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SHORT COMMUNICATION

Does Weight Impact Anidulafungin Pharmacokinetics?

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Abstract Bodyweight has been shown to influence anidulafungin exposure, but data from obese patients are lacking. We determined anidulafungin pharmacokinetics (100-mg single dose) in eight morbidly obese subjects (body mass index >40 kg/m^2). Anidulafungin exposure was on average 32.5 % lower compared with the general patient population, suggesting dose increases may be required in this population.

Key Points

Anidulafungin exposure was on average 32.5 % lower compared with the general patient population.

To normalize the exposure to population values, increasing the anidulafungin maintenance dose by 50 % (i.e., 150 mg) could be considered.

To achieve adequate exposure at the beginning of therapy, increasing the loading dose by 50 % (i.e., 300 mg) could be considered.

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1 Introduction

The global prevalence of overweight and obesity has increased at an alarming rate during the previous few decades. If recent trends continue, nearly 58 % of the world's adult population will be overweight or obese in 2030 [1]. Obesity increases the risk of a wide array of co-morbidities and is an established risk factor for nosocomial infections. Because obese patients are subject to a variety of (patho)physiological changes compared with non-obese patients, the pharmacokinetic (PK) and/or pharmacodynamic profile of antimicrobials might be altered [2].

Anidulafungin is an echinocandin antifungal agent approved for the intravenous treatment of invasive candidiasis and candidemia [3]. At standard doses (200-mg loading dose, 100-mg maintenance dose), anidulafungin displays linear PK, with a volume of distribution close to total body water (0.6 L/kg), a clearance of about 1 L/h, and an elimination half-life of approximately 24 h [3, 4].

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The PK of anidulafungin has been well described in healthy subjects and several patient populations [4–10], although the weight range in these studies was small. Weight has been reported to be an influential factor on anidulafungin exposure [4, 8–10]. This may therefore result in suboptimal exposure of anidulafungin in obese patients, possibly requiring a different dosing strategy in this population. In this study, we aim to describe the PK of anidulafungin in morbidly obese subjects with body mass index (BMI) >40 kg/m^2.

2 Materials and Methods

2.1 Study Design and Subjects

This open-label phase IV study (ClinicalTrials.gov Identifier: NCT02021123) was approved by the Ethics Committee of the Radboud University Medical Center in 2014 and conducted in accordance with the declaration of Helsinki. Before inclusion, all subjects gave written informed consent.

From August until October 2014, adult morbidly obese subjects (BMI >40 kg/m^2; with no fungal infection) undergoing laparoscopic gastric bypass or sleeve surgery were eligible for inclusion. Subjects were excluded in the case of hypersensitivity to echinocandins and/or abuse of alcohol or drugs for the previous 3 months.

2.2 Study Procedure

Upon inclusion, patient demographics, clinical characteristics, and concomitant medications were reported. Subjects received a single intravenous 100-mg dose of anidulafungin before laparoscopic bariatric surgery. The anidulafungin infusion was administered 2.5 h before induction of anesthesia with an infusion rate of 1.1 mg/min [3]. There were no restrictions in the protocol with regard to concomitant medication.

A PK curve was drawn at predefined times of $T = 0.5$, 1, 1.5 (end of infusion), 2, 4, 6, 8, 10, 12, 24, and 48 h post-infusion ($n = 11$). Blood samples were collected in lithium-heparin-containing tubes (non-gel) and centrifuged at $1900 \times g$ (3000 rpm) for 5 min at 4 °C within 30 min of collection. Plasma was immediately stored at -80 °C. Anidulafungin samples were measured by ultra-performance liquid with fluorescence detection [8].

2.3 Analytical Assay

Anidulafungin samples were measured by ultra-performance liquid chromatography with fluorescence detection (dynamic range for anidulafungin in plasma:

0.008–8.43 mg/L with a concentration-dependent accuracy range [$n = 15$] of 94.2–103.5 %). A seven-point calibration curve with three quality-control samples was used. Intraday precision ranged between 0.87 and 1.84 % ($n = 5$) and interday precision varied between 0.53 and 1.58 % ($n = 15$). Anidulafungin recovery was 93 %. Stability of anidulafungin remained unchanged by three freeze–thaw cycles.

2.4 Safety

Blood samples for the purpose of laboratory safety were collected at $T = 0$, 24, and 48 h for the determination of biochemical and hematological parameters (sodium, potassium, chloride, calcium, phosphate albumin, blood urea nitrogen, aspartate aminotransaminase, alanine aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, bilirubin (total), lactate dehydrogenase, C-reactive protein, triglycerides, creatinine kinase, creatinine, uric acid, hemoglobin, hematocrit, white blood cells differential, platelets, and red blood cell count).

