

Multiple-dose pharmacokinetics of anidulafungin during continuous venovenous haemofiltration

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Background: Clinical studies support a role for anidulafungin as first-line treatment of invasive candidiasis in critically ill patients and postulate no need for dose adjustments in mild to severe renal failure. Although intensive care patients requiring renal replacement therapy are at particular risk of invasive fungal infection, no pharmacokinetic data on anidulafungin during continuous venovenous haemofiltration (CVVHF) are available.

Patients and methods: Ten patients with CVVHF due to acute renal failure were included. Anidulafungin was infused on 3 consecutive days starting with a loading dose of 200 mg on day 1, followed by doses of 100 mg on each of days 2 and 3. During the 72 h study phase of CVVHF, blood and ultrafiltrate samples were collected at corresponding times. Anidulafungin concentrations were determined by HPLC.

Results: Peak plasma concentrations were reached 3 h after the start of infusion and were 8.5 ± 3.6 mg/L at the pre-filter port. The mean arterial area under the curve (AUC_{0-24}) of the study population was 109.9 ± 49.82 mg·h/L, the total clearance was 1.08 ± 0.41 L/h, the volume of distribution was 41.97 ± 22.64 L and the elimination half-life was 28.78 ± 10.40 h. Anidulafungin was not filtered, but CVVHF resulted in a substance loss of ~20%, due to adherence to synthetic surfaces.

Conclusions: Pharmacokinetics of anidulafungin during CVVHF resembled findings in healthy adults and adults with fungal infections. Therefore we recommend a loading dose of 200 mg intravenous anidulafungin on the first day and 100 mg on consecutive treatment days in patients during CVVHF.

Keywords: renal replacement therapy, antifungal treatment, acute renal failure

Introduction

Anidulafungin is a novel cyclic lipopeptide antifungal agent of the echinocandin class. Echinocandins inhibit the synthesis of glucan polymers in fungal cell walls.¹ Anidulafungin is used in several different *Candida* and *Aspergillus* infections. Susceptibility data, pharmacokinetic and pharmacodynamic studies and clinical studies show efficacy in the treatment of oesophageal candidiasis and support a role as first-line therapy for the treatment of candidaemia and various forms of invasive candidiasis.²

The risk of fungal infections is increased in intensive care patients due to long-term and multiple antibiotic usage, mechanical ventilation, use of steroids or other immunosuppressive drugs, central venous catheter and renal replacement therapy.^{3,4}

Although systemic antifungal therapy is usually administered in the critically ill patient with various degrees of hepatic and renal

dysfunction, pharmacokinetic studies are rare in these particular patients. Prior investigations in non-intensive care patients have suggested that anidulafungin does not necessitate dose adjustment in patients with mild to moderate hepatic or renal impairment.⁵ No data are available on the pharmacokinetics of anidulafungin during continuous venovenous haemofiltration (CVVHF) for acute renal failure. Since the adequate dosage in these patients is unclear this study investigates the 3 day pharmacokinetics of anidulafungin during CVVHF in intensive care patients.

Methods

Patients

Ten critically ill patients with acute renal failure and suspected or proven systemic *Candida* infection were included. Patients were anuric and did

Table 1. Patient demographics

Patient	Sex	Age (years)	Weight (kg)	Height (cm)	Diagnosis
1	male	67	109	180	cardiogenic shock, myocardial infarction
2	female	89	58	169	cardiogenic shock after aortic valve replacement
3	male	46	85	180	septic shock, renal transplantation
4	male	63	82	178	septic shock, candidaemia with <i>C. albicans</i>
5	female	59	82	155	Hodgkin's lymphoma, urinary tract infection with <i>C. albicans</i>
6	female	57	100	167	acute myeloid leukaemia, pneumonia
7	female	80	92	165	acute respiratory distress syndrome
8	male	69	105	172	cardiogenic shock, myocardial infarction
9	female	77	71	165	cardiogenic shock, ventricular septal repair
10	male	79	68	168	septic shock, extensive burns

not receive albumin substitution. All patients required mechanical ventilation. None of the patients had a known hypersensitivity to echinocandins. Pregnant or neutropenic patients, patients with liver failure and those with a history of alcohol dependency or epilepsy were not eligible for participation. The study protocol was approved by the local ethics committee (EK681/2008) and registered at ClinicalTrials.gov (NCT00892359).

