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ORIGINAL PAPER

Influence of echinocandin administration on hemodynamic parameters in medical intensive care unit patients: a single center prospective study

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Abstract
Purpose Fungal infections present a constant risk to critically ill and immunocompromised patients. Therefore, treatment guidelines recommend echinocandins as first-line antifungals in critically ill patients to improve patient outcomes. Echinocandins are usually well tolerated; nevertheless, rare adverse events can occur. There are reports of temporary deterioration of hemodynamic parameters during loading doses, especially in critically ill patients. The objective of this study is to analyze the hemodynamic changes during adminstration of the echinocandin antifungals, caspofungin and anidulafungin, in medical intensive care unit patients.
Methods A prospective study in medical ICU patients receiving echinocandins was monitored using single-indicator transpulmonary thermodilution (TPTD). TPTD measurements were performed immediately before, directly after, and 4 h after echinocandins on two following days.
Results Mean arterial pressure and also diastolic blood pressure showed significant changes ($p < 0.042$ and $p < 0.007$) after echinocandin application in the measurement immediately after application, but not after 4 h. Basic hemodynamic parameters as well as the TPTD-derived cardiac function parameters did not significantly change after echinocandin application at all. In patients with the need for norepinephrine therapy, the vasopressor dose was not statistically significantly altered.
Conclusion To conclude, adminstration of echinocandins in this observed study population is safe, even in severely critically ill patients if application rules of these agents are followed. However, adverse effects could be observed and practitioners should be cognizant of these effects. These observations can be optimized by high-level assessments, such as the pulse contour cardiac output monitoring, and clinicians should continue to be vigilant with cardiac monitoring of patients receiving echinocandin antifungals.

Keywords Echinocandin · Hemodynamic · PiCCO · Critical ill

Introduction

Fungal infections present a constant risk to critically ill and immunocompromised patients. Especially, invasive candidal infections are a high risk for ICU patients and are often associated with severe complications and increased mortality [1].Therefore, early and adequate antifungal therapy is essential to improve patient outcomes.

Pharmacotherapy of such infections is more challenging than with bacterial infections due to greater cellular similarity between the eukaryotic host and pathogen. Treatment guidelines recommend echinocandins as first-line antifungals in critically ill patients [1, 2].

Besides their excellent activity against most *Candida* species, clinical studies of echinocandins consistently report low rates of severe adverse effects and few significant drug–drug interactions [3, 4].

Therapy against these infections has always been only marginally effective and riddled with adverse events. The discovery and subsequent marketing of the echinocandin antifungals gave practitioners an arsenal of agents with

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apparently lower toxicity relative to older agents [3, 5]. Nonetheless, as these agents have become more widely used in critically ill and other at-risk patients, novel adverse reactions have been surfacing. Echinocandins are usually well tolerated; nevertheless, rare adverse events can occur [5].

Following the package leaflet of caspofungin with a frequency of >1/100 hypotension, cardiac insufficiency, and arrhythmia could be observed.

Moreover with a frequency of >1/100 and >1/1000, other adverse events, e.g., dyspnea, vomiting or elevated liver parameters, were described [6]. Similar effects were described for anidulafungin [7].

Due to reported cardiac effects, especially development of cardiac insufficiency and hemodynamic instability during administration of an echinocandin in ICU patients in small case series, these effects were not maintained in a prospective study with critically ill patients [3].

These reports of temporary deterioration of hemodynamic parameters lead us to this study analyzing hemodynamic changes during adminstration of the echinocandin antifungals, caspofungin and anidulafungin, in medical intensive care unit patients.

Methods

Study design

A prospective study was conducted in medical ICU patients receiving echinocandins in a German university hospital. Patients (18 years of age or older) monitored using single-indicator transpulmonary thermodilution (TPTD) in ICU patients who received echinocandins were eligible for study inclusion. The indication for echinocandin treatment was made independently from the study by the ICU physician in charge.

In patients included in the study, TPTD measurements were performed immediately before, directly after, and 4 h after echinocandins on two following days to document possible changes in the initial echnocandin and the maintenance dosage.

