Fluconazole dosing in continuous veno-venous haemofiltration (CVVH): need for a high daily dose of 800 mg

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Abstract
To cover intermediate sensitive Candida glabrata in ICU patients, fluconazole plasma peak levels at least in the range of 16–32 μg/ml appear necessary for treatment. Previous studies did not reach these fluconazole levels under continuous veno-venous haemofiltration (CVVHF) with dosages of 200–600 mg fluconazole daily. In the present study, nine patients simultaneously requiring CVVHF for treatment of acute oligoanuric renal failure and antimycotic therapy of Candida septicemia received fluconazole 800 mg/day. Fluconazole plasma levels were determined to evaluate whether this dosage is adequate to reach the advised fluconazole levels. Patients were dialysed on two consecutive days with an ultrafiltration rate (UF) of 1000 ml/h or 2000 ml/h, respectively, in a randomized order. The predilution was 800 ml/h and 1800 ml/h, respectively. The treatment was tolerated without adverse effects. All patients reached plasma fluconazole concentrations between 16 and 32 μg/ml, remaining in this range for a minimum of 1 up to 24 h with a mean of 9.6 h and a UF rate of 2000 ml/h, and 15.7 h with a UF rate of 1000 ml/h. So far, there are no in vivo data on the fluconazole plasma concentrations required for effective treatment. However, our data demonstrate, that at least the fluconazole concentrations desirable on the basis of in vitro susceptibility testing can be reached in critically ill patients on CVVHF in an ICU setting. However, in these patients, 800 mg fluconazole/day are necessary to achieve fungicidal drug concentrations.

Keywords: Candida septicemia; CVVHD; fluconazole dosing; fluconazole levels; haemofiltration; ultrafiltration rates

Introduction
Fluconazole is an azole antifungal agent with a molecular weight of 306 Da. The protein binding is low with 12% [1]. Fluconazol gets easily distributed throughout the tissues and allows the treatment of a variety of systemic fungal infections. The concentrations of fluconazole in blood after administration of single doses correlated well with the administered dose. About 80% of fluconazole will be eliminated unchanged via the kidneys within 25–30 h. The renal clearance in healthy volunteers ranges from 15 to 19 ml/min [1,2].

With the low protein binding, the low molecular weight and the high fraction of renal elimination, fluconazole will be eliminated effectively by haemodialysis and haemofiltration [3]. About 25–40% will be removed during a single haemodialysis over a 3–4 h period [4,5]. Continuous arteriovenous haemodialfiltration will allow a clearance of 23 ml/min [6], with continuous haemofiltration of 21 ml/min [7]. This demonstrates that continuous renal replacement therapy results in a fluconazole clearance similar to that of individuals with normal renal function. Convective removal used in haemofiltration is not affected by molecular weight up to the cut off value of the dialyser-membrane, which is usually about 20000–50000 Da in haemofiltration. Theoretical calculations of the convective clearance allow us to equate this in fluconazole with the ultrafiltration rate [8].

Intensive care unit (ICU) patients with septicemia often suffer also from acute renal failure requiring renal replacement therapy, like CVVHD (continuous veno-venous haemodialysis) or CVVHF (continuous veno-venous haemofiltration). Because of its smaller effect on blood pressure in critically ill patients, the CVVHF is more suitable in these patients. So, it is very important to know the influence of CVVH on fluconazole elimination.
In vitro testing differentiates Candida into sensitive (MIC <8 μg/ml), medium (MIC 16–32 μg/ml) and resistant (MIC >64 μg/ml) species. In a recent study of 6970 isolates of Candida spp. in 95–97% in vitro growth was inhibited by fluconazole concentrations between 16–32 μg/ml. Candida albicans were sensitive also for lower concentrations (MIC<sub>90</sub> 0.5 μg/ml) [9, 10]. In contrast, Candida glabrata needed higher fluconazole concentrations for growth suppression. Consequently, in patients, fluconazole plasma levels at least in the range of 16–32 μg/ml appear necessary for treatment in ICU patients to cover also intermediate sensitive C. glabrata. Previous studies did not reach this range of fluconazole levels under CVVHF/CVVHD with dosages of 200–600 mg fluconazole daily [11–15].

