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Pharmacokinetics of anidulafungin in critically ill patients with Candida peritonitis

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ABSTRACT

Objective: To describe the pharmacokinetic (PK) profile of anidulafungin and to evaluate its concentration in the peritoneal fluid (PF) of patients suspected of suffering from peritoneal infection undergoing abdominal surgery, in order to ensure that therapeutic levels are achieved within the peritoneal cavity.
Methods: A descriptive, open, prospective, observational, multicentre and non-interventional study was performed. Anidulafungin was used at conventional doses. Blood and PF samples were obtained on day 2 of treatment or on any of the following days.
Results: A total of 31 patients in a serious clinical condition, as demonstrated by high mean clinical severity scale scores (APACHE II and SOFA scores), were included in the study. The mean area under the curve (AUC) in PF was 30% (31 ± 19%) of that determined in the plasma and the maximum concentration (Cmax) reached in PF (mg/l) was close to 1 (0.9 ± 0.5). No adverse effects were observed in any of the 31 patients.
Conclusions: Anidulafungin at conventional doses reaches PF concentrations that exceed the minimum inhibitory concentration of the usual *Candida spp*, which explains the proven efficacy of this echinocandin in the treatment of Candida peritonitis in critically ill patients.

Introduction

Anidulafungin is a potent antifungal agent that belongs to the echinocandin family. When administered intravenously, it displays a predictable pharmacokinetic (PK) profile, characterized by plasma concentrations proportional to the administered dose and by reduced variability among subjects.

Upon intravenous administration, anidulafungin is rapidly and widely distributed to tissues, with a volume of distribution of 30–50 litres, reaching a state of steady equilibrium within the first 48 h following administration of the initial loading dose of 200 mg (Ecalta, 2018). Progressive elimination of anidulafungin is brought about by a spontaneous and slow non-enzymatic degradation that transforms it into inactive metabolites. Less than 10% of the drug is eliminated in faeces as an unchanged compound. Plasma clearance of anidulafungin is approximately 1 l/h, with negligible renal clearance (Ecalta, 2018). The half-life rate of elimination is approximately 1 day; hence, it is administered once a day.

The absence of hepatic and renal elimination allows the administration of this drug without any adjustment of the dose for patients with hepatic and renal alterations, including those undergoing haemodialysis techniques (Ecalta, 2018). Anidulafungin is not dialyzable and can therefore be administered without considering haemodialysis times. In patients requiring external clearance techniques, no PK changes have been described (De Rosa et al., 2013; Burkhardt et al., 2009; Aguilar et al., 2014a; Aguilar et al., 2014b).

However, some discrepancies exist regarding the PK behaviour – maximum plasma concentration (Cmax) and area under the curve (AUC) – in critically ill patients; results vary from being similar to those obtained in healthy subjects (Liu et al., 2013) to reductions by half of these parameters (Sinnollareddy et al., 2015).

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As reflected in the latest available guidelines, echinocandins including anidulafungin are the recommended initial treatment for candidemia (degree of evidence AI, "strong recommendation") (Cornely et al., 2012; Ruhnke et al., 2012; Dimopoulos et al., 2012).

The admission of patients to the intensive care unit (ICU) due to multi-organ failure and/or the presence of intra-abdominal infection is frequent (de Ruiter et al., 2009). In addition, the use of aggressive therapeutic and supportive techniques significantly increases the risk of intra-abdominal candidiasis (León et al., 2014). This disease, which is a very frequent complication in surgical patients (León et al., 2014; Montravers et al., 2006; Montravers et al., 2013), is certainly life-threatening and can impact the prognosis substantially (Montravers et al., 2006), hence the importance of treatment and of reaching sufficient peritoneal concentrations of the antifungal drug.

The main objective of this study was to describe the PK profile of anidulafungin and to evaluate its diffusion into the peritoneal fluid (PF) of critically ill patients with Candida peritonitis when administered at conventional doses. Knowledge of the concentration of the drug in the PF would permit us to determine whether the levels of the drug are maintained above the minimum inhibitory concentration (MIC).

