



HAL
open science

Pharmacokinetic study of anidulafungin in ICU patients with intra-abdominal candidiasis

H. Dupont, L. Massias, Boris Jung, N. Ammenouche, P. Montravers

► To cite this version:

H. Dupont, L. Massias, Boris Jung, N. Ammenouche, P. Montravers. Pharmacokinetic study of anidulafungin in ICU patients with intra-abdominal candidiasis. *Journal of Antimicrobial Chemotherapy*, 2017, 72 (5), pp.1429-1432. 10.1093/jac/dkw568 . hal-01792510

HAL Id: hal-01792510

<https://hal.science/hal-01792510>

Submitted on 21 Apr 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Pharmacokinetic study of anidulafungin in ICU patients with intra-abdominal candidiasis

H. Dupont^{1,2*}, L. Massias^{3,4}, B. Jung⁵, N. Ammenouche¹ and P. Montravers⁶

¹Department of Anaesthesiology and Critical Care Medicine, CHU Amiens Picardie, Amiens, France; ²INSERM UMR 1088, University of Picardy Jules Verne, Amiens, France; ³Pharmacology—Toxicology Laboratory, CHU Bichat Claude Bernard, Paris, France; ⁴IAME, UMR 1137, University Paris Diderot, Sorbonne Paris Cité, Paris, France; ⁵Department of Anaesthesiology and Critical Care Medicine, CHU Saint-Eloi, Montpellier, France; ⁶Department of Anaesthesiology and Critical Care Medicine, CHU Bichat Claude Bernard, Paris, France

*Corresponding author. Pole d'Anesthésie-Réanimations, CHU Amiens Picardie, 80054 Amiens cedex, France. Tel: +33-322087980; Fax: +33-322089984; E-mail: dupont.herve@chu-amiens.fr

Background: Only limited pharmacokinetic data are available for anidulafungin in ICU patients, especially in patients treated for severe intra-abdominal infection (IAI).

Methods: This was a prospective multicentre observational study in ICU patients with suspected yeast IAI. All patients received an intravenous loading dose of 200 mg of anidulafungin, followed by 100 mg/day. Thirteen blood samples were drawn between day 1 and day 5 for pharmacokinetic analysis. Samples were analysed by an HPLC-tandem MS method. Demographics and SAPS2 and SOFA scores were recorded.

Results: Fourteen patients with a median age (IQR) of 62 years (48–70) and with a mean BMI of 30.5 kg/m² were included from three centres; 57.1% were women. Their median (IQR) SAPS2 score was 54 (45–67) and their median (IQR) SOFA score was 8 (7–12). Six patients with community-acquired IAI and eight patients with nosocomial-acquired IAI were included. Twelve yeasts were isolated: six *Candida albicans*, two *Candida glabrata*, two *Candida tropicalis*, one *Candida parapsilosis* and one *Candida krusei*. Pharmacokinetic parameters were as follows [mean (% coefficient of variation)]: C_{max} (mg/L) = 6.0 (29%); T_{max} (h) = 1.6 (25.8%); C_{min} (mg/L) = 3.2 (36.8%); AUC_{0-24} (mg·h/L) = 88.9 (38.6%); $t_{1/2}$ (h) = 42.1 (68.2%); CL (L/h) = 1.2 (42.3%); and V (L) = 72.8 (87.8%). A two-compartment model best described the anidulafungin concentrations in the population pharmacokinetic study.

Conclusions: The pharmacokinetic parameters of anidulafungin in critically ill ICU patients with complicated IAI are similar to those observed in the literature. However, an increased V and a longer $t_{1/2}$ were observed in this study. (EudraCT No. 2010-018695-25)

Introduction

Anidulafungin is indicated for the treatment of candidiasis¹ and has also been proposed as first-line therapy in the most critically ill patients.² The pharmacokinetic (PK) profile of anidulafungin may be useful in ICU patients without the need for dosage adjustment due to impaired renal or liver function.³ Moreover, the reported lack of interaction with other treatments would also constitute an advantage in the ICU.^{4,5} Very limited PK data are available for anidulafungin in the ICU.^{6–8} Previous PK studies were essentially performed in candidaemic patients, excluding patients with intra-abdominal infections (IAI) except for the study by van Wanrooy *et al.*⁸ The aim of the current study was to evaluate the impact of abdominal candidiasis (IAC) on the PK of anidulafungin in ICU patients.

