Pharmacokinetics of sulfobutylether-beta-cyclodextrin (SBECO) and voriconazole in patients with end-stage renal failure during treatment with two hemodialysis systems and hemodiafiltration.

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SBECO and VRC during renal replacement therapy
ABSTRACT

Sulfobutylether-beta-cyclodextrin (SBEC), a large cyclic oligosaccharide that is used to solubilize voriconazole for intravenous administration, is eliminated mainly by renal excretion. The pharmacokinetics of SBEC and voriconazole in patients undergoing extracorporeal renal replacement therapies is not well defined.

We performed a three-period randomized cross-over study in 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 two-hour infusion of voriconazole 4 mg per kg body weight solubilized with SBEC. SBEC, voriconazole and voriconazole-N-oxide concentrations were quantified in plasma and dialysate samples by HPLC/fluorescence and LC/MS/MS, and analyzed by noncompartmental methods. Nonparametric repeated measures ANOVA was used to analyze differences between treatment phases.

SBEC and voriconazole recoveries in dialysate were 67% and 10% of the administered doses. SBEC concentrations declined with a half-life ranging from 2.6 ± 0.6 hours (Genius-dialysis) to 2.4 ± 0.9 hours (hemodialysis) and 2.0 ± 0.6 hours (hemodiafiltration) (p <0.01 for Genius dialysis vs. hemodiafiltration). Prediction of steady-state conditions indicated that even with daily hemodialysis SBEC will still exceed SBEC exposure of patients with normal renal function by a factor of 6.2.

SBEC was effectively eliminated during 6 hours of renal replacement therapy by all methods, using high-flux polysulfone membranes, whereas elimination of voriconazole was quantitatively insignificant. The SBEC half-life during renal replacement therapy was nearly normalized, but the average SBEC exposure during repeated administration is expected to be still increased.
INTRODUCTION

Voriconazole, a triazole broad spectrum antifungal agent, is used for systemic treatment of severe fungal infections including invasive aspergillosis and invasive candidiasis (7, 10). 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 (11,16). This structure leads to an inclusion complex with the lipophilic voriconazole in its center (5). 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 (6). SBECD is a pharmacologically inert agent. The terminal half-life of SBECD in humans with normal renal function is 1.8 hours (1) and the steady state volume of distribution is approximately 0.2 l/kg, which is similar to extracellular fluid volume in humans and evidence of very little penetration into tissues (3). SBECD is renally excreted (ninety-five percent 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, 18). Preliminary data from four patients with end-stage renal failure on intermittent hemodialysis indicated an extracorporeal SBECD clearance of 3.3 L/h and removal of approximately 46% of SBECD during four hours of hemodialysis (13).

Voriconazole is extensively metabolised by the hepatic cytochromes CYP2C19, CYP2C9, and CYP3A4 with a terminal elimination half-life ($t_{1/2}$) of approximately 7 hours. 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 L/h (3) 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 non-linear pharmacokinetics, presumably due to a saturation of metabolism, which can be described by a 2-compartment model with saturable elimination (9). 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 added, 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 (4). Dialysis settings differ between countries. In Germany dialysis durations of 4 to 5 hours and blood flow rates between 200 and 300 ml/min are usually applied whereas in the United States dialysis durations of 3 to 4 hours and blood flow rates over 300 ml/min are commonly used (14). SBEC and voriconazole pharmacokinetics in patients with renal failure undergoing different renal replacement therapies is still unknown. The aim of the present study was to determine the pharmacokinetics of SBEC and voriconazole in patients undergoing Genius dialysis, hemodialysis, or hemodiafiltration.
METHODS

Study population. Fifteen patients with end-stage renal failure on long-term hemodialysis and with residual urine production <500 mL/d were enrolled in the study in three hemodialysis centers in Germany (Heimdialyse Heidelberg, Dialysis center in Villingen-Schwenningen, Dialysis center in Stuttgart). Exclusion criteria were age below 18 years, failure to provide written informed consent, concomitant treatment with vinca alkaloids, methadone, HIV-protease inhibitors, non-nucleoside reverse transcriptase inhibitors, ciclosporin, 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 or the concomitant drug itself within a period of less than 5 times the respective elimination half-life, or any concomitant drug with the potential to prolong the QTc interval. Further exclusion criteria were: therapeutic indication for voriconazole, clinically relevant anemia (hemoglobin <10 g/dL), cardiac arrhythmia or myocardial infarction within the previous two 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 (12).