Patients and methods

The study was designed as a pilot, descriptive, open, prospective, observational, multicentre and non-interventional study, in which the PK of anidulafungin was examined in patients undergoing abdominal surgery suspected of suffering from, or with a known, fungal infection and who required treatment with anidulafungin according to the conventional dosage regimen. It was designed as a multi-centre study in order to achieve the recruitment of a sufficient number of patients in a short period of time. Four departments of intensive and critical care participated in the study: University Hospital of Badajoz (1039 beds), University Hospital San Pedro de Alcántara (530 beds), Mérida General Hospital (381 beds), and Hospital D. Benito-Villanueva (327 beds).

The following inclusion criteria were applied: age >18 years, history of previous recent abdominal surgery, presence of intra-abdominal drainage, current diagnosis of secondary or tertiary peritonitis, patients requiring antifungal treatment with anidulafungin according to medical criteria and either suspected or intraoperative evidence of invasive candidiasis. Furthermore, a signature of informed consent provided by the patient or a legal representative was required.

Exclusion criteria were history of hypersensitivity to anidulafungin or any other echinocandin, body mass index (BMI) <19 kg/m^2 or >35 kg/m^2, fructose intolerance, pregnancy or lactation, and no signed informed consent.

The patients were treated with the conventional intravenous dosage regimen of anidulafungin: 200 mg on day 1, followed by 100 mg/day thereafter.

The samples needed for this study were obtained on day 2 of treatment or on any of the following days. Before obtaining the samples, it was required that the patient had adequately received the loading dose and at least one maintenance dose. The study was performed regardless of the total duration of treatment with anidulafungin.

Each patient had a venous blood sample collected at the following times: prior to the infusion of anidulafungin and then at 1, 3, 6, 12, 18, and 24 h after administration of the drug. The extraction of peritoneal fluid was conducted at the same time as the plasma samples were obtained, by draining pre-existing intra-abdominal fluid.

All samples were processed as follows: the sample was transferred to a tube containing ethylenediaminetetraacetic acid (EDTA); this was manually agitated approximately five times and then immediately deposited on ice. After 15 min, it was centrifuged at 4 °C in a refrigerated centrifuge at 4000–5000 rpm for 10 min. The plasma obtained was transferred to another tube, which was duly labelled and stored at a temperature of −70 °C until transfer to the Pharmacokinetics Laboratory of the University Hospital of Navarra for analysis, which was conducted at −20 °C.

The analytical technique consisted of using pure anidulafungin as a reference substance, which was obtained from Toronto Research Chemicals (Toronto, Canada). Drug-free human plasma was acquired from the Blood Bank of the University Hospital of Navarra. Concentrations of anidulafungin were determined by high performance liquid chromatography (HPLC) using Agilent 1200 SL equipment. For the chromatographic separation, a reverse-phase Gemini NX C18 110A column was used (150 × 2.1 mm, 3 μm; Phenomenex, Torrance, CA, USA). Anidulafungin was detected at 304 nm with a time of 11.5 min.

Table 1
Characteristics of patients included in the study.

Total patients	Age (years)	Sex (% male)	Diagnosis and surgery performed (Number of patients)	Charlson comorbidity score
	Mean ± SD			Mean ± SD
31	73 ± 11	71	Secondary peritonitis (28) Tertiary peritonitis (3) Surgery: + complicated colon (17) + complicated surgery of the small intestine (11) + complicated bile duct (3)	3 ± 1.9
BMI (kg/m2) Mean ± SD 32 ± 11 Septic shock Number of patients (%) 29 (93.5)	APACHE II score Mean ± SD 22.7 ± 5.9 Mechanical ventilation Number of patients (%) 26 (83.8)	SOFA score Mean ± SD 10.3 ± 3.5 Blood cultures (Number of patients) Not available (7) Negative (7) Positive (15) Bacteria (13) *Candida* spp. (2) *Candida lusitaniae* (1) *Candida albicans* (1)	Candida score Mean ± SD 3.3 ± 0.4 Peritoneal fluid culture (Number of patients) Not available (3) Negative (22) Positive (6) Bacteria (5) *Candida glabrata* (1) *Candida tropicalis* (1)	MOD Number of patients (%) 25 (80.6)

SD, standard deviation; ia, ; BMI, body mass index; APACHE II score, Acute Physiology and Chronic Health Evaluation score; SOFA score, Sequential Organ Failure Assessment score; MOD, multi-organ dysfunction (two or more organs with dysfunction, according to the SOFA score).