Methods

Study design

This prospective multicentre observational trial evaluated the PK parameters of anidulafungin in adult ICU patients with suspected IAC.

The inclusion criterion was suspicion of IAC in a patient admitted to the ICU for complicated IAI after surgery. Patients with direct examination of peritoneal fluid positive for yeast⁹ or presenting at least three of the following criteria were eligible for inclusion: cardiovascular failure requiring vasopressor support, upper gastrointestinal tract perforation, ongoing antimicrobial therapy for ≥ 48 h and female gender.¹⁰ Patients with primary peritonitis and infected acute pancreatitis were excluded from the study.

All patients received a loading dose of anidulafungin (200 mg intravenously) then 100 mg intravenously per day. Concomitant antimicrobial treatment was left to the discretion of the centres according to their protocols. Demographic data, SAPS2 score¹¹ and SOFA score¹² were noted.

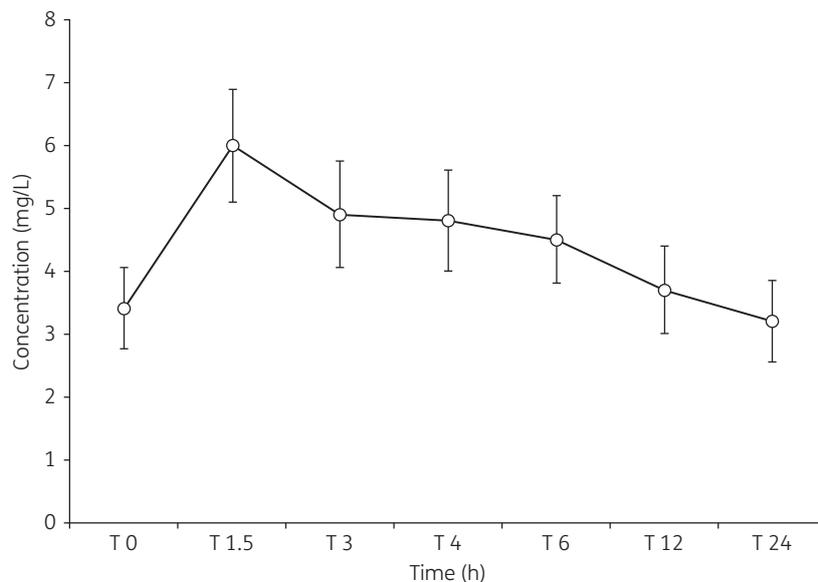


Figure 1. Mean (SD) steady-state anidulafungin concentrations.

Identification of yeasts was performed according to routine procedures in the mycology laboratory.

Ethics

The study was approved by the regional ethics committee (Comité de Protection des Personnes Nord-Ouest 2, No. 2010-10). Three centres were involved in France. All patients or their representatives signed an informed consent form.

Sampling and anidulafungin assay

Thirteen 5 mL blood samples were drawn from each patient and centrifuged for 10 min at 4000 rpm after freezing (day 1: T0, T_{max} , T24; day 3: T0, T_{max} , T24; day 5: T0, T_{max} , T3, T4, T6, T12 and T24). All samples were stored at -80°C and analysed simultaneously at the end of the study. An HPLC-tandem MS assay for anidulafungin detection in human plasma was developed and validated according to previous recommendations.¹³ The method is described in the Supplementary data available at JAC Online.

PK analysis

The PK parameters of anidulafungin were determined by non-compartmental methods, using WinNonlin® version 5.1 (Pharsight, Mountain View, CA, USA). The model used was based on intravenous infusion and data derived from steady-state plasma concentrations. The maximum plasma anidulafungin concentration (C_{max}) and the time to C_{max} (T_{max}) were determined from individual plasma concentration curves.

