concentrations at 6 and 6.5 h.

To estimate the effects of hemodialysis on SBECD disposition at steady state, drug concentrations after repeated doses were predicted on the basis of the parameter values determined in the present study and published values for patients with normal and moderately impaired renal function (1). We applied a linear one-compartment model with zero-order input that was specified by differential equations and allows for intermittent changes in total drug clearance due to renal replacement therapy. Since the SBECD clearance in patients with end-stage renal failure between hemodialysis sessions ($CL_{tot,off}$) is unknown, an estimate had to be made based on the difference between total drug clearance during hemodialysis and extracorporeal clearance.

Pharmacokinetic calculations and simulations were done using WinNonlin 5.1 software (Pharsight Corporation, Mountain View, CA) and Microsoft Excel (Microsoft Corporation, Redmond, WA).

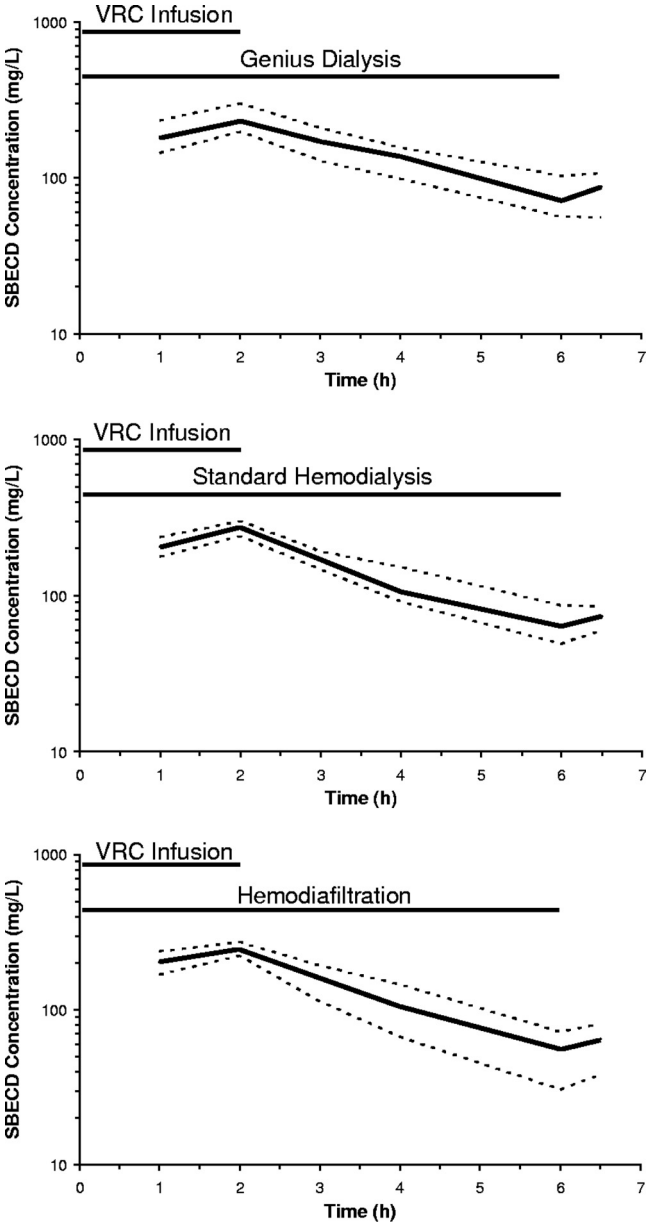

FIG. 1. Measured SBECD concentrations in patients with end-stage renal failure on renal replacement therapy. The fastest decline in concentrations was observed during hemodiafiltration. Concentrations are shown as median (continuous line) and interquartile range (broken lines). VRC, voriconazole.