Calibration curves were calculated via the internal standard method, with drug-free human serum and standard ultrafiltrate solutions obtained at concentrations in the range 0.5–40 mg/l (mean correlation coefficient >0.995). Intra-day variability was determined at four concentration levels (0.5, 1.5, 150, 350 mg/l). The test was reproducible with inter-day variability in the range of 2.15–4.01%.

The PK analysis of concentration for all evaluable patients was conducted by means of a non-compartmental method. The following PK parameters of anidulafungin were calculated for each subject after administration: Cmax = maximum concentration. $AUC_{0\text{-}t}$ = area under the curve versus time to the last quantifiable sample (time t), calculated using the trapezoidal method. $AUC_{0\text{-}\infty}$ = area under the curve versus time, extrapolated to infinity calculated as follows:

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{k_e},$$

where C_t is the last quantitated concentration at time t and k_e is the elimination constant. The latter was obtained by linear regression analysis in the last mono-exponential elimination phase (WinNonLin Professional program, version 5.2). In every case, at least three concentration values were used to define this phase. tmax = time when Cmax is reached. The half-life elimination rate, $t_{1/2}$, was determined by the following expression: $t_{1/2} = \ln 2/k_e$. Clt = total clearance, calculated by the following expression: Clt = dose/$AUC_{0\text{-}\infty}$. Vss = volume of distribution in stationary equilibrium, calculated as follows:

$$Vss = dose \times \frac{AUC_{0-\tau} + \tau * AUC_{\tau-\infty}}{(AUC_{0-\tau})^2}$$

where τ is the administration interval.

Any adverse events observed or communicated voluntarily, regardless of the causal relationship with the product under investigation, were notified and evaluated.

Prior to the execution of this study, the protocol, the proposed informed consent form, and other information about patients were reviewed and approved by the Research and Ethics Committee of the University Hospital of Badajoz and by the Spanish Agency of Medicines and Health Products.

Results

A total of 31 patients, whose most relevant clinical characteristics are shown in Table 1, were included in the study. The group had a high average age (73 years), a predominance of males (71%), and a high average BMI (32 kg/m^2). All of the patients had undergone some type of urgent abdominal surgery and were in a serious clinical condition, as demonstrated by high mean APACHE II (Knaus et al., 1985) and SOFA (Vincent et al., 1996) scores.

All of the patients presented a clinical diagnosis of suspected peritoneal infection caused by *Candida spp* with a 'Candida score' value higher than 3 points. A strain of *Candida* was isolated in the peritoneal fluid of four patients and in the blood cultures of two more. All patients were treated with anidulafungin at the conventional dose.

Table 2 shows the length of stay in the hospital and in the ICU, as well as mortality in the ICU and in hospital. All data are in correspondence with the high scores on the clinical severity scales (APACHE II and SOFA) shown by the patients.

The PK parameters determined in plasma and PF samples are described in Table 3.

One patient had an external biliary drain through which concentrations of anidulafungin between 6.38 mg/l and 20 mg/l were determined, correlated with plasma levels of 20–30%. Cmax (mg/l) was 4.3 ± 1.6. A graphical representation of plasma and peritoneal concentrations is depicted in Figure 1.

No adverse effects were observed in any of the 31 patients.