CVVHF

CVVHF was performed as described previously⁶ using a polyethylene sulphone haemofilter with a membrane surface of 1.2 m² (Aqua Max HF 12; Fresenius, Germany). CVVHF was accomplished with a roller pump (Brady, Vienna, Austria) in connection with an automatic balancing system (Equaline; Amicon, Ireland). The blood flow rate was 160–180 mL/min; flow rates were adjusted according to clinical demand. The ultrafiltration rate was 25 mL/min.

Drug administration and sampling

Anidulafungin (Ecalta[®] 100 mg powder and solvent; Pfizer Corporation Austria GesmbH, Vienna, Austria) was administered intravenously after dilution on 3 consecutive days. On the first day 200 mg of anidulafungin diluted in 500 mL of isotonic saline solution was infused over 3 h. On the following days 100 mg of anidulafungin was diluted in 250 mL of isotonic saline solution and administered over 1.5 h.

Anidulafungin was infused into a central venous catheter, different from the venous catheter used for CVVHF. Blood samples were taken on days 1, 2 and 3 from the arterial and venous lines of the extracorporeal circuit before the start and at the end of the infusion, as well as at 2, 4, 6, 8 and 24 h. Ultrafiltration samples, collected from the outlet of the ultrafiltrate compartment of the haemofilter, were taken at corresponding times. Plasma was separated immediately after collection and stored together with the ultrafiltration samples at –70°C until analysis. Patients with only 1 day of analysis, e.g. due to shorter duration of CVVHF, were followed for their single-dose pharmacokinetic profile.

Drug assay

The concentration of anidulafungin in plasma and ultrafiltrate was assessed by HPLC. Frozen patient samples were thawed at room temperature and then centrifuged at 13000 g for 5 min. Briefly, after the addition of 500 µL of methanol to 250 µL of serum or ultrafiltrate, the samples were centrifuged (13000 g for 5 min) and 80 µL of the supernatant was injected onto the HPLC column. Determination of anidulafungin was performed using a Dionex 'UltiMate 3000' system (Dionex Corp.,

Sunnyvale, CA, USA) with UV detection at 300 nm. Chromatographic separation was carried out on a Hypersil BDS-C₁₈ column (5 µm, 250×4.6 mm internal diameter; Thermo Fisher Scientific, Inc., Waltham, MA, USA), preceded by a Hypersil BDS-C₁₈ precolumn (5 µm, 10×4.6 mm internal diameter). The mobile phase consisted of a continuous linear gradient, mixed from 10 mM ammonium acetate/acetic acid buffer, pH 4.0 (mobile phase A) and methanol (mobile phase B), at a flow rate of 1 mL/min and the column oven was set at a temperature of 35°C. The mobile phase was filtered through a 0.45 µm filter (HVLPO4700; Millipore, Vienna, Austria). The gradient ranged from 50% methanol (0 min) to 90% B at 20 min, where it remained constant until 30 min. Subsequently, the percentage of methanol was decreased within 2 min to 50% in order to equilibrate the column for 8 min before application of the next sample. Calibration of the chromatogram was accomplished using the external standard method. Linear calibration curves were calculated from the peak areas of anidulafungin compared with the external standard by spiking drug-free human serum and ultrafiltrate with standard solutions of anidulafungin to obtain a concentration range of 0.05–10 mg/L (average correlation coefficients >0.99). Intra-day variability was in the range 2.3%–5.1% and inter-day variability was in the range 3.7%–6.5% using anidulafungin concentrations of 0.1 and 1 mg/L serum.

Pharmacokinetic analysis

The serum concentration–time curves of anidulafungin in plasma were analysed using Statistica 6.0 (StatSoft, Tulsa, OK, USA) and graphs were designed with Microsoft Excel for Windows and OriginPro7 (OriginLab, Northampton, MA, USA).

The following parameters were calculated: area under the concentration curve from 0 to 24 h (AUC_{0–24}) using the linear trapezoidal rule; total clearance (CL_{tot}); volume of distribution (V); and elimination half-life (t_{1/2β}).

Results

Ten critically ill patients (five male and five female) with acute renal failure and suspected (*n*=8) or proven (*n*=2) invasive candidiasis were included. The mean age was 69±13 years and the mean height and weight were 170±8 cm and 85±17 kg, respectively. Table 1 summarizes the demographic findings in the study population. Eight of the 10 included patients were on CVVHF for the scheduled 3 days; in two patients the CVVHF was stopped prematurely. In patient #5 the stop after 25 h was due to technical problems with the CVVHF machine and in

patient #6 the CVVHF was stopped after 37 h due to restart of urine production. The population concentration–time profile is illustrated in Figure 1.