Study design and procedures. We performed a three-period, randomized, cross-over study. The patients received 6 hours of standard hemodialysis, hemodialysis with the Genius system, or
hemodiafiltration instead of their usual renal replacement therapy, with a wash-out phase of
fourteen days between study days. At the start of the renal replacement therapy the patients
received a single two-hour infusion of 4 mg/kg ‘dry’ body weight voriconazole (VFEND®,
Pfizer, Berlin, Germany). After reconstitution with water for injection, the product nominally
contained 10 mg/mL voriconazole and 160 mg/mL SBEC.D. In order to obtain accurate doses the
concentrations of voriconazole and SBEC.D 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 SBEC.D 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, for safety laboratory
screening was withdrawn (hemoglobin, hematocrit, complete blood count, serum or plasma
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). Venous blood samples for quantification of SBEC.D,
voriconazole, and voriconazole-N-oxide were taken immediately before and 1, 2, 3, 4, 6, and 6.5
hours after start of intravenous voriconazole administration. All blood samples were taken from a
peripheral vein or a central or peripheral intravenous catheter different to 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 hours after start of drug
administration. In 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 hours. For hemodialysis and hemodiafiltration the complete dialysate/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/cm²), stirred, and 5 samples were taken for quantification of SBEC 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 m² (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 to 250 mL/min in all three systems and kept constant during the six-hour session. The dialysate flow rate was 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 case of hemodiafiltration the ultrafiltration rate was increased by 50 mL/min and the substitution fluid was administered in post-dilution mode. The following parameters were documented: cumulative blood volume every hour and ultrafiltrate volume (Genius dialysis), cumulative ultrafiltrate volume, and cumulative blood volume every hour (hemodialysis), cumulative blood volume, infusion volume every hour, and ultrafiltrate volume (hemodiafiltration). From these values effective flow rates were calculated and used for pharmacokinetic calculations where appropriate.
Quantification of SBEC in plasma and dialysate. Reference grade Captisol® (SBEC sodium salt, Batch Number CY-03A-02053) with an average degree of substitution of 6.6 was supplied by CyDex Inc. (Overland Park, KS, USA) and used as analytical reference compound. Analytical procedures were established and validated as previously described (2,5). 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 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 HPLC (HP 1050 System, Agilent, Waldbronn, Germany). Size exclusion chromatography on a BioSep-SEC-S 3000 column (300x7.8 mm, 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). Lower limit of quantification was 4.0 µg/mL with a linear calibration range between 4 µg/mL and 540 µg/mL. Correlation coefficients were always r²>0.99.

Accuracy and precision for SBEC in plasma and dialysate were always within 100% ± 15% and standard deviation <15%. Accuracy and precision for voriconazole and voriconazole-N-oxide in plasma and dialysate were always within 100% ± 15% and standard deviation <15%.
This analytical assay was validated according to Food and Drug Administration guideline ‘Guidance for Industry: Bioanalytical method validation’ and fulfilled all quality demands for stability, recovery, accuracy, and precision.

Quantification of voriconazole and voriconazole-N-oxide in plasma and dialysate.