Statistical methods. Data are shown as mean values ± standard deviations (SDs). Nonparametric repeated-measures analysis of variance (ANOVA) with Dunn's post hoc test was used to compare the pharmacokinetic parameters between groups (InStat 3; GraphPad Software Inc., San Diego, CA). Post hoc tests were carried out only if the ANOVA model was significant ($P < 0.05$). A P value below 0.05 was considered significant.

RESULTS

Fifteen Caucasian patients (9 males and 6 females; mean age, 52.6 ± 15.5 years; mean weight, 72.1 ± 18.6 kg) partici-

TABLE 1. Pharmacokinetic parameters of SBECD in 14 patients with end-stage renal failure on renal replacement therapy

Pharmacokinetic parameter	Value (mean ± SD) for SBECD after[a]:		
	Genius dialysis	Hemodialysis	Hemodiafiltration
Parameters based on plasma values			
$T_{1/2}$ (h)	2.6 ± 0.6	2.4 ± 0.9	2.0 ± 0.6**
C_{max}[b] (mg/liter)	254.6 ± 56.7	269.9 ± 41.1	245.8 ± 38.3
V_z (liter)	20.1 ± 7.4	18.8 ± 6.9	19.0 ± 6.0
CL_{tot} (liter/h)	5.4 ± 1.1	5.5 ± 0.9	6.7 ± 1.5**
$CL_{extra,plasma\text{-}based,2h}$ (liter/h)[c]	3.9 ± 1.2	4.5 ± 1.5	5.8 ± 0.4*
$CL_{extra,plasma\text{-}based,3h}$ (liter/h)[c]	3.9 ± 0.9	4.6 ± 1.7	5.9 ± 0.8**/+
A_{total} (%)	74.9 ± 7.6	79.4 ± 9.5	84.2 ± 7.8***
A_{total} (mg)	4,631.7 ± 907.6	4,929.8 ± 854.3*	5,332.4 ± 1,180.1***
Parameters based on dialysate values			
$CL_{extra,dialysate\text{-}based}$ (liter/h)	5.0 ± 2.0	4.7 ± 1.6	5.3 ± 1.6
A_{extra} (%)	69.0 ± 16.0	66.1 ± 13.1	66.9 ± 19.2
$A_{dialysate}$ (mg)	4,432.6 ± 1,861.1	4,228.0 ± 1,511.7	4,254.9 ± 1,472.9

[a] Values for the patients treated by Genius dialysis that are significantly different from the values for patients treated by hemodialysis or hemodiafiltration are indicated as follows: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. Values for the patients treated by hemodialysis that are significantly different ($P < 0.05$) from the values for patients treated by hemodiafiltration are indicated (+).
[b] C_{max}, maximum concentration of drug in serum.
[c] $n = 11$ for 2-h clearance (CL). $n = 10$ for 3-h CL.

pated in the study. One patient was excluded from analysis due to a dosing error.

SBECD was effectively eliminated with half-lives of 2.0 to 2.6 h (Fig. 1). Approximately two-thirds of the administered SBECD dose was recovered in the dialysate and ultrafiltrate after 6 h of Genius dialysis, standard hemodialysis, and hemodiafiltration (Table 1 and Fig. 2).

The rebound values of SBECD concentrations 30 min after the end of renal replacement therapy were 6.8% ± 16.5% for Genius dialysis, 8.7% ± 16.0% for hemodialysis, and 20.4% ± 24.2% for hemodiafiltration.

The pharmacokinetic simulations of SBECD concentrations after repeated doses every 12 h and hemodialysis every 48 h or every 24 h indicated that despite effective elimination during renal replacement therapy, the SBECD exposure is still expected to be considerably higher than in patients with normal renal function (Fig. 3A to C). The predicted steady-state AUC of SBECD was 10.3 times higher in anuric patients compared to normal AUC in humans with normal renal function. This is reduced to a 7.7 and 6.2 times higher AUC by applying hemodialysis every 48 or every 24 h. In the hypothetical case of hemodialysis during each voriconazole/SBECD infusion (i.e., every 12 h), the steady-state AUC was predicted to be still 2.1 times higher than the normal AUC and to be half of the steady-state AUC predicted for patients with moderate renal impairment.