In the present study, the fluconazole dosage was adjusted by a factor of 0.5 for a creatinine clearance <11 ml/min and then multiplied by 2.2 for CAVHF/CVVHF [13, 16] in order to achieve plasma levels of fluconazole between 16 μg/ml and 32 μg/ml during CVVHF. According to Pfaller et al. [9], 16 μg/ml can be assumed to be the overall MIC for all relevant Candida species. Because of the better handling, the calculated total dosage of 880 mg/day was reduced to 800 mg/day. The aim of the investigation was to explore whether fluconazole plasma peak levels of 16–32 μg/ml were reached by this regimen. Since fluconazole has a wide therapeutic range and previous studies demonstrated that fluconazole peak levels up to 91.8 μg/ml were tolerated without adverse events [17], the risk of reaching toxic fluconazole levels was very low.

Study design

The study was designed as a monocentre prospective observer blinded randomized cross-over investigation with intra-individual comparison of two different ultrafiltration rates in CVVHF. The study was conducted at the Medizinische Klinik A, Klinikum der Stadt Ludwigshafen, in accordance with the principles of the Declaration of Helsinki in its revised version and the specific legal requirements in Germany. The study was approved by the Ethics Committee of the State Chamber of Physicians of Rheinland-Pfalz. Informed consent was obtained from the patients or their representatives or relatives; in addition, an independent physician not involved in the study had to give written approval of study participation. In case a patient initially could not give informed consent him- or herself, plasma samples were stored until the patient’s condition improved so that the patient’s informed consent could be obtained in addition to the consent of the representative.

Patients

Nine patients were included in the study and six participated in both trial periods. In two patients only phase B was performed, because they reached a defined endpoint, and therefore they were excluded from analysis. One patient was excluded from the evaluation because he did not complete one 24 h period. In one patient, the sampling of the ultrafiltrate was missed on study day 1; therefore, the respective filtration rate was run again on the next day. Only the second run was included into data analysis. In another patient, the 2000 ml filtration rate was erroneously run for 2 days prior to switching to the 1000 ml filtration rate. Again, only the samples of the second run were analysed. This was judged not to be misleading, since the measurements were scheduled to be done in a steady state.

Treatment regimens

Fluconazole 800 mg was scheduled as an intravenous infusion over 40 min. After the starting dose, fluconazole treatment was continued with 800 mg daily. Both an ultrafiltration rate of 1000 ml/h (A) and of 2000 ml/h (B) were used over a 24 h period in order to examine the influence of different ultrafiltration rates on fluconazole elimination. The sequence of the ultrafiltration rates was randomized. The laboratory personnel determining fluconazole levels was blinded for the ultrafiltration rates (observer blinded study).

Dialysis technique

The CVVHF was performed with a polysulfon high-flux filter HF 60 (surface 1.3 m², Fresenius, Bad Homburg, Germany) and predilution. The predilution was 800 ml/h (A) or 1800 ml/h (B), resulting in a net ultrafiltration of 200 ml/h in each patient. The bloodflow was 180–200 ml/min. All patients received an anticoagulation treatment with heparin, individually adjusted by coagulation parameters (Heptest, haemaChem Inc., St Louis, USA). The fluid balance was corrected by systemic infusions (Figure 1).

Sampling procedures

Blood and ultrafiltrate sampling for determination of fluconazole concentrations was scheduled for two successive days. Blood samples (6 ml) were collected before fluconazole infusion (0 h), at the end of the infusion (40 min), and at 1, 2, 3, 4, 8, 12 and 24 h after the start of the infusion. Ultrafiltrate
samples 10 ml were collected after 1 and 12 h; in addition, the whole ultrafiltrate was collected over a 24 h period. Blood samples were taken from the blood access line to the haemofilter. All blood samples were centrifuged for 5 min at 4000 rounds/min. Until analysis plasma and ultrafiltration samples were stored frozen at −32°C.

In case a patient’s condition would not allow to acquire further blood samples or if CVVHF was no longer necessary or practicable, the study participation could be discontinued prematurely. If blood sampling could be completed for at least 24 h, the results were included in the evaluation.