Basic hemodynamic data such as systolic and diastolic blood pressure, mean arterial pressure (MAP), heart rate, and central venous pressure (CVP) as well as type and dose of sedative and vasoactive drugs infused were documented. According to our ICU standard operating procedures, vasoactive agents were titrated to maintain an MAP above 65 mmHg.

Echinocandins were applied through central venous catheters at an application rate for caspofungin 1.1 mg/ml (1.6 ml/min) and for anidulafungin 1.1 mg/min (1.4 ml/min), respectively. The dosage was 70 mg on the first day and 50 mg on the second day for caspofungin and 200 mg on the first day and 100 mg on the second day for anidulafungin, respectively.

This prospective study was approved by the institutional review board of the Technical University of Munich, Germany. Written informed consent was obtained by the patient or their legal representatives.

Measurement of hemodynamic parameters

TPTD measurements were performed in triplicate using a 5-French femoral arterial catheter (Pulsiocath, Pulsion Medical Systems, Munich, Germany) and a PiCCOplus or PiCCO2 monitor (Pulsion Medical Systems).

Cardiac index (CI), global end-diastolic volume index (GEDVI), systemic vascular resistance index (SVRI), extravascular lung water index (EVLWI), pulmonary vascular permeability index (PVPI), and index of left ventricular contractility (dP_{max}) were measured. CI was obtained by indexation of cardiac output (CO) to body surface area. Stroke volume (SV) was calculated by dividing CO by heart rate. Cardiac power index (CPI) was calculated as follows: $CPI = MAP \times CI \times 0.0022$.

Statistical analyses

We used IBM SPSS Statistics 22 (SPSS inc., Chicago, IL, USA) for all statistical analyses in this study. To present descriptive statistics, we calculated mean ± standard deviation for normally distributed continuous data, and absolute and relative frequencies for categorical data.

To compare the hemodynamic variables before and after echinocandin application (primary endpoint) as well as before and 4 h after, we performed the *t* test for paired samples and the Wilcoxon signed rank test for paired samples for normally distributed data and not normally distributed data, respectively. A p value below a significance level of 5 % ($p < 0.05$) indicates statistical significance.

Based on previous hemodynamic studies, sample size was estimated as follows. Assuming cardiac index (CI) of 4.1 in the overall patient population (within the normal range between 3 and 5) and a standard deviation of ±1, and using a two-sided test with 0.05 type I error and 0.2 type II error, we needed 15 patients on two following days of three times measurement to detect a 10 % absolute difference in CI.

Results

Patients' characteristics

Fifteen patients who received echinocandins (each patient received an initial and a maintenance dosage) were

Table 1 Patient characteristics

Sex, male, *n* (%)	9 (60)
Age, years	60 ± 12
Apache II Score	28 ± 4
Sofa Score	
Before echinocandin administration	14 ± 3
After echinocandin administration	13 ± 2
TISS Score	
Before echinocandin administration	22 ± 7
After echinocandin administration	19 ± 6
Reason for ICU	All septic shock
Reason for echinocandin	
Candidaemia, *n* (%)	10 (66)
Neutropenia/sepsis, *n* (%)	5 (34)
Days in ICU before echinocandin	9 ± 7
Kind of echinocandin:	
Caspofungin, *n* (%)	12 (80)
Anidulafungin, *n* (%)	3 (20)
History of	
Hypertension, *n* (%)	9 (60)
Atrial fibrillation, *n* (%)	5 (33)
Coronary heart disease, *n* (%)	2 (14)
History of diabetes mellitus, *n* (%)	2 (14)
Mechanical ventilation, *n* (%)	12 (80)
FiO_2 day 1	0.65 ± 15
FiO_2 day 5	0.6 ± 15
PEEP day 1	12 ± 2
PEEP day 5	10 ± 4
Norepinephrine therapy, *n* (%)	14 (95)
Volume balance (ml)	
Day 1	+2450 ± 460
Day 5	+4840 ± 670
Mortality rate (%)	7 (46 %)

Data are presented as mean ± standard deviation

Acute Physiology and Chronic Health Evaluation (*APACHE*), Sequential Organ Failure Assessment Score (*SOFA*), Therapeutic Intervention Scoring System (*TISS*)

included in the final analysis. The demographic and clinical characteristics of these patients are presented in Table 1.