Voriconazole (UK-109,496) and the internal standard, a structural analogue of voriconazole (UK-115,794), were kindly provided by Pfizer Inc. (New York, USA) and used as analytical reference compound. 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 sec) and centrifugation (10 min / 16000 g) 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 a 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 C18 column (Synergy 4µ polar-RP 10A 150*2 mm; 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 - 5000 ng/mL) were calculated from peak area ratios using weighted linear least squares regression. Lower limit of quantification was 30 ng/mL. Correlation
coefficients were always greater than 0.99. Accuracy and precision for voriconazole and
voriconazole-N-oxide in plasma and dialysate were always within 100% ± 15% and standard
deviation <15%. This analytical assay was validated according to Food and Drug Administration
guideline ‘Guidance for Industry: Bioanalytical method validation’ and fulfilled all quality
demands for stability, recovery, accuracy, and precision.

Pharmacokinetic analysis. The pharmacokinetics of SBEC, 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 \( \lambda_z \) represents the slope of the terminal part of the plasma
concentration-time curve up to 6 hours as obtained by log-linear regression. The area under the
curve from 0 to 6 hours (AUC\(_{0-6}\)) was calculated by the linear trapezoidal rule. The area under the
plasma 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 hours. The area under the plasma concentration-time curve from hour 0 to
infinity was calculated as AUC\(_{0-\infty}\) = AUC\(_{0-6}\) + AUC\(_{6-\infty}\). The total systemic clearance (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 SBEC the measured
dose was used for calculation of SBEC pharmacokinetics, for voriconazole the nominal dose
was used.

The apparent terminal volume of distribution was calculated as \( V_z = CL_{tot} / \lambda_z \). The clearance by
the extracorporeal renal replacement therapy itself (CL\(_{extra}\)) was calculated by two methods. (1)
CL\(_{extra}\) was calculated by dividing the recovered amount \( A_{dialysate} \) (as quantified in the
dialysate/ultrafiltrate) by the AUC during renal replacement therapy as CL\(_{extra,dialysate-based}\) =
\( A_{dialysate} / AUC_{0-6} \). (2) CL\(_{extra}\) was calculated using the plasma concentrations from the blood lines

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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\textsubscript{extra} was calculated as:

$$CL_{\text{extra,plasma-based}} = \frac{(C_A \cdot Q_{\text{plasma,in}} - C_V \cdot (Q_{\text{plasma,in}} - Q_{\text{UF}}))}{C_A},$$

with $Q_{\text{plasma,in}}$ being the plasma flow as calculated from blood flow and hematocrit ($Q_{\text{plasma,in}} = Q_{\text{blood}} \cdot (1 - \text{hct})$) and $Q_{\text{UF}}$ the ultrafiltration rate. In addition, the total amount eliminated during renal replacement therapy ($A_{\text{total}}$), which is due to residual elimination capacity of the patient and renal replacement therapy, was estimated based on plasma values as $A_{\text{total}} = CL_{\text{tot}} \cdot AUC_{0-6}$ and expressed as percent of the administered dose. The potential rebound in concentrations after the end of renal replacement therapy was calculated from the 6 and 6.5 hour concentrations.

To estimate the effects of hemodialysis on SBECBD disposition at steady-state, pharmacokinetics after repeated doses were predicted based on 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 SBECBD clearance in patients with end-stage renal failure between hemodialysis sessions ($CL_{\text{tot,off}}$) 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, USA.) and Microsoft® Excel (Microsoft Corporation, Washington, DC, USA).
Statistical methods. Data are shown as mean values ± standard deviation (SD). Nonparametric repeated measures ANOVA (Friedman ANOVA) with Dunn’s posthoc test was used to compare the pharmacokinetic parameters between groups (InStat 3, GraphPad Software Inc., San Diego, USA). Posthoc-tests were only carried out if the ANOVA model was significant (p < 0.05). A p value below 0.05 was considered significant.

RESULTS
Fifteen Caucasian patients (9 males, 6 females, mean age 52.6 ± 15.5 years, mean dry weight 72.1 ± 18.6 kg) participated in the study. One patient was excluded from analysis due to a dosing error.