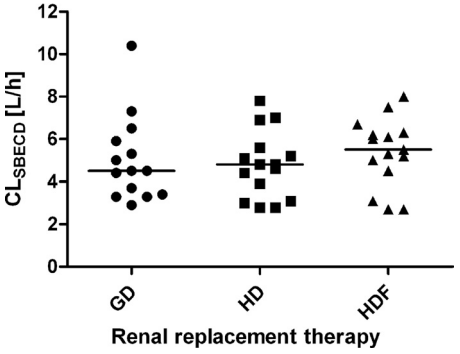

FIG. 2. SBECD extracorporeal clearance in 14 patients with end-stage renal failure on different renal replacement therapies, Genius dialysis (GD), hemodialysis (HD), or hemodiafiltration (HDF), as determined based on dialysate measurements. The median values are shown as short black lines. Each symbol is the value for one patient.

Voriconazole was poorly removed by renal replacement therapy (Table 2). The recovery of unchanged voriconazole in dialysate/ultrafiltrate was 8 to 13% of the administered dose. Approximately 8 to 11% of voriconazole was recovered as voriconazole-*N*-oxide. The values for extracorporeal clearance ($CL_{extra,dialysate\text{-}based}$) ranged from 4.9 to 7.1 liters/h for voriconazole and from 12.2 to 16.8 liters/h for voriconazole-*N*-oxide, with hemodiafiltration being more effective. The calculated voriconazole half-lives were very short, 2 to 3 h, and presumably reflect distribution rather than elimination. Thus, the terminal half-life of voriconazole in our patients is unknown, and total clearance and apparent volume of distribution could not be calculated.

Adverse effects. The infusion of voriconazole and SBECD was well tolerated in all patients without serious adverse events. The rare adverse events that occurred during the study were all transient. In one female patient, an increase of creatine kinase up to 2,100 U/liter was observed, but it was judged to be unrelated to the study medication and related to strenuous exercise. In one male patient, a transient increase in liver enzymes occurred (aspartate aminotransferase [62 U/liter] and gamma glutamyltransferase [94 U/liter]). Other adverse events, which were all judged to be unrelated to the study medication, were vascular access bleeding (1 patient), lumbar back pain (1 patient), hypotension and sweating due to self medication with 47.5 mg metoprolol (1 patient), drop in blood pressure (1 patient), diarrhea (twice in 1 patient), and dyspnea and angina pectoris due to fluid overload (1 patient).

DISCUSSION

Our study revealed that the solvent SBECD was extensively and rapidly eliminated by all applied renal replacement mo-