Anidulafungin was well tolerated in all patients. Peak plasma concentrations were reached with the 200 mg anidulafungin dose on the first treatment day and were 8.5 ± 3.6 mg/L at the pre-filter port 3 h after the start of infusion. Peak concentrations with the 100 mg dose on days 2 and 3 were 6.5 ± 3.1 mg/L and 5.9 ± 2.0 mg/L, respectively (Figure 1). Mean pre-filter port trough concentrations were 3.1 ± 1.5 mg/L, 3.0 ± 1.0 mg/L and 2.9 ± 1.1 mg/L at 24, 48 and 72 h, respectively.

The individual and population AUC, CL_{tot} , $t_{1/2\beta}$ and V of anidulafungin during the first 24 h are summarized in Table 2. No anidulafungin levels were measurable in the dialysate. Maximal differences in anidulafungin concentrations between the venous and arterial port (AV differences) were measured at 2 h ($19 \pm 6\%$) and steadily decreased to $14 \pm 4\%$ at 24 h,

$10 \pm 2\%$ at 48 h and $9 \pm 2\%$ at 72 h (Figure 2). The difference in AUC_{0-24} of the pre- and post-filter measurements was $\sim 20\%$. In seven patients AUC was higher at the pre-filter port and in three patients (#2, #3 and #8) there were no relevant differences between pre- and post-filter AUC (Table 2). One patient (#7) was pretreated with 100 mg of anidulafungin the day before study entry and therefore had measurable plasma concentrations at baseline.

The mean arterial AUC_{0-24} of the study population was 109.9 ± 49.82 mg·h/L, the CL_{tot} was 1.08 ± 0.41 L/h, the V was 41.97 ± 22.64 L and the $t_{1/2\beta}$ was 28.78 ± 10.40 h.

Discussion

Elimination of anidulafungin takes place via slow, non-enzymatic degradation to inactive metabolites.⁷ Less than 10% and 1% of the initially administered drug is excreted unchanged into faeces and urine, respectively.⁸ No dose adjustments in mild, moderate or severe renal insufficiency and dialysed patients are recommended.⁹ Although intensive care patients requiring CVVHF are at particular risk of invasive fungal infection, clinical pharmacokinetics of anidulafungin are not available. Here, we show the 3 day pharmacokinetics of anidulafungin during CVVHF in 10 intensive care patients.

Pharmacokinetics of anidulafungin during CVVHF resembled pharmacokinetic findings in healthy adults and patients with fungal infections^{9,10} (Table 3). Although the mean terminal half-life of the first anidulafungin dose (200 mg) was slightly longer than 24 h, no relevant accumulation of anidulafungin was seen after cumulative doses (100 mg on days 2 and 3) during 72 h of CVVHF (Figure 1). Even the lowest individual trough concentration measured in this study (1.54 mg/L) was above the previously published MIC_{90s} for *Candida albicans* (0.03 mg/L), *Candida glabrata*, *Candida tropicalis* and *Candida krusei* (all 0.13 mg/L), *Candida dubliniensis* (0.06 mg/L) and *Candida lusitanae* (0.25 mg/L),¹¹ as well as the published minimum effective concentration (MEC)_{90s} for *Aspergillus fumigatus* (0.12 mg/L), *Aspergillus flavus* and *Aspergillus niger* (both 0.25 mg/L).¹² Only the MIC_{90} for *Candida parapsilosis* (2 mg/L) was slightly higher.

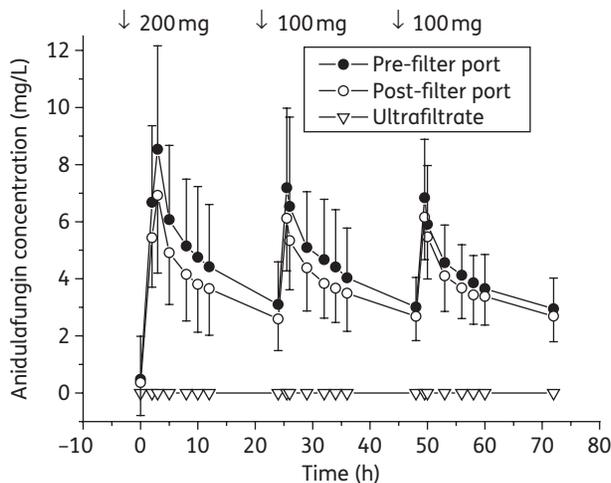


Figure 1. Concentration–time profile of the study population. Anidulafungin concentrations after intravenous infusions of 200 mg on day 1 and 100 mg on days 2 and 3, sampled from the arterial (pre-filter) port, venous (post-filter) port and the ultrafiltrate during 72 h of CVVHF. Data are means \pm SD.