SBECED was effectively eliminated with half-lives of 2.0 to 2.6 hours (Figure 1). Approximately 2/3 of the administered SBECED dose was recovered in the dialysate / ultrafiltrate after 6 hours of Genius dialysis, standard hemodialysis, and hemodiafiltration (Table 1).

The rebound of SBECED concentrations 30 minutes after the end of renal replacement therapy was 6.8 ± 16.5% for Genius dialysis, 8.7 ± 16.0% for hemodialysis, and 20.4 ± 24.2% for hemodiafiltration.

The pharmacokinetic simulations of SBECED concentrations after repeated doses every 12 hours and hemodialysis every 48 or every 24 hours indicated that despite effective elimination during renal replacement therapy the SBECED exposure is expected to be still considerably higher as compared to that in patients with normal renal function (Figure 3A-C). The predicted steady-state AUC of SBECED was 10.3 times higher in anuric patients as 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 hours. In the hypothetical case of hemodialysis during each voriconazole/SBECED infusion (i.e. every 12 hours) 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.

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. Extracorporeal clearance ($\text{CL}_{\text{extra dialysate-based}}$) ranged from 4.9 to 7.1 L/h for voriconazole and from 12.2 to 16.8 L/h for voriconazole-N-oxide, with hemodiafiltration being more effective. The calculated voriconazole half-lives were very short with 2 to 3 hours and presumably rather reflect distribution 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/ SBECV was well tolerated in all patients without serious adverse events. The rare adverse events occurring during the study were all transient. In one female patient an increase of creatine kinase up to 2100 U/L was observed, but was judged 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/L and gamma glutamyltransferase 94 U/L). Other adverse events, which were all judged 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 of blood pressure (1 patient), diarrhea (twice in 1 patient), dyspnea and angina pectoris due to fluid overload (1 patient).
DISCUSSION

Our study revealed that the solvent SBECO was extensively and rapidly eliminated by all applied
renal replacement modalities (Genius dialysis, standard hemodialysis, and hemodiafiltration). The
observed half-lives were very similar to the half-life of 1.8 hours in healthy individuals (1)
consistent with efficient SBECO 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 SBECO body load
by a 4-hour hemodialysis (3). Unfortunately, the details of the latter study are not available.

SBECO elimination in our study was estimated by three different approaches using (1) total
plasma clearance (2) the extracorporeal clearance after two and three hours, and (3) the amount of
SBECO recovered in dialysate. The clearances calculated in these different ways were
consistently ranging between 3.9 L/h (extracorporeal clearance after 2 hours for Genius dialysis)
and 6.7 L/h (total plasma clearance of for hemodiafiltration).

The observed clearance values in our study were higher than described before, where
hemodialysis eliminated SBECO with a clearance of 3.3 L/h (3, 13). 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 co-workers (18) who
observed a considerable increase of SBECO in four critically ill patients despite intermittent
dialysis. In three of these patients SBECO plasma concentrations of up to 580 mg/L were
observed. In one of these patients, in whom concentrations were measured before and after
dialysis on the same day, SBECO concentration was only 3% lower after hemodialysis (18)
indicating negligible elimination. The apparent discrepancy between this and our data is likely

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due to the use of low-flux filter membranes (cut-off approximately 1000 Dalton) by von Mach
and high-flux filter membranes (cut-off approximately 20000 Dalton) in our study. SBECID has a
molecular weight of 2163 Dalton.