Population PK analysis

Population PK analysis was performed using Monolix 4.1.2 software (<http://www.lixoft.eu>).

A basic population PK model was developed, in which one-, two- and three-compartment models were compared. The most appropriate pharmacostatistical model was selected on the basis of the following criteria: (i) smaller value of Bayesian information criterion (BIC); (ii) adequate

goodness-of-fit plots; and (iii) low relative standard error (RSE) in estimated PK parameters.

Also see the Supplementary data available at JAC Online.

Results

Fourteen patients were included in the study. Their characteristics and evolution are presented in Table S1 (available as Supplementary data at JAC Online). Steady-state anidulafungin concentrations observed on PK analysis are presented in Figure 1. The results of non-compartmental analysis were the following [mean \pm SD (% coefficient of variation)]: maximum concentration (C_{max} in mg/L) = 6.0 ± 1.8 (29.0); minimum concentration (C_{min} in mg/L) = 3.2 ± 1.2 (36.8); time to reach maximal concentration (T_{max} in h) = 1.6 ± 0.4 (25.8); area under the curve over a 24 h dosing interval (AUC_{0-24} in mg·h/L) = 88.9 ± 34.3 (38.6); half-life ($t_{1/2}$ in h) = 42.1 ± 28.7 (68.2); clearance (CL in L/h) = 1.2 ± 0.5 (42.2); and volume of distribution at steady-state (V in L) = 72.8 ± 63.9 (87.8).

The one- and three-compartment models did not provide acceptable validation conditions. Evaluation of the two-compartment model was performed with constant, proportional and combined residual error models (Table 1). All of these models had a low BIC. However, analysis of RSE showed that only the constant residual error model was acceptable. Individual predictions were correctly estimated when compared with observed concentrations (Figure S1). Shrinkage is presented in Figure S2. Individual weighted residuals (IWRES) were uniformly distributed around the line of individual prediction and according to time (Figure S3). Normalized prediction distribution error (NPDE) analysis confirmed the good predictive properties of the model both according to time and predicted concentrations (Figure S3). The visual predictive check (VPC) graph did not reveal any deficiency of the model, as the majority of points were included in the calculated prediction interval (Figure S4).

Table 1. Population PK models of anidulafungin

	Values	RSE (%)	BIC
Constant residual error			
CL (L/h)	0.87	11	242.87
V1 (L)	22.3	16	
Q (L/h)	18.2	32	
V2 (L)	48.7	28	
ω CL (L/h)	0.321	27	
ω V1 (L)	0.255	66	
ω Q (L/h)	0.748	36	
ω V2 (L)	0.848	27	
a	0.53	10	
Proportional residual error			
CL (L/h)	0.938	11	242.3
V1 (L)	6.33	103	
Q (L/h)	34.3	33	
V2 (L)	52.1	18	
ω CL (L/h)	0.378	21	
ω V1 (L)	1.4	45	
ω Q (L/h)	0.165	437	
ω V2 (L)	0.251	76	
b	0.141	10	
Combined residual error			
CL (L/h)	0.899	12	245.54
V1 (L)	22.9	16	
Q (L/h)	17.1	33	
V2 (L)	45.7	28	
ω CL (L/h)	0.364	24	
ω V1 (L)	0.235	83	
ω Q (L/h)	0.732	38	
ω V2 (L)	0.798	29	
a	0.418	34	
b	0.0265	126	

Q, inter-compartmental CL; ω , variability of kinetic parameters in the model.

Discussion

This study shows that PK parameters of anidulafungin in ICU patients with IAC are similar to those observed in previous publications. However, several differences were demonstrated, with a higher V and a longer $t_{1/2}$.

The different PK values of published studies on anidulafungin are presented in Table S2. Seven studies have been published, including five in the ICU,^{6–8,14,15} one in healthy volunteers⁵ and one in infected patients on wards.¹⁶ One ICU study has focused on continuous haemofiltration¹⁴ and one case has been reported with albumin dialysis.¹⁷

The C_{max} , C_{min} , AUC_{0-24} and CL we observed in this study are in the range of published studies (Table S2), even in patients with continuous haemofiltration.¹⁴

The main differences in PK parameters observed in this study were a higher V and a longer $t_{1/2}$. V was 72.8 L (87.8% coefficient of variation) in our study, distributed according to the population PK model into a central V1 of 22.3 L and a peripheral V2 of 48.7 L.

