Pharmacokinetics of Anidulafungin in critically ill patients in the Intensive Care Unit with suspected or proven invasive fungal infections.

R. J. M. Brüggemann, PharmD, PhD,[1, #]; V. Middels-Baars[2$]; D.W. de Lange,MD, PhD[3]; A. Colbers, MSc[1]; A.R.J. Girbes, MD, PhD[4]; R.P. Pickkers, MD, PhD[5]; E.L.Swart, PharmD, PhD[2]

1) Department of Pharmacy, Radboud University Medical Center, Nijmegen, The Netherlands ; 2) Department of Pharmacy, VU Medical Centre, Amsterdam, The Netherlands ; 3) Department of Intensive Care, University Medical Centre Utrecht, Utrecht , The Netherlands ; 4) Department of Intensive Care, VU Medical Centre, Amsterdam, The Netherlands ; 5) Department of Intensive Care, Radboud University Medical Center, Nijmegen, The Netherlands

Roger Brüggemann
Radboud university medical center
roger.bruggemann@radboudumc.nl

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ABSTRACT

Background:
Anidulafungin is first line treatment for candidemia or invasive candidiasis in critically ill patients. There is conflicting data on the pharmacokinetics of anidulafungin in ICU patients. Thus we set out to explore anidulafungin pharmacokinetics in ICU patients.

Methods:
Adult ICU patients (from 3 hospitals) receiving anidulafungin as antifungal treatment were eligible. All patients received anidulafungin according to the label indication, constituting of a loading dose of 200 mg on day 1 followed by a maintenance dose of 100 mg from day 2 onward; there were no exclusion criteria for the study. Patients were evaluable when a pharmacokinetic curve on day 3 was completed. In addition, daily trough samples and a PK curve on day 7 were taken. Samples were measured by a validated UPLC-fluorescence method. PK analysis was performed using a standard two-stage approach (Phoenix and SPSS). AUC on day 7 was compared to day 3 using a paired T-test on the log-transformed AUC values.

Results:
23 out of 36 patients (7 female, 16 male) were evaluable. Median (range) age and bodyweight were 66 (28-88) yr and 76 (50-115) kg. Pharmacokinetic sampling on day 3 (n=23) resulted in a median anidulafungin AUC0-24h of 72.1 (IQR 61.3-94.0) mg*h*L-1, a median C24 of 2.2 (IQR 1.9-2.9) mg/L, a median Cmax of 5.3 (IQR 4.1-6.0) mg/L, a median Vd of 46.0 (IQR 32.2-60.2) L and a median CL of 1.4 (IQR 1.1-1.6) L*h-1. Pharmacokinetic sampling on day 7 (n=13) resulted in a median AUC0-24h of 82.7 (IQR 73.0 – 129.5) mg*h*L-1, a median Cmin of 2.8 (IQR 2.2 - 4.2) mg/L, a median Cmax of 5.9 (IQR 4.6 – 8.0) mg/L, a median Vd of 39.7 (IQR 32.2 – 54.4) L and a median CL of 1.2 (IQR 0.8 – 1.4) L*h-1. The Geometric Mean Ratio for AUCday7 / AUCday3 was 1.13 (90% CI 1.03 – 1.25); visual inspection of daily trough concentrations did reveale a slight increase over time. We did not identify any significant covariates on anidulafungin pharmacokinetics (e.g. bodyweight, albumin, liver function). Anidulafungin was well tolerated.

Conclusions:
Exposure of anidulafungin in ICU patients was lower compared to healthy volunteers or other patient populations. The exposure in the ICU patient population was comparable to previous reports on anidulafungin in ICU patients. The interindividual variability in pharmacokinetics was moderate whereas the intra-individual variability was limited. No significant covariates could be identified. Larger cohorts of patients or pooled data analyses is necessary to retrieve relevant covariates and to resolve the impact of the lower exposure.

METHODS

Primary objective:
To determine the pharmacokinetics of anidulafungin given to ICU patients.

Secondary objectives:
To identify covariates of influence on the pharmacokinetics of anidulafungin.
To determine the safety of anidulafungin in this patient population.

METHODS (CONTINUED)

Design:
- Open-label, multi-centre, multiple dose, observational trials
- ICU patients from 3 hospitals received anidulafungin for suspected or proven fungal infection or as prophylaxis.
- Anidulafungin treatment: loading dose of 200 mg on day 1, followed by 100 mg once daily from day 2 onward.

Pharmacokinetic curves:
Two PK curves on days 3 and 7
Sampling PK curve 1 (day 3 +/- 1 day) : t=0 (pre-dose), end of infusion (90 minutes), 2, 4, 8, 12, 18, and 24 hours post infusion (8 samples).
Sampling PK curve 2 (day 7 +/- 1 day) : t=0 (pre-dose), end of infusion, 6, 12, and 24 hours post infusion (5 samples)
Additional trough samples were drawn on all other study days and until 3 days after stopping anidulafungin.
Patients were eligible if at least the first PK curve was completed.
All patients were managed with a central venous catheter or arterial catheter.