Discussion

Table 4 presents the study results, together with those published by other authors. Differences in plasma concentrations and pharmacokinetic parameters of anidulafungin determined in the different studies can be observed in this table. Analysis of the results revealed that the concentrations found in the present study patients are quite similar to those found in critically ill patients, as reported by van Wanrooy et al. in a previous study (van Wanrooy et al., 2014), but are lower than those reported by other authors in the same population (Aguilar et al., 2014a; Aguilar et al., 2014b; Liu et al., 2013; Brüggemann et al., 2017). However, as published by several authors, exposure to anidulafungin is clearly lower in critically ill patients as compared to healthy subjects (Dowell et al., 2005; Dowell et al., 2007).

A recent study involving seven patients (Welte et al., 2018), reported anidulafungin concentrations in the range of 0.12–0.99 mg/l in ascitic fluid, which is consistent with the average obtained from the data in the present study.

The tendency to observe lower concentrations has been found in several studies, but has not been linked to PK behaviour, since the concentrations of the drug do not vary in relation to the most common clinical alterations such as renal failure, impaired hepatic function, dialysis, or with the use of continuous renal replacement techniques. Possible factors that can influence low concentrations of the drug could be a high volume of distribution (common in critical care patients) and high clearance of the drug with a concomitant boost of the free-fraction.

The convenience of administering a 25% higher loading dose to patients with morbid obesity has been identified in a recent study (Wasmann et al., 2018), in order to compensate for the tendency towards reduced concentrations in this group of patients.

The in vitro activity of anidulafungin against the different species of *Candida* is very important, since *Candida albicans* presents MIC values ≤0.5 mg/l, with MIC 90% of 0.01–0.12 mg/l. *Candida parapsilosis* presents values of 1–4 mg/l, *Candida glabrata* presents values of 0.03–0.25 mg/l, *Candida tropicalis* presents values of 0.06–0.125 mg/l, and *Candida krusei* presents values of 0.25–1 mg/l. Therefore, the concentrations reached in PF (Cmax close to 1 mg/l), although lower than those achieved in blood, are higher than the MIC of practically all *Candida spp* (Pfaller et al., 2008; Pfaller et al., 2005; Morace et al., 2009; Ruan et al., 2008).

Table 2
Clinical outcomes of the patients: stay and mortality.

ICU stay (days) Mean ± SD	Hospital stay (days) Mean ± SD	ICU mortality Number of patients (%)	In-hospital mortality[a] Number of patients (%)
10.7 ± 12.2	25.5 ± 26.7	12 (38.7%)	15 (48.3%)

ICU, intensive care unit; SD, standard deviation.
[a] In-hospital mortality up to 30 days after surgery.

Table 3
Anidulafungin pharmacokinetic parameters (mean ± standard deviation values).

Parameter (number of patients)	Plasma	PF	Ratio PF/plasma (%)
Cmax (mg/l) (23)	4.3 ± 1.6	0.9 ± 0.5	20.9
Cmin (mg/l) (19)	2.2 ± 1.0	0.7 ± 0.42	28.3
AUC_{0-t} (mg h/l) (19)	57.9 ± 17.2	16.76 ± 8.15	31 ± 19
Clt (l/h) (19)	1.9 ± 0.6	–	–
V (l) (9)	120 ± 92	–	–
$t_{1/2}$ (h) (9)	46.9 ± 30	–	–

PF, peritoneal fluid; Cmax, maximum plasma concentration; Cmin, concentration prior to the dose; AUC_{0-t}, area under the curve versus time to the last quantifiable sample; Clt, total clearance; V, volume of distribution; $t_{1/2}$, elimination half-life.