Adverse events (AEs) were reported regardless of potential relationship to anidulafungin (including adverse drug reactions, illness that developed during the study, exacerbations of pre-existing illness, or abnormal laboratory values requiring intervention or diagnostic evaluation) until discharge.

There were no restrictions in the protocol with regard to concomitant medication.

2.5 Anidulafungin PK Data Analysis

PK parameters were calculated using non-compartmental analysis (Phoenix WinNonlin 6.3; Pharsight Corp, Mountain View, CA, USA). The area under the plasma concentration–time curve from 0 to time of last sample ($AUC_{0–48}$) was calculated using the linear up-log down trapezoidal rule. The AUC from 0 to infinity ($AUC_{0–inf}$) was determined as follows:

$$AUC_{0–inf} = AUC_{0–48} + \text{last observed concentration}/k_e.$$

Anidulafungin exposure in this cohort of morbidly obese subjects was compared with the exposure in the general patient population [10], given that $AUC_{0–inf}$ (single dose) $= AUC_{0–24}$ (steady state).

Maximum plasma concentration was directly observed from the data. Total body clearance was calculated as $D/AUC_{0–inf}$ and volume of distribution (V_D) was calculated as $D/AUC_{0–inf} \times k_e$. Half-life was calculated by $\ln(2)/k_e$. Elimination rate constant (k_e) was estimated by log-linear regression of the terminal portions (minimum of four points, user defined) of the plasma concentration-vs.-time curves.

2.6 Statistical Analysis

Descriptive statistics (e.g., geometric mean, range, inter-patient variability [calculated as geometric coefficient of variation]) were calculated for anidulafungin PK parameters. A Spearman's correlation was run to assess the correlation between AUC and weight in SPSS 20.0 (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered statistically significant. Using a power calculation (alpha = 0.05, power = 0.8) based on the exposure and standard deviation in the general patient population [9, 10] and the assumption of a mean AUC_{0-inf} of 75 mg × h/L in the target obese population, this would require eight patients.

3 Results

3.1 Subjects

Eight subjects (three male, five female; all Caucasian) were included. Median (range) age was 43 years (29–66 years). Geometric mean (range) weight, BMI, lean body mass (calculated according to Janmahasatian et al. [11], and body surface area and waist/hip ratio were 144.7 kg (124.1–166.5), 48.9 kg/m^2 (39.9–57.6), 72.4 kg (58.3–91.0), 2.49 m^2 (2.20–2.78), and 0.93 (0.85–1.11), respectively (Table 1). Individual and average plasma concentration–time curves of anidulafungin are shown in Fig. 1.

3.2 Anidulafungin PK

Geometric mean (range) PK parameters were: AUC_{0-inf} 72.9 mg × h/L (46.3–100.1), AUC_{0-48} 54.1 mg × h/L (35.0–68.9), maximum plasma concentration 3.2 mg/L (2.6–4.1), volume of distribution 46.9 L (39.6–56.7), clearance 1.4 L/h (1.0–2.2), half-life 23.7 h (17.0–29.8), and k_e 0.029 1/h (0.023–0.041), see Table 1. In total, 35.1 % of the AUC_{0-48} was extrapolated to AUC_{0-inf}. Limited inter-individual variability was seen with AUC_{0-inf} (coefficient of variation (CV) of 20.7 %; calculated on the arithmetic mean). No concurrent medications known to significantly influence anidulafungin PK were administered [3].

A strong non-significant negative correlation between anidulafungin AUC_{0-inf} and absolute bodyweight or anidulafungin AUC_{0-inf} and body surface area was found: $r_s(8) = -0.6429$, $p = 0.096$ and $r_s(8) = -0.7066$, $p = 0.058$, respectively. Other parameters such as lean body mass resulted in poorer correlations. For the purpose of comparison with other studies, we also calculated the arithmetic mean AUC. The mean AUC_{0-inf} (74.4 mg × h/L, CV 20.7 %); range 46.3–100.1) following a single dose in our patient population was on average 32.5 % lower compared with the mean AUC_{0-24} at steady state in the general patient population (110.3 mg × h/L, CV 32.5 %) [10]. With this, the AUC_{0-inf} in this cohort of morbidly obese patients is at the lower end of the exposure distribution of the general patient population.