The first batch of fluconazole plasma levels was determined after four patients completed the investigation in order to be able to correct the fluconazole dosage in case the plasma peak levels were far off the desirable range of 16–32 μg/ml.

**Fluconazole determination**

Fluconazole was extracted from alkalinized plasma and ultrafiltrate by liquid/liquid extraction with tert-butylmethyl ether, evaporated to dryness under a stream of nitrogen, and reconstituted in the mobile phase. The extracts were measured with isotropic reversed phase HPLC on a RP18 column coupled to mass spectrometry with atmospheric pressure chemical ionization. Deuterated fluconazole was used as internal standard. Chromatographic peaks were detected in the single ion mode with m/z 307.2 for the fluconazole and m/z 310.2 for the deuterated fluconazole. The analytical method validation was performed according to the recommendations of the FDA.

The calibration curves for fluconazole in the respective materials were linear over the range of 0.1 ng/ml–30 ng/ml with correlation coefficients (r²) always greater than 0.998. The limit of quantification for fluconazole in plasma and ultrafiltrate was 0.1 ng/ml with an accuracy of 101±10% and 94±16.2%. The extraction recovery for fluconazole from plasma was 45.5% at 10.2 ng/ml plasma and 44.9% at 19.7 ng/ml. The recoveries for fluconazole in the ultrafiltrate at the same concentrations were 39.3 and 36.8 ng/ml, respectively.

The method validation gave the following results: precision RSD within-batch ranged from 1.0–4.6% for plasma and 1.8–15.5% for the ultrafiltrate. Precision batch-to-batch in plasma was 11.7% at the low, 3.1% at the middle, and 4.0% at the high concentrations of the quality control samples. Mean accuracy (n=18) was 112.3, 105.2 and 105.3% at the same concentrations. Precision batch-to-batch in ultrafiltrate was 13.4% at the low, 5.4% at the middle, and 5.7% at the high concentrations of the quality control samples. Mean accuracy (n=18) was 97.9, 102.8, and 106.6% at the same concentrations.

**Biometrical evaluation**

C_{max}, C_{24}, and T_{max} were directly obtained from the raw data. The area under the plasma concentration time curve of fluconazole from 0 to 24 h (AUC_{0–24}) was calculated according to the linear trapezoidal rule.

The CVVHF fluconazole clearance was calculated with the following formula:

\[
\text{Clearance}_{\text{CVVHF}} = \frac{C_{\text{fluconazole}} \times \text{ml}[\text{ultrafiltrate}_{24h}]}{\text{AUC}_{0–24}}
\]

where C_{fluconazole} is the fluconazole concentration in the ultrafiltrate sampled over 24 h. Total body clearance was determined by dividing the applied daily dose by AUC_{0–24}. Mean values were calculated of the fluconazole plasma concentrations, the area under the plasma concentration–time curve (AUC) and the clearance of fluconazole during CVVHF. Results are given as mean values±SD and were compared by t-test. Significance was assumed if P-values were <0.05.

**Results**

Fluconazole was well tolerated and fluconazole peak concentrations between 16–32 μg/ml were reached in all patients. The average fluconazole peak level (C_{max}) was 27.3±4.0 μg/ml for the dialysis regimen (A) and 24.4±6.8 μg/ml for (B), respectively (n.s.) (Figure 2). The mean AUC_{0–24} was 28 390±7865 μg/ml min (A) and 23 079±7723 μg/ml min (B). The mean amount of fluconazole, eliminated in the ultrafiltrate over 24 h was 358±241 mg (A) and 390±192 mg (B) of the daily dose of 800 mg. The extracorporeal clearance on average was 11.8±5.3 ml/min (UF 1000 ml/min) and 18.9±9.3 ml/min (UF 2000 ml/min) (n.s.). The total body clearance was 30.2±9.1 ml/min (A) and 37.4±10.0 ml/min (B). The plasma fluconazole