Follow-up calculations of SOFA and TISS score were not statistically significant. Also, changes during mechanical ventilation did not reach statistical significance.

Effect of echinocandin on hemodynamics

The effects of echinocandin therapy on hemodynamic parameters measured immediately after and 4 h after application are presented in Table 2.

The basic hemodynamic parameters including heart rate and systolic blood pressure showed no statistically significant changes after echinocandin application. MAP and also diastolic blood pressure showed significant changes ($p < 0.042$ and $p < 0.007$) in the measurement directly after echinocandin application but not after 4 h.

Also, the TPTD-derived cardiac function parameters did not significantly change after echinocandin application. Following echinocandin application, there was no significant change in CI, CPI, dP_{max}, or GEF. Moreover, CO and SV showed no changes at all. The only significant variable in TPTD-derived measurement with a significant change was SVI. In addition, echinocandin application did not significantly alter EVLWI or PVPI. In patients with the need for norepinephrine therapy, the vasopressor dose was not statistically significantly altered.

Discussion

Candida infections are a relevant risk to critically ill patients resulting in increased mortality [1, 2]. An adequate antifungal treatment is essential in patients with sepsis or septic shock to prevent irreversible damage due to microbial load, systemic inflammation, and organ failure [9].

Over the last few years, echinocandins have become antifungal agents of first choice in the primary therapy for all forms of candidiasis, especially in severely ill patients with organ dysfunction [2]. This is based on to the broad activity against most *Candida* strains and the favorable safety profile [2, 3].

Pharmacotherapy of such infections is still challenging; however, the echinocandin antifungals gave practitioners an arsenal of agents with apparently lower toxicity relative to older agents. Nonetheless, as these agents have become more widely used in ICUs and other patients with an increased risk, novel adverse reactions have been surfacing [8].

Due to reported cardiac effects, especially temporary deterioration of hemodynamic parameters, following echinocandin administration seen in ICU patients in small case series, these effects were not maintained in a prospective study [8, 10]. Therefore, we observed in our study prospectively 15 patients with septic shock who received echinocandins under close hemodynamic monitoring.

Echinocandins are known to be associated with histamine liberation causing urticaria, rash, angioedema, or bronchospasm [11–14]. Rare serious adverse events such as pulmonary edema during echinocandin administration can also be found in the literature without the exact frequency of occurrence [11].

By keeping the infusion rate as low as 1.1 mg/min, these adverse effects occur infrequently. Moreover, experiments in rats documented a significantly decreased cardiac contractility in different concentrations of caspofungin and