3.3 Safety

No serious AEs were reported. All single-dose infusions were well tolerated. Subjects experienced 48 new or aggravated AEs during follow-up (laboratory safety until 48 h and clinical AEs until discharge), of which 16 (33.3 %) were possibly related to anidulafungin. These AEs are most likely related to the surgical procedure (e.g., increase in aspartate aminotransferase, alanine aminotransferase, creatinine kinase, nausea, headache) but a relation with anidulafungin infusion could not be excluded. All AEs were mild, transient, and resolved spontaneously.

4 Discussion

To our knowledge, this is the first clinical study investigating the influence of extreme bodyweight (BMI > 40 kg/m^2) on anidulafungin PK. The findings from this study show that this cohort of morbidly obese subjects has a lower exposure compared with the exposure in non-obese individuals as described in the literature [5, 10]. The inter-individual variability of anidulafungin in this population is comparable to healthy non-obese volunteers [7].

Previously, it has been suggested that increased body size results in lower anidulafungin exposure, as weight was identified as a covariate affecting anidulafungin clearance [4, 9, 10] and central volume of distribution [4, 8]. Although the weight range was limited in those studies (only seven patients were >120 kg), it was predicted that anidulafungin exposure could be 30 % lower in a typical 150-kg male patient compared with a typical 60-kg male patient [10]. In the study of Liu et al., a patient weighing 240 kg was included, in whom a dose increase to 150 mg/day resulted in exposure comparable to other critically ill patients, albeit at the lower end of the AUC range (AUC_{0-24} 92.7 vs. 55.3 mg × h/L; 37 mg × h/L if extrapolated to 100 mg) [7]. The above findings of decreasing exposure as a function of weight were also observed with the other echinocandins, caspofungin and micafungin [12, 13].

We show that none of the morbidly obese patients included in our study obtain the AUC of the general patient population at standard doses of anidulafungin (Table 1), thereby possibly introducing the risk of therapeutic failure.

Table 1 Demographics and anidulafungin pharmacokinetic parameters (mean ± SD) for morbidly obese subjects receiving 100-mg i.v. anidulafungin single dose ($n = 8$)

Subject	Sex	Race	Age (years)	Weight (kg)	BMI (kg/m²)	Lean body mass (kg; according to Janmahasatian)	Body surface area (m²)	Waist/hip ratio	Bariatric surgery procedure	AUC_{0-inf} (mg × h/L)	AUC_{0-48} (mg × h/L)	C_{max} (mg/L)	V_D (L)	CL (L/h)	$t_{1/2}$ (h)	k_e (h⁻¹)
01	M	Caucasian	54	156.7	46.8	86.5	2.69	0.99	Gastric bypass	76.5	53.9	2.8	51.5	1.3	27.3	0.025
02	M	Caucasian	33	127.9	39.9	77.5	2.43	0.90	Gastric bypass	73.1	56.1	3.3	45.3	1.4	23.0	0.030
03	F	Caucasian	43	150.1	51.3	64.0	2.51	0.93	Gastric sleeve	46.3	35.0	2.7	52.9	2.2	17.0	0.041
04	F	Caucasian	50	166.5	57.6	65.3	2.62	0.88	Gastric sleeve	70.2	55.0	3.3	43.6	1.4	21.2	0.033
05	F	Caucasian	36	130.5	49.1	67.6	2.29	0.85	Gastric bypass	77.8	60.9	4.1	39.6	1.3	21.4	0.032
06	F	Caucasian	29	124.1	49.1	58.3	2.20	1.11	Gastric bypass	100.1	68.9	4.0	42.9	1.0	29.8	0.023
07	M	Caucasian	66	158.9	44.0	91.0	2.78	0.90	Gastric sleeve	66.2	48.6	2.6	56.7	1.5	26.0	0.027
08	F	Caucasian	43	149.2	55.5	75.5	2.43	0.90	Gastric sleeve	84.9	61.5	3.2	44.8	1.2	26.4	0.026
Median			43													
GM				144.7	48.9	72.4	2.49	0.93		72.9	54.1	3.2	46,9	1.4	23.7	0.029
Min			29	124.1	39.9	58.3	2.20	0.85		46.3	35.0	2.6	39,6	1.0	17.0	0.023
Max			66	166.5	57.6	91.0	2.78	1.11		100.1	68.9	4.1	56,7	2.2	29.8	0.041