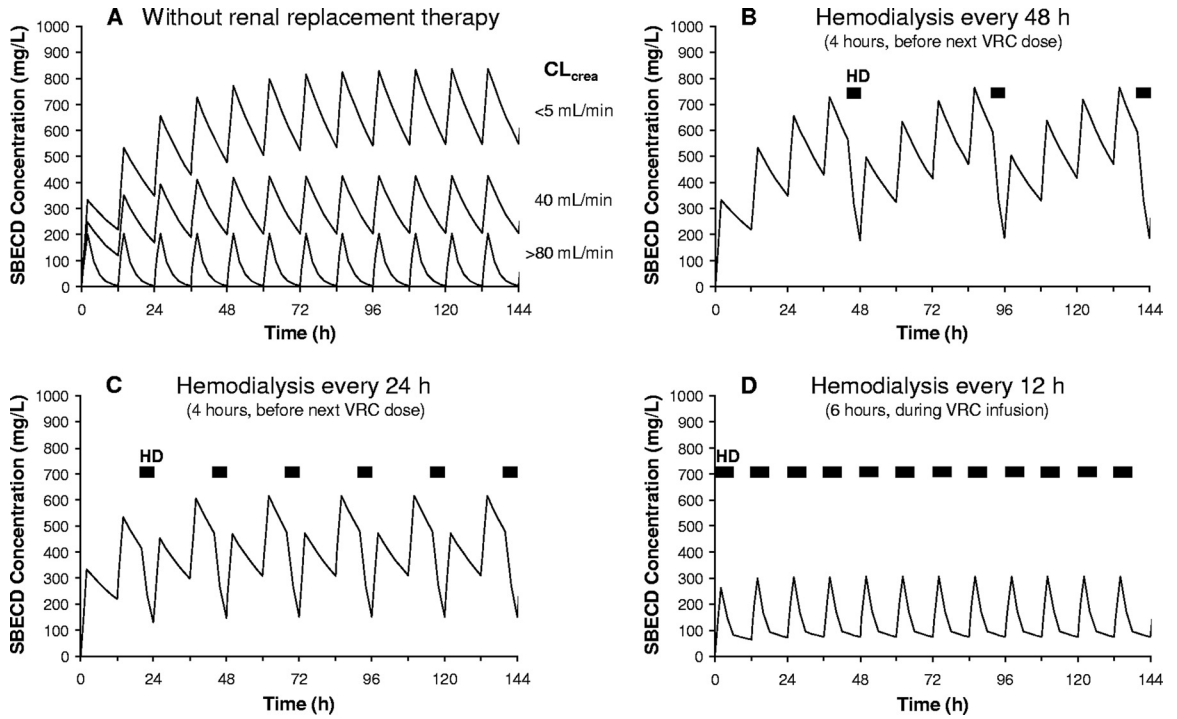

FIG. 3. Predicted SBECD concentrations after repeated administration of 6,600 mg SBECD in patients with normal renal function, impaired renal function, and renal failure without hemodialysis (A), renal failure with hemodialysis every 2 days (B), renal failure with hemodialysis every day (C), and hemodialysis every 12 h during VRC infusion (D). The parameter values were as follows: CL_{tot} = 8.5 liters/h and V = 23 liters for normal renal function; CL_{tot} = 1.8 liters/h and V = 24.8 liters for impaired renal function (based on data from Abel et al. [1]); and $CL_{tot,off}$ = 0.8 liter/h, $CL_{tot,on}$ = 5.5 liters/h, and V = 19 liters for renal failure (based on data from the present study). CL_{crea}, creatinine clearance; VRC, voriconazole.

dalities (Genius dialysis, standard hemodialysis, and hemodiafiltration). The observed half-lives were very similar to the half-life of 1.8 h in healthy individuals (1) consistent with efficient SBECD removal during the time period where renal replacement therapy was performed. Our estimate of approximately 67% removal by the 6-hour renal replacement therapy is in concordance with previous data indicating removal of 49% of the SBECD body load by a 4-hour hemodialysis (17). Unfortunately, the details of the latter study are not available.

SBECD elimination in our study was estimated by three

TABLE 2. Pharmacokinetic parameters of voriconazole and voriconazole-*N*-oxide in 14 hemodialysis patients on renal replacement therapy