Medical history, physical examination	Upon inclusion
Vital signs	Daily
Laboratory safety	3 days per week + PK days
APACHE II score	Upon ICU admission
SOFA - and Child Pugh score	Upon inclusion + PK days
Adverse events (AE)	Report of AE in addition to medical observations on all study days

Table 1: Safety parameters and time points

RESULTS

Demographics	Evaluable ICU patients (n=23)
Gender	
Male (n [%])	16 (70%)
Female (n [%])	7 (30%)
Median age (range) (yr	66 (28-88)
Elderly (≥65yr)	14 (61%)
Race	
Caucasian (n [%])	21 (91%)
African (n [%])	2 (9%)
Mean weight (range) (kg)	76 (50-115)
Mean BMI (range) (kg/m2)	25 (17-33)
Clinical Characteristics	
Kidney function/renal replacement therapy (n [%])	
MDRD >50ml/min/1.73m2	13 (57%)
MDRD 31-50ml/min/1.73m2	4 (17%)
MDRD 10-30ml/min/1.73m2	6 (26%)
Any form of dialysis	11 (48%)
Hypoalbuminaemia (n [%])	
25-34 g/L	2 (9%)
15-24 g/L	10 (43%)
<15 g/L	11 (48%)
Disease Severity scores	
Mean SOFA score (range)	
Day 3 (n=22)	8.6 (range 3-19)
Day 7 (n=8)	5.9 (range 3-11)
APACHE II score upon admission to ICU	
Mean (range)	25 (16-43)
≤20	3 (14%)
>20	19(86%)

Table 2: Baseline characteristics of patients

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RESULTS (CONTINUED)

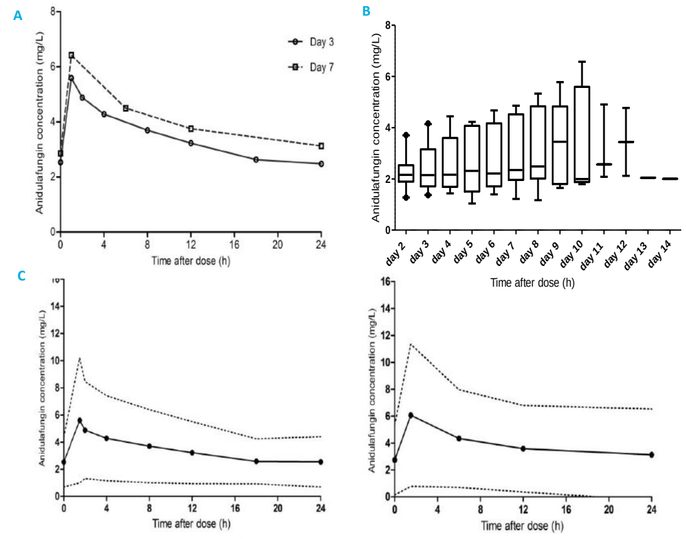

Figure 1a. Anidulafungin PK curve of day 3 (solid line) versus day 7 (dashed line)
Figure 1b. Daily Ctrough concentration from day 2 onwards
Figure 1c. Anidulafungin concentration versus time curve. Mean anidulafungin concentration with 95% CI upper and lower limit. Left panel represents day 3 and right panel represents day 7.

	Day 3 (n=23)	Day 7 (n=13)
AUC0-24 (mg*h/L)	72.1 (61.3 – 94.0)	82.7 (73.0 – 129.5)
CL (L/h)	1.39 (1.06 – 1.63)	1.21 (0.78 – 1.37)
Vd (L)	46.0 (32.2 – 60.2)	39.7 (32.2 – 54.4)
C24 (Trough concentration)	2.17 (1.91 – 2.87)	2.78 (2.23 – 4.23)
Cmax (Peak concentration)	5.27 (4.08 – 5.99)	5.86 (4.64 – 8.02)
T1/2 (h)	23.4 (21.0 – 25.9)	27.2 (20.9 – 35.1)

Table 3: Median pharmacokinetic data of ANI of PK curve 1 and PK curve 2 plus IQR_{25-75}
AUC0-24h: 24h area under the concentration-time curve, Cmax: maximum plasma concentration, C24: plasma trough concentration, t1/2: elimination half-life, VD: volume of distribution, CL: clearance

Steady state:
The GMR for AUCday7 / AUCday3 was 1.13 (90% CI 1.03 – 1.25) indicating that statistical significant differences were not reached.
Anidulafungin C24 correlated well with AUC on day 3 (r2 = 0.954) and day 7 (r2 = 0.968)

Intra-individual variability:
The median inter-individual coefficient of variation (CV) of anidulafungin trough concentrations (day 2–end of therapy) was 46.7% (n=22; range 29.4 – 63.9%; 105 C24) and the median intra-individual CV to 14.6% (n=22; range 0.9 – 29.6%) over the same period.

Covariates:
Anidalufungin PK parameters AUC0-24h, clearance and volume of distribution were not influenced by covariates (gender, bodyweight, APACHE II score, SOFA score, Child Pugh Score, renal function, renal replacement therapy and serum albumin (n=23 patients per variable).

CONCLUSIONS

-Anidulafungin PK on day 7 was comparable to day 3.
-Anidulafungin AUC and Ctrough were well correlated
-Anidulafungin exposure was lower compared to healthy volunteers but confirmed lower exposure in ICU studiesreported earlier.
The clinical consequence of this is subject to debate.