This value is considerably different from V values reported by other studies. A long $t_{1/2}$ of 42 h (68% coefficient of variation) was also reported in this study. Note that Dowell *et al.*³ reported slight variations in $t_{1/2}$ according to hepatic (33.7–42 h) or renal insufficiency (31.2–38.9 h). However, these parameters were associated with the highest coefficients of variation.

The only study reporting patients with candida peritonitis⁸ reported lower C_{max} , C_{min} and AUC_{0-24} , but higher CL, than in our study focusing on the same population. However, they include 35% with candidaemia, which could modify the results when compared with IAI alone. Patients were older with lower severity scores. Grau *et al.*¹⁸ reported no significant variations of PK in the same population with micafungin.

Many explanations can be proposed for these slight discrepancies between studies. First of all, the composition of the study population is important, as factors such as age, BMI, renal or hepatic insufficiency, disease severity, total protein concentrations, bilirubin or total body water may influence the PK parameters of anidulafungin. However, individually, none of these parameters was really associated with a modification of PK parameters. No modification of PK parameters was observed in patients with renal or hepatic insufficiency in the study by Dowell *et al.*³ The impact of BMI on PK parameters did not exceed 20% in a population PK study by Dowell *et al.*¹⁹ and no modification of PK parameters was observed in ICU patients on haemofiltration.¹⁴ Liu *et al.* found no relationship between plasma albumin concentration and anidulafungin,⁶ as confirmed by another study.⁸ Only one study reported a possible correlation between total body water and bilirubin concentration with anidulafungin exposure,⁸ but this correlation was not reported elsewhere. One study reported results that differ considerably from those reported in all other studies.⁷ However, it was not based on complete steady-state analysis of the drug, but only on three blood samples, which could explain these results.

We found that anidulafungin concentrations were best described by a two-compartment model, in accordance with previously published studies.^{15,16,19} Due to the small sample size of this study, various covariables and their impact on the proposed PK model could not be studied. However, the equation proposed in the linear regression model in the article by van Wanrooy *et al.*¹⁵ for the development of limited sampling strategies was validated by our sample with an $AUC_{0-24} = 93$ mg·h/L (SD = 36.5).

Some limitations of this study should be discussed. First of all, this study was based on a small sample size, though this was similar to the sample sizes of many PK studies in the ICU. The main difficulty related to small sample size is that covariables are difficult to assess in a small number of patients. Further studies including biomarkers as covariables should be performed.

Secondly, we did not sample peritoneal fluid, which is the source of infection, as recently published in relation to micafungin.¹⁸ Lastly, no relationship with clinical outcome could be determined in this type of PK study, in particular because MICs of the strains were not collected. There is no prospective randomized controlled trial showing better outcome with treatment, although there are many cohort studies showing higher mortality with IAC. Experts suggest that treatment is mandatory, but this advice is not evidence based.

In conclusion, PK parameters measured in severe ICU patients with IAC are similar to those observed in healthy volunteers, or other types of ICU patients. Higher V and longer $t_{1/2}$ were observed and could be due to this specific study population.

Funding

This study was sponsored by a grant from Pfizer France. The sponsor played no role in design, analysis and interpretation of the study.

Transparency declarations

H. D. has received fees for consulting or lectures for advisory boards and symposia from Astellas, Pfizer, Gilead, AstraZeneca, Novartis, Merck, Cubist and Paratek. B. J. declares honoraria from Merck and travel expenses from Pfizer and Astellas. P. M. has received fees for consulting or lectures for advisory boards and symposia from Astellas, Pfizer, AstraZeneca, Merck, Tetraphase, Basilea, The Medicine Company and Paratek. L. M. and N. A.: none to declare.

Supplementary data

Supplementary data, including Tables S1 and S2 and Figures S1–S4, are available at.