Pharmacokinetic parameter	Value (mean ± SD) for drug after[a]:		
	Genius dialysis	Hemodialysis	Hemodiafiltration
Parameters based on plasma values			
Voriconazole			
C_{max} (mg/liter)	1.8 ± 0.6	1.7 ± 0.5	1.9 ± 0.5
$CL_{extra,plasma\text{-}based,2h}$ (liter/h)[b]	3.6 ± 2.4	4.0 ± 0.7	6.3 ± 1.0**/++
$CL_{extra,plasma\text{-}based,3h}$ (liter/h)[b]	3.6 ± 1.4	4.0 ± 0.8	5.6 ± 0.8**
Voriconazole-*N*-oxide			
$CL_{extra,plasma\text{-}based,2h}$ (liter/h)[b]	5.0 ± 1.6	4.1 ± 1.4	6.6 ± 1.3+++
$CL_{extra,plasma\text{-}based,3h}$ (liter/h)[b]	5.2 ± 1.3	6.0 ± 1.3	6.0 ± 1.4
Parameters based on dialysate values			
Voriconazole			
A_{extra} (%)	8.8 ± 3.3	12.7 ± 3.5	13.1 ± 5.8
$A_{dialysate}$ (mg)	26.6 ± 13.7	37.2 ± 15.3	35.7 ± 15.9**
$CL_{extra,dialysate\text{-}based}$ (liter/h)	4.9 ± 1.5	7.1 ± 1.3	6.9 ± 2.4
Voriconazole-*N*-oxide			
A_{extra} (%)	8.8 ± 7.2	7.7 ± 4.7	9.3 ± 7.6
$A_{dialysate}$ (mg)	24.0 ± 19.3	20.9 ± 10.9	24.5 ± 15.0
$CL_{extra,dialysate\text{-}based}$ (liter/h)	13.0 ± 13.6	12.2 ± 9.4	16.8 ± 17.2

[a] Values for the patients treated by Genius dialysis ($P < 0.01$) that are significantly different from the values for patients treated by hemodialysis or hemodiafiltration are indicated (**). Values for the patients treated by hemodialysis that are significantly different from the values for patients treated by hemodiafiltration are indicated as follows: ++, $P < 0.01$; +++, $P < 0.001$.

[b] n = 11 for 2-h clearance (CL). n = 10 for 3-h CL.

different approaches using (i) total plasma clearance, (ii) extracorporeal clearance after 2 and 3 h, and (iii) the amount of SBECD recovered in dialysate. The clearance values calculated in these different ways consistently ranged between 3.9 liters/h (extracorporeal clearance after 2 h for Genius dialysis) and 6.7 liters/h (total plasma clearance for hemodiafiltration).

The observed clearance values in our study were higher than described before, where hemodialysis eliminated SBECD with a clearance of 3.3 liters/h (12, 17). This may be explained by differences in membrane material and surface area of the applied dialyzer as well as by differences in blood, dialysate, and ultrafiltrate flow rates. The extensive clearance observed in our study appears to be contradictory to the recent study of von Mach and coworkers (19) who observed a considerable increase of SBECD in four critically ill patients despite intermittent dialysis. In three of these patients, plasma SBECD concentrations of up to 580 mg/liter were observed. In one of these patients, in whom concentrations were measured before and after dialysis on the same day, the SBECD concentration was only 3% lower after hemodialysis (19), indicating negligible elimination. The apparent discrepancy between this data and our data is likely due to the use of low-flux filter membranes (cutoff approximately 1,000 Da) by von Mach and high-flux filter membranes (cutoff approximately 20,000 Da) in our study. SBECD has a molecular mass of 2,163 Da.

Voriconazole (VRC) was poorly eliminated by hemodialysis. Approximately one-tenth of the voriconazole dose was recovered in the dialysate during 6 h of renal replacement therapy. Extracorporeal clearance values up to 7.1 liters/h appear to be high compared to the average total clearance of voriconazole known from healthy subjects. However, extracorporeal elimination is quantitatively still insignificant due to the large volume of distribution.

There appears to be a discrepancy for SBECD where plasma-based parameter estimates indicate a more rapid elimination during hemodiafiltration compared to Genius dialysis, whereas dialysate-based values do not. This might be explained by an initially higher clearance by hemodiafiltration that declines more rapidly during the treatment time, e.g., due to formation of a so-called secondary membrane that consists of plasma proteins binding to the dialyzer membrane. The calculated rebound was based on a single concentration 30 min after the end of dialysis. Thus, we cannot exclude the possibility that the full rebound effect may not have been captured. However, the estimation of pharmacokinetic parameters, as applied in the present study, is largely independent from a concentration rebound after the end of dialysis.