AUC_{0-48} area under the plasma concentration–time curve from 0 to time of last sample, AUC_{0-inf} AUC from 0 to infinity, CL clearance, C_{max} maximum plasma concentration, F female, GM geometric mean, i.v. intravenous, k_e elimination rate constant, M male, Max maximum, Min minimum, SD standard deviation, $t_{1/2}$ half-life, V_D volume of distribution
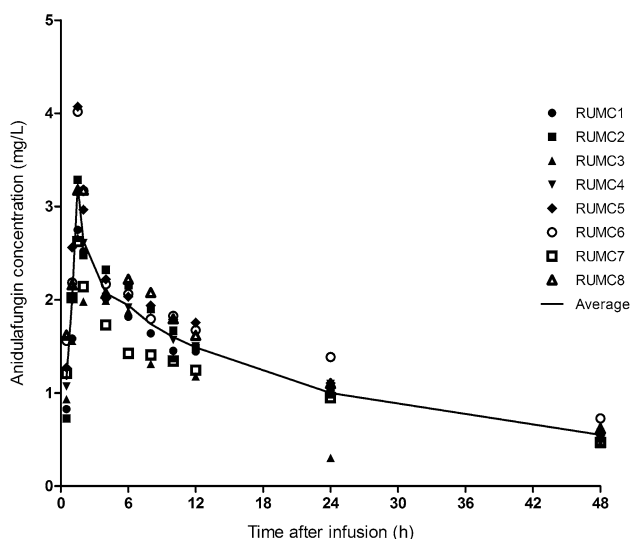
Fig. 1 Individual and average plasma concentration–time curves of anidulafungin ($n = 8$)

No specific clinical target AUC value for anidulafungin is established. In addition, it must be noted that a successful clinical response was observed in patients with invasive candidiasis (including candidemia) and low exposure in another study [10]. Our hypothesis is that a favorable response is likely associated with an infection with very susceptible species. Nevertheless, morbidly obese patients infected with pathogens with reduced susceptibility are still at risk for therapeutic failure. Considering the fact that anidulafungin is well tolerated in doses up to 300 mg [8], and pathogen susceptibility at the start of therapy is often unknown, we propose an approach to adapt the empiric dose to achieve the general population average exposure (AUC_{0-24} 110 mg $\times$ h/L) in this cohort of patients (BMI > 40 kg/m^2) [10]. To normalize the exposure to population values, increasing the anidulafungin maintenance dose to 150 mg (+50 %) would proportionally increase the AUC_{0-24} to nearly 110 mg $\times$ h/L (based on linear kinetics) [3]. In parallel, increasing the loading dose by 50 % (i.e., 300 mg) could be considered to achieve adequate exposure at the beginning of therapy [5, 10].

A different approach would be to increase the dose based on clinical failure or by using therapeutic drug monitoring (individualized drug dosing based on the measurement and interpretation of drug concentrations taking into account pathogen susceptibility). The first option will likely save drug costs. The latter approach is a more personalized schedule that can be deployed in patients with a high a priori risk of low exposure such as the intensive care unit population [10]. Being obese may have an additive effect on exposure. In other words, the exposure in critically ill, morbidly obese patients with

candidemia/invasive candidiasis may be even more pronounced compared with an intensive care unit population or obesity alone. The use of therapeutic drug monitoring in such a clinical situation deserves further study.

Our study is conducted with a relatively small sample size, without a non-obese control group. Ideally, anidulafungin PK in this cohort of morbidly obese patients is directly compared with PK in non-obese individuals also receiving a single 100-mg dose. We did not have a control group in our study design as this study was established for exploratory purposes. Instead, we calculated AUC_{0-inf} after a single dose of 100 mg anidulafungin, which would allow for comparisons with AUC_{0-24} at steady state in the literature (next to a comparison with single-dose studies). Because of the relatively long half-life of anidulafungin of 23.7 h (Table 1), more than 20 % of the AUC_{0-48} was extrapolated to AUC_{0-inf} (35.1 %), which may bias this estimation of AUC_{0-inf}. We expect this bias to be minimal. Ideally, sampling up until 72 h would have been done to better estimate AUC_{0-inf}. In our situation, patients were discharged after 48 h, so this was the compromise between patient burden and PK results. A strong negative but non-significant correlation between body weight and AUC as well as body surface area and AUC was found. We want to highlight that these results should be interpreted with caution as there is only eight people in the analysis and the relation is not significant. Therefore, these results should be regarded as explorative for anidulafungin PK in obese subjects.

5 Conclusion

The lower anidulafungin exposure in our 'healthy' morbidly obese subjects compared with literature values in non-obese patients suggests that anidulafungin dosing could be optimized in (extreme) morbidly obese patients with fungemia. As a priori dosing information regarding the appropriate dose of anidulafungin for heavy patients is lacking, the results of the current study show that increases of both the loading dose and maintenance dose should be considered in patients with a BMI >40 kg/m^2. We propose a 50 % increased loading and maintenance dose for morbidly obese patients.

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