Voriconazole was poorly eliminated by hemodialysis. Approximately one tenth of the
voriconazole dose was recovered in the dialysate during 6 hours of renal replacement therapy.
Extracorporeal clearance values up to 7.1 L/h appear to be high as 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 SBECID where plasma-based parameter estimates indicate a
more rapid elimination during hemodiafiltration as 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 minutes after the end of dialysis.
Thus, it is possible that we did not capture the full rebound effect. 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/SBECID was administered during dialysis (i.e. intradialytic).
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 (8, 15, 17). The present study provides evidence that
intradialytic administration could be a better choice for voriconazole/SBECD in order to rapidly 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 (Figure 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 be still 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 from 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.
REFERENCES


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CONFLICT OF INTEREST STATEMENT

The Department of Clinical Pharmacology and Pharmacoepidemiology 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.
Table 1 Pharmacokinetic parameters of SBECD in 14 patients with end-stage renal failure on renal replacement therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Genius dialysis</th>
<th>Hemodialysis</th>
<th>Hemodiafiltration</th>
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<tbody>
<tr>
<td><strong>Based on plasma values</strong></td>
<td></td>
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<tr>
<td>$T_1/2$ (h)</td>
<td>2.6 ± 0.6</td>
<td>2.4 ± 0.9</td>
<td>2.0 ± 0.6**</td>
</tr>
<tr>
<td>$C_{max}$ (mg/L)</td>
<td>254.6 ± 56.7</td>
<td>269.9 ± 41.1</td>
<td>245.8 ± 38.3</td>
</tr>
<tr>
<td>$V_z$ (L)</td>
<td>20.1 ± 7.4</td>
<td>18.8 ± 6.9</td>
<td>19.0 ± 6.0</td>
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<tr>
<td>$CL_{tot}$ (L/h)</td>
<td>5.4 ± 1.1</td>
<td>5.5 ± 0.9</td>
<td>6.7 ± 1.5**</td>
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<tr>
<td>$CL_{extra,plasma-based,2h}$ (L/h)$^{(1)}$</td>
<td>3.9 ± 1.2</td>
<td>4.5 ± 1.5</td>
<td>5.8 ± 0.4*</td>
</tr>
<tr>
<td>$CL_{extra,plasma-based,3h}$ (L/h)$^{(1)}$</td>
<td>3.9 ± 0.9</td>
<td>4.6 ± 1.7</td>
<td>5.9 ± 0.8**/*+</td>
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<td>$A_{total}$ (%)</td>
<td>74.9 ± 7.6</td>
<td>79.4 ± 9.5</td>
<td>84.2 ± 7.8***</td>
</tr>
<tr>
<td>$A_{total}$ (mg)</td>
<td>4631.7 ± 907.6</td>
<td>4929.8 ± 854.3*</td>
<td>5332.4 ± 1180.1***</td>
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<tr>
<td><strong>Based on dialysate values</strong></td>
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<tr>
<td>$CL_{extra,dialysate-based}$ (L/h)</td>
<td>5.0 ± 2.0</td>
<td>4.7 ± 1.6</td>
<td>5.3 ± 1.6</td>
</tr>
<tr>
<td>$A_{extra}$ (%)</td>
<td>69.0 ± 16.0</td>
<td>66.1 ± 13.1</td>
<td>66.9 ± 19.2</td>
</tr>
<tr>
<td>$A_{dialysate}$ (mg)</td>
<td>4432.6 ± 1861.1</td>
<td>4228.0 ± 1511.7</td>
<td>4254.9 ± 1472.9</td>
</tr>
</tbody>
</table>

Values are Mean ± SD
Genius dialysis versus hemodialysis/ hemodiafiltration: * P<0.05, ** P<0.01, *** P<0.001,
hemodialysis versus hemodiafiltration: + P<0.05