In the present study, voriconazole and SBECD were administered during dialysis (i.e., intradialytic administration). Intradialytic administration of drugs is rarely used, since unintended drug removal is to be avoided. Predialytic drug administration is sometimes used to maintain intradialytic concentrations of antiepileptics in patients with seizures and has been tried for administration of aminoglycosides and carboplatin (7, 14, 16). The present study provides evidence that intradialytic administration could be a better choice for voriconazole-SBECD in order to remove the solvent from the circulation.

Due to single dose administration of voriconazole-SBECD, steady-state conditions were not reached in this study. Instead, SBECD concentrations after repeated administration were predicted (Fig. 3). For voriconazole, a prediction was not possible based on the derived parameters due to its nonlinear pharmacokinetics.

Despite rapid elimination of SBECD by hemodialysis using high-flux membranes, it was predicted that SBECD exposure will still be considerably higher after repeated doses because SBECD elimination is "normalized" only intermittently. Thus, a dosing adjustment might be suggested, but this is impossible because of the disparate effects of renal replacement therapy on voriconazole and its solvent. Hence, voriconazole, which is eliminated largely independent of renal function and hemodialysis, has to be administered in regular doses in order to be effective. Therefore, it appears necessary to accept a higher SBECD exposure in patients with renal failure if oral administration of voriconazole (which does not contain SBECD) is impossible. However, it is still unknown whether such SBECD concentrations are associated with clinically relevant toxicity. If high SBECD concentrations are to be avoided, continuous renal replacement therapy should be considered.

ACKNOWLEDGMENTS

This study was supported in part by a grant from Pfizer, Germany. The Department of Clinical Pharmacology and Pharmacoepidemiology of the University of Heidelberg has received a grant from Pfizer, Germany, to establish and make available an HPLC method for the determination of voriconazole in plasma that is validated according to FDA standards.

None of the authors has financial or personal relationships that could potentially be perceived as influencing the research described herein.

We thank Marlies Stützle-Schnetz for study support and Andrea Deschlmayr, Magdalena Longo, and Jutta Kocher for excellent technical assistance and the Coordination Centre for Clinical Trials (KKS) Heidelberg for clinical monitoring.

REFERENCES

1. **Abel, S., R. Allan, K. Gandelman, K. Tomaszewski, D. J. Webb, and N. D. Wood.** 2008. Pharmacokinetics, safety and tolerance of voriconazole in renally impaired subjects: two prospective, multicentre, open-label, parallel-group volunteer studies. Clin. Drug Investig. **28:**409–420.
2. **Bayliss, M. A. J., R. Gage, A. M. Edgington, and R. F. Venn.** 2000. Fluorescence determination of sulphobutylether-beta-cyclodextrin sodium in human plasma and urine by size-exclusion chromatography with inclusion complex formation. Chromatographia **52:**S83–S86.
3. **Fliser, D., and J. T. Kielstein.** 2006. Treatment of renal failure in the intensive care unit with extended dialysis. Nat. Clin. Pract. Nephrol. **2:**32–39.
4. **Gage, R., R. F. Venn, M. A. Bayliss, A. M. Edgington, S. J. Roffey, and B. Sorrell.** 2000. Fluorescence determination of sulphobutylether-beta-cyclodextrin in human plasma by size exclusion chromatography with inclusion complex formation. J. Pharm. Biomed. Anal. **22:**773–780.
5. **Ghannoum, M. A., and D. M. Kuhn.** 2002. Voriconazole–better chances for patients with invasive mycoses. Eur. J. Med. Res. **7:**242–256.
6. **Herbrecht, R., D. W. Denning, T. F. Patterson, J. E. Bennett, R. E. Greene, J. W. Oestmann, W. V. Kern, K. A. Marr, P. Ribaud, O. Lortholary, R. Sylvester, R. H. Rubin, J. R. Wingard, P. Stark, C. Durand, D. Caillot, E. Thiel, P. H. Chandrasekar, M. R. Hodges, H. T. Schlamm, P. F. Troke, and B. de Pauw.** 2002. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N. Engl. J. Med. **347:**408–415.
7. **Kamel Mohamed, O. H., I. M. Wahba, S. Watnick, S. B. Earle, W. M. Bennett, J. W. Ayres, and M. Y. Munar.** 2007. Administration of tobramycin in the beginning of the hemodialysis session: a novel intradialytic dosing regimen. Clin. J. Am. Soc. Nephrol. **2:**694–699.
8. **Karlsson, M. O., I. Lutsar, and P. A. Milligan.** 2009. Population pharmacokinetic analysis of voriconazole plasma concentration data from pediatric studies. Antimicrob. Agents Chemother. **53:**935–944.
9. **Kullberg, B. J., J. D. Sobel, M. Ruhnke, P. G. Pappas, C. Viscoli, J. H. Rex, J. D. Cleary, E. Rubinstein, L. W. P. Church, J. M. Brown, H. T. Schlamm, I. T. Oborska, F. Hilton, and M. R. Hodges.** 2005. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet **366:** 1435–1442.