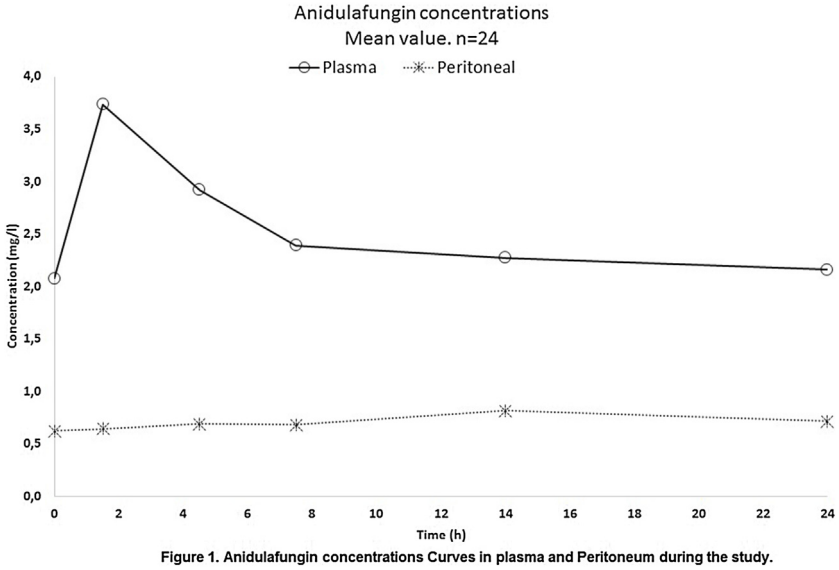

Figure 1. The curves represent Anidulafungin concentration in Plasma and PF during the study.

Table 4
Results of anidulafungin pharmacokinetic studies.

Study population	Cmax (mg/l)	Cmin (mg/l)	AUC (mg h/l)	Clt (l/h)	V (l)	$t_{1/2}$ (h)	Author
Healthy	7.5 (32.5)	2.8 (32.8)	104 (28.7)	1.04 (33.1)			Dowell et al. (2005)
Healthy	–	–	70 ± 13.4	0.74 ± 0.15	28.5 ± 6.5	31.2 ± 1.5	Dowell et al. (2007)
DE	6.2 ± 1.7		104 ± 20				Aguilar et al. (2014a)
Critical	5.27 (4.08–5.99)	2.17 (1.91–2.87)	72.1 (61–94)	1.39 (1.06–1.93)	46 (32.2–60.2)	23.4 (21–25.9)	Brüggemann et al. (2017)
Critical	7.7 (56)	3 (44)	92.7 (41)	1.3 (51)	38.8 (51)	–	Liu et al. (2013)
Critical	4.7 ± 1.4	2.2 ± 0.8	69.8 ± 24.1	–	–	–	van Wanrooy et al. (2014)
Critical	4.3 ± 1.6	2.2 ± 1.0	57.9 ± 17.2	1.9 ± 0.6	120 ± 92	46.9 ± 30	Present study

Cmax, maximum plasma concentration; Cmin, concentration prior to the dose; AUC, area under the curve; Clt, total clearance; V, volume of distribution; $t_{1/2}$, elimination half-life; DE, external debugging.

However, if any doubt remains regarding possible underexposure to the drug in the PF due to the high volume of distribution, it is possible to increase the dose as a result of the good tolerability and apparent absence of adverse effects even at elevated doses.

In conclusion, anidulafungin at conventional doses reaches PF concentrations that exceed the MIC of the usual *Candida spp*, which explains the proven efficacy of this echinocandin in the treatment of Candida peritonitis in critically ill patients. Caution must be taken in the case of possible *Candida krusei* or *Candida parapsilosis* infections and also in obese patients and situations of large capillary hyperpermeability, in the two latter cases due to a higher volume of distribution. In these situations higher doses of the drug must be considered.

Summary

An adequate understanding of the concentrations reached in peritoneal fluid (PF) by an antifungal agent in patients suspected of suffering from peritoneal infection is of great interest to ensure that therapeutic levels are achieved within the peritoneal cavity. To this end, a study was conducted on 31 patients with suspected fungal infection of the abdominal cavity. Patients were treated with the conventional dose of anidulafungin (initial 200 mg loading dose and 100 mg every 24 h thereafter). Venous blood and PF samples were collected on the second day of treatment. The mean area under the curve (AUC) in PF was 30% of that determined in the plasma. No patient experienced adverse effects.

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Conflict of interest

The authors declare no conflict of interest.

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