References

- 1 Reboli AC, Rotstein C, Pappas PG *et al.* Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med* 2007; **356**: 2472–82.
- 2 Kett DH, Shorr AF, Reboli AC *et al.* Anidulafungin compared with fluconazole in severely ill patients with candidemia and other forms of invasive candidiasis: support for the 2009 IDSA treatment guidelines for candidiasis. *Crit Care* 2011; **15**: R253.
- 3 Dowell JA, Stogniew M, Krause D *et al.* Anidulafungin does not require dosage adjustment in subjects with varying degrees of hepatic or renal impairment. *J Clin Pharmacol* 2007; **47**: 461–70.
- 4 Dowell JA, Schranz J, Baruch A *et al.* Safety and pharmacokinetics of coadministered voriconazole and anidulafungin. *J Clin Pharmacol* 2005; **45**: 1373–82.
- 5 Dowell JA, Stogniew M, Krause D *et al.* Lack of pharmacokinetic interaction between anidulafungin and tacrolimus. *J Clin Pharmacol* 2007; **47**: 305–14.
- 6 Liu P, Ruhnke M, Meersseman W *et al.* Pharmacokinetics of anidulafungin in critically ill patients with candidemia/invasive candidiasis. *Antimicrob Agents Chemother* 2013; **57**: 1672–6.
- 7 Sinnollareddy M, Roberts J, Lipman J *et al.* Pharmacokinetic variability and exposures of fluconazole, anidulafungin and caspofungin in ICU patients. Data from multinational Defining Antibiotic Levels in Intensive Care Unit (DALI) patients study. *Crit Care* 2015; **19**: 33.
- 8 van Wanrooy MJ, Rodgers MG, Uges DR *et al.* Low but sufficient anidulafungin exposure in critically ill patients. *Antimicrob Agents Chemother* 2014; **58**: 304–8.
- 9 Dupont H, Paugam-Burtz C, Muller-Serieys C *et al.* Predictive factors of mortality due to polymicrobial peritonitis with *Candida* isolation in peritoneal fluid in critically ill patients. *Arch Surg* 2002; **137**: 1341–6.
- 10 Dupont H, Bourichon A, Paugam-Burtz C *et al.* Can yeast isolation in peritoneal fluid be predicted in intensive care unit patients with peritonitis? *Crit Care Med* 2003; **31**: 752–7.
- 11 Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European-North American multicenter study. *JAMA* 1993; **270**: 29057–68.
- 12 Vincent JL, Moreno R, Takala J *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22**: 707–10.
- 13 Alebic-Kolbah T, Modesitt MS. Anidulafungin—challenges in development and validation of an LC-MS/MS bioanalytical method validated for regulated clinical studies. *Anal Bioanal Chem* 2012; **404**: 2043–55.
- 14 Aguilar G, Azanza JR, Carbonell JA *et al.* Anidulafungin dosing in critically ill patients with continuous venovenous haemodiafiltration. *J Antimicrob Chemother* 2014; **69**: 1620–3.
- 15 van Wanrooy MJ, Proost JH, Rodgers MG *et al.* Limited-sampling strategies for anidulafungin in critically ill patients. *Antimicrob Agents Chemother* 2015; **59**: 1177–81.
- 16 Liu P. Population pharmacokinetic-pharmacodynamic analysis of anidulafungin in adult patients with fungal infections. *Antimicrob Agents Chemother* 2013; **57**: 466–74.
- 17 Aguilar G, Azanza JR, Sadaba B *et al.* Pharmacokinetics of anidulafungin during albumin dialysis. *Crit Care* 2014; **18**: 422.
- 18 Grau S, Luque S, Campillo N *et al.* Plasma and peritoneal fluid population pharmacokinetics of micafungin in post-surgical patients with severe peritonitis. *J Antimicrob Chemother* 2015; **70**: 2854–61.
- 19 Dowell JA, Knebel W, Ludden T *et al.* Population pharmacokinetic analysis of anidulafungin, an echinocandin antifungal. *J Clin Pharmacol* 2004; **44**: 590–8.