$^{(1)}$ CL 2h: n = 11, CL 3h: n =10

SBECOD and VRC during renal replacement therapy
Table 2 Pharmacokinetic parameters of voriconazole and voriconazole-N-oxide in 14 hemodialysis patients on renal replacement therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Genius dialysis</th>
<th>Hemodialysis</th>
<th>Hemodiafiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Based on plasma values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} ) (mg/L)</td>
<td>1.8 ± 0.6</td>
<td>1.7 ± 0.5</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td>( \text{CL}_{\text{extra,plasma-based,2h}} ) (L/h)&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td>3.6 ± 2.4</td>
<td>4.0 ± 0.7</td>
<td>6.3 ± 1.0***</td>
</tr>
<tr>
<td>( \text{CL}_{\text{extra,plasma-based,3h}} ) (L/h)&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td>3.6 ± 1.4</td>
<td>4.0 ± 0.8</td>
<td>5.6 ± 0.8**</td>
</tr>
<tr>
<td>Voriconazole-N-oxide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{CL}_{\text{extra,plasma-based,2h}} ) (L/h)&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td>5.0 ± 1.6</td>
<td>4.1 ± 1.4</td>
<td>6.6 ± 1.3+++</td>
</tr>
<tr>
<td>( \text{CL}_{\text{extra,plasma-based,3h}} ) (L/h)&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td>5.2 ± 1.3</td>
<td>6.0 ± 1.3</td>
<td>6.0 ± 1.4</td>
</tr>
<tr>
<td><strong>Based on dialysate values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( A_{\text{extra}} ) (%)</td>
<td>8.8 ± 3.3</td>
<td>12.7 ± 3.5</td>
<td>13.1 ± 5.8</td>
</tr>
<tr>
<td>( A_{\text{dialysate}} ) (mg)</td>
<td>26.6 ± 13.7</td>
<td>37.2 ± 15.3</td>
<td>35.7 ± 15.9**</td>
</tr>
<tr>
<td>( \text{CL}_{\text{extra,dialysate-based}} ) (L/h)</td>
<td>4.9 ± 1.5</td>
<td>7.1 ± 1.3</td>
<td>6.9 ± 2.4</td>
</tr>
<tr>
<td>Voriconazole-N-oxide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( A_{\text{extra}} ) (%)</td>
<td>8.8 ± 7.2</td>
<td>7.7 ± 4.7</td>
<td>9.3 ± 7.6</td>
</tr>
<tr>
<td>( A_{\text{dialysate}} ) (mg)</td>
<td>24.0 ± 19.3</td>
<td>20.9 ±10.9</td>
<td>24.5 ± 15.0</td>
</tr>
<tr>
<td>( \text{CL}_{\text{extra,dialysate-based}} ) (L/h)</td>
<td>13.0 ± 13.6</td>
<td>12.2 ±9.4</td>
<td>16.8 ± 17.2</td>
</tr>
</tbody>
</table>

Values are Mean ± SD

Genius dialysis versus hemodialysis/ hemodiafiltration: * \( P<0.05 \), ** \( P<0.01 \), *** \( P<0.001 \), hemodialysis versus hemodiafiltration: + \( P<0.05 \), ++ \( P<0.01 \), +++ \( P<0.001 \)

<sup>(1)</sup> CL 2h: \( n = 11 \), CL 3h: \( n = 10 \)
Figure Legends

**Figure 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.

**Figure 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.

**Figure 3**: Predicted SBECD concentrations after repeated administration of 6600 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 hours during VRC infusion (D). Parameter values were: \( CL_{tot} = 8.5 \text{ L/h} \), \( V = 23 \text{ L} \) for normal renal function, \( CL_{tot} = 1.8 \text{ L/h} \), \( V = 24.8 \text{ L} \) for impaired renal function (based on data from Abel et al. 2008 (1)), and \( CL_{tot,off} = 0.8 \text{ L/h} \), \( CL_{tot,on} = 5.5 \text{ L/h} \), \( V = 19 \text{ L} \) for renal failure (based on data from the present study). VRC = voriconazole.
Figure 1
Figure 2
Figure 3

- **A** Without renal replacement therapy
- **B** Hemodialysis every 48 h (4 hours, before next VRC dose)
- **C** Hemodialysis every 24 h (4 hours, before next VRC dose)
- **D** Hemodialysis every 12 h (6 hours, during VRC infusion)