![Fig. 2. Mean fluconazole plasma concentration time curves (±SD) for the different ultrafiltration rates. CVVHF was performed with an ultrafiltration rate of 1000 ml/h (A) and with an ultrafiltration rate of 2000 ml/h (B). Infusion was applied over 40 min in both groups. Note the different time scales from 0 to 60 min and thereafter.](https://academic.oup.com/ndt/article-lookup/21/4/1019/1932000)
concentrations fell only slightly below the intended target concentration between 1 and 24 h; as a mean, they remained above the limit of 16 μg/ml for 17.0±8.0 h when using an UF rate of 1000 ml/h, and 9.1±8.3 h with an UF rate of 2000 ml/h, the corresponding AUC above MIC (16 μg/ml) was 6924±5935 μg/ml min and 3394±5578 μg/ml min, respectively. The peak to MIC ratio was independent of UF rate with 1.80 and 1.59, respectively. Inter-individual variability of the plasma concentration–time profiles was considerable (Table 1).

**Discussion**

The proportion of infections due to *Candida albicans* and *Candida glabrata* increased over time from 1992–2001 in Europe, USA and Canada. Only a little variation in fluconazole susceptibility was observed among isolates of *C.albicans*. These species accounted for 78% of all infections detectable in blood cultures and remained highly susceptible to fluconazole from 1992 to 2001 irrespective of geographic origin. The prevalence of fluconazole resistance among *C.glabrata* isolates was variable both over time and among various countries and regions. The highest resistance to fluconazole among *C.glabrata* isolates existed in the USA and varied by US census region (range 0–23%) [18].

The present study demonstrates that a dosage of 800 mg/day fluconazole is indeed necessary in patients receiving CVVHF to actually reach the desired fungicidal fluconazole peak concentrations from 16 to 32 μg/ml. The dosage was well tolerated; no adverse effects occurred. In contrast, previous studies [12–14] had found only fluconazole peak levels between 11.9 and 14.1 μg/ml when using fluconazole dosages of 200–600 mg daily. In all these studies, only in two patients with dosages of 800 mg/day plasma peak levels of 17.9 and 24 μg/ml were documented [14], achieving our aimed serum levels.

In some patients, we found a delayed peak level. The infusion time was scheduled to 40 min, but the real time was not documented in the patient record, so we can only assume that this finding is from longer infusion time than intended.

In addition, our study demonstrates that the influence of different ultrafiltration rates with 1000 and 2000 ml/h is low. The extracorporeal fluconazole clearance did not change significantly; the AUC also was not changed to a relevant extent. The fluconazole plasma levels were more diluted with increased ultrafiltration rate. But the increasing predilution eliminated nearly the same amount of fluconazole with a greater volume. So the dosage of fluconazole did not have to be adapted according to different ultrafiltration rates between 1000 and 2000 ml/h, if predilution was used. Previous dosing recommendations for fluconazole were made with an ultrafiltration rate of 500 ml/h [16]. After dose reduction to 50% in anuric patients, a factor of 2.2 for the compensation of extracorporeal clearance with haemofiltration was recommended in these theoretical considerations. However, the filtration rate preferred in many centres in recent years has changed to 1000 and 2000 ml/h. So developing fluconazole dosage recommendations for these filtration rates is necessary. In our study, a factor of 2.0 was used because of better feasibility.

**Table 1.** Individual and mean values of fluconazole plasma peak concentrations (Cmax) and time of peak (Tmax), and minimal fluconazole plasma concentration (C24h), AUC0–24, extracorporeal clearance (CLCVVHF), total body clearance (CLTOTAL), volume of distribution (Vz), and terminal elimination half-life (t1/2).

<table>
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<th>Patient</th>
<th>Tmax (min)</th>
<th>Cmax (μg/ml)</th>
<th>C24h (μg/ml)</th>
<th>AUC0–24 (min μg/ml)</th>
<th>CLTOTAL (ml/min)</th>
<th>CLCVVHF (ml/min)</th>
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The present study shows that the recommendations for fluconazole dosing in CVVHF [13,16] partially based on theoretical considerations can be followed in a setting of critically ill patients in an intensive care ward. In patients with life-threatening Candida infections and the need of CVVHF due to acute renal failure a dose of 800 mg fluconazole/day is necessary to achieve therapeutic drug concentrations, and this is applicable without any problems.

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Conflict of interest statement. None declared.

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