10. **Loftsson, T., and M. E. Brewster.** 1996. Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. J. Pharm. Sci. **85:**1017–1025.
11. **Mansour, D., P. Inki, and K. Gemzell-Danielsson.** 2010. Efficacy of contraceptive methods: a review of the literature. Eur. J. Contracept. Reprod. Health Care **15:**4–16.
12. **Muhl, E.** 2005. Antimycotic drugs under continuous renal replacement therapy. Mycoses **48:**56–60.
13. **Saran, R., J. L. Bragg-Gresham, N. W. Levin, Z. J. Twardowski, V. Wizemann, A. Saito, N. Kimata, B. W. Gillespie, C. Combe, J. Bommer, T. Akiba, D. L. Mapes, E. W. Young, and F. K. Port.** 2006. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. Kidney Int. **69:**1222–1228.
14. **Sowinski, K. M., S. J. Magner, A. Lucksiri, M. K. Scott, R. J. Hamburger, and B. A. Mueller.** 2008. Influence of hemodialysis on gentamicin pharmacokinetics, removal during hemodialysis, and recommended dosing. Clin. J. Am. Soc. Nephrol. **3:**355–361.
15. **Stella, V. J., and R. A. Rajewski.** 1997. Cyclodextrins: their future in drug formulation and delivery. Pharm. Res. **14:**556–567.
16. **Takezawa, K., I. Okamoto, M. Fukuoka, and K. Nakagawa.** 2008. Pharmacokinetic analysis of carboplatin and etoposide in a small cell lung cancer patient undergoing hemodialysis. J. Thorac. Oncol. **3:**1073–1075.
17. **U.S. Food and Drug Administration Antiviral Drugs Advisory Committee.** 2001. 4-October-2001 Briefing document for voriconazole (oral and intravenous formulations). U.S. Food and Drug Administration, Rockville, MD. http://www.fda.gov/ohrms/dockets/AC/01/briefing/3792b2_01_Pfizer.pdf.
18. **U.S. Food and Drug Administration Biopharmaceutics Coordinating Committee.** 2001. Guidance for industry: bioanalytical method validation. Biopharmaceutics Coordinating Committee, Center for Drug Evaluation and Research (CDER) in cooperation with Center for Veterinary Medicine (CVM) at the U.S. Food and Drug Administration, Rockville, MD. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf.
19. **von Mach, M. A., J. Burhenne, and L. S. Weilemann.** 2006. Accumulation of the solvent vehicle sulphobutylether beta cyclodextrin sodium in critically ill patients treated with intravenous voriconazole under renal replacement therapy. BMC Clin. Pharmacol. **6:**6.