Table 2. Pharmacokinetics of anidulafungin in the patients on CVVHF, day 1

Patient	Dose (mg)	AUC_{0-24} (mg·h/L), arterial	AUC_{0-24} (mg·h/L), venous	Difference in AUC_{0-24} (mg·h/L)	CL_{tot} (L/h)	V (L)	$t_{1/2\beta}$ (h)
1	200	77.83	53.88	23.95	1.50	44.91	20.73
2	200	55.88	55.26	0.62	1.71	62.72	25.38
3	200	72.01	71.09	0.92	0.99	62.50	45.38
4	200	66.02	57.87	8.15	1.24	84.19	46.97
5	200	155.2	113.3	41.9	1.48	23.41	23.57
6	200	155.0	97.3	57.7	0.56	15.57	19.68
7	200	209.4	173.2	36.2	0.44	17.01	26.72
8	200	78.04	78.72	-0.68	0.91	48.32	36.51
9	200	114.6	100.8	13.8	1.03	28.92	19.35
10	200	106.2	84.40	21.8	0.94	32.16	23.50
Mean \pm SD	200 \pm 0	109.9 \pm 49.82	88.58 \pm 36.02	20.44 \pm 19.79	1.08 \pm 0.41	41.97 \pm 22.64	28.78 \pm 10.40

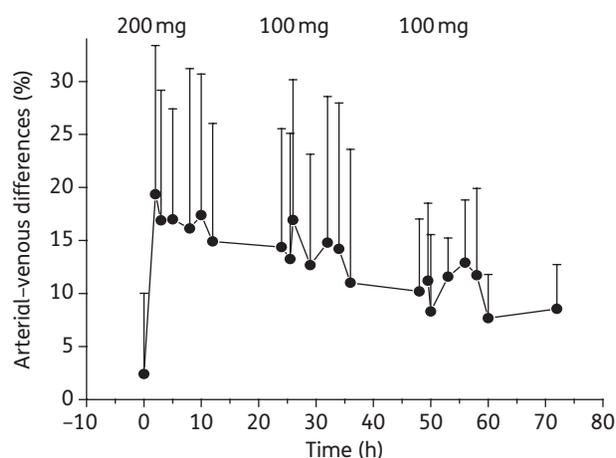


Figure 2. Differences in anidulafungin concentration between the venous and arterial ports (AV differences). Maximal AV differences were measured at 2 h ($19 \pm 6\%$) and steadily decreased to $14 \pm 4\%$ at 24 h, $10 \pm 2\%$ at 48 h and $9 \pm 2\%$ at 72 h. Data are means \pm SD.

Table 3. Comparison between pharmacokinetic parameters of healthy adults, patients with fungal infection and patients with suspected or proven fungal infection on CVVHF

Patient group	C_{max} (mg/L)	AUC_{0-24} (mg·h/L)	V (L)	$t_{1/2\beta}$ (h)
Healthy adults ¹⁰	8.6	111.8	30–50	—
Patients with fungal infection ¹⁰	7.2	110.3	—	26.5
Patients on CVVHF ^a	8.5	109.9	42	28.8

^aPre-filter port measurements.

Anidulafungin was not eliminated from the circulation by filtration. The high protein binding ($\sim 85\%$)¹³ and adsorption to the synthetic surfaces of the CVVHF equipment might explain the lack of quantifiable amounts of anidulafungin in the ultrafiltrate. Adsorption to the synthetic surfaces further resulted in anidulafungin concentration differences between the arterial and venous ports (AV differences). Similar findings were previously described for ceftriaxone, teicoplanin and flucloxacillin during renal replacement therapy, substances with an even higher protein binding rate than anidulafungin.^{14–16} The time-dependent decline in the AV difference (Figure 2) might be due to saturation of the synthetic surfaces.

Although the number of patients in our study was small, this is usual in pharmacokinetic studies of antimicrobial agents during continuous renal replacement therapies and currently the largest series on anidulafungin pharmacokinetics during CVVHF.^{17–21} Due to the exclusion of neutropenic patients and patients with liver failure the findings are not transferable to these patient populations. Further, we cannot exclude a change in extracorporeal anidulafungin removal with different filtration rates. However, according to our findings and the pharmacological properties of anidulafungin, the necessity of dose adaptation of anidulafungin is unlikely in critically ill patients during CVVHF.

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