Table 2 Effects of echinocandins on hemodynamic parameters

Parameter	Before echinocandin	After echinocandin	*p* value compared to baseline	4 h after echinocandin application	*p* value compared to baseline
Basic hemodynamic parameters					
Heart rate (bpm)	107 ± 19	106 ± 21	0.791	103 ± 17	0.124
Systolic blood pressure (mmHg)	121 ± 19	119 ± 30	0.694	127 ± 19	0.079
Diastolic blood pressure (mmHg)	55 ± 13	58 ± 13	**0.007**	56 ± 12	0.303
MAP (mmHg)	75 ± 13	78 ± 12	**0.042**	78 ± 14	0.101
Infused volume in mL	77	77		76	
Cardiac preload					
CVP (mmHg)	16 ± 6	16 ± 5	1.0	15 ± 5	0.572
GEDVI (ml/m^2)	701 ± 132	717 ± 193	0.627	731 ± 190	0.408
Cardiac function					
CO (l/min)	8.37 ± 1.82	8.43 ± 2.67		8.47 ± 2.83	
CI (l/min/m^2)	4.10 ± 0.97	4.36 ± 1.03	0.119	4.40 ± 1.06	0.157
SV (ml)	90 ± 18	94 ± 27		95 ± 28	
CPI (W/m^2)	0.72 ± 0.20	0.73 ± 0.22	0.941	0.91 ± 0.31	0.120
dP_{max} (mmHg/s)	1527 ± 644	1509 ± 611	0.817	1579 ± 657	0.309
GEF (%)	24 ± 5	24 ± 5	0.546	24 ± 5	0.586
SVI (ml/m^2)	40 ± 10	42 ± 8	**0.049**	43 ± 8	**0.033**
Vascular resistance					
SVRI (dyn × s × cm^{-5} × m^2)	1297 ± 429	1243 ± 441	0.216	1243 ± 366	0.341
Pulmonary hydration and permeability					
EVLWI (ml/kg)	13 ± 5	13 ± 5	0.082	13 ± 5	0.574
PVPI	2.6 ± 1.2	3.2 ± 1.2	0.124	2.3 ± 1.1	0.108
Norepinephrine dosage (ug/kg/h)	**10.3 ± 4.1**	**9.2 ± 3.7**	0.446	**11.3 ± 3.9**	0.380

Data are presented as mean ± standard deviation; statistically significant parameters are highlighted

MAP mean arterial pressure, *CVP* central venous pressure, *GEDVI* global end-diastolic volume index, *CI* cardiac index, *CO* cardiac output, *SV* stroke volume, *CPI* cardiac power index, dP_{max} index of left ventricular contractility, *SVRI* systemic vascular resistance index, *EVLWI* extravascular lung water index, *PVPI* pulmonary vascular permeability index

anidulafungin [15]. Especially, enlarged mitochondria and disintegrating myofibrils could be detected which may be combined with a dose-dependent inhibition of oxidative phosphorylation [15, 16]. Some of these data suggest that these agents inhibit several steps in the mitochondrial oxidation pathway [15, 16].

As reported above, in one study, it was hypothesized that a potential mechanism of toxicity is histamine release. However, a complete dose-ranging study on histamine in a rat model observed no dose-associated decrease in cardiac contractility [15].

As part of the clinical sight, development of septic cardiomyopathy during septic shock may be a crucial pathogenic part of hemodynamic instability, which aggravates tissue hypoperfusion and organ failure.

However, reflecting the results of our study, there was no cardiac impairment detectable after echinocandin adminstration. Basic hemodynamic parameters were stable along the observation time. Most of the hemodynamic parameters measured directly after and 4 h after application of TPTD showed no significant changes. Even the significantly changed parameters do not represent a deterioration of the hemodynamic situation of the patient; these parameters were in all cases better than before echinocandin administration.

Nonetheless, a history or concomitant use of certain medications (anthracycline agents, thiazolidinediones, itraconazole, trastuzumab, anti-arrhythmics, and amphotericin B) may contribute to exacerbate the cardiotoxic effects of the echinocandins [3].

Furthermore, cardiac events were reported in patients who had preexisting left ventricular hypertrophy and/or dysfunction [8, 10]. Given the excess metabolic demands during critical illness, as well as the fragile Starling curve

of a failing heart, these patients warrant close monitoring while receiving echinocandin.

In our study cohort, patients with a history of cardiac events such as hypertension or atrial fibrillation showed no increased risk for cardiac impairment during echinocandin application.

We have also not seen, as reported in former case reports, that patients receiving anidulafungin or caspofungin through central venous catheters, given the proximity of infusion to the heart, have more cardiac adverse events.

Limitations of the study

The low number of patients studied and the fact that we performed our study in a single ICU are limitations of our study. Furthermore, the use of vasoactive drugs during echinocandin administration and study measurements might have influenced the results of hemodynamic monitoring.

Conclusion

To conclude, adminstration of echinocandin in this observed study population is safe, even in severe critically ill patients if application rules of these agents are followed.

However, adverse effects could be observed and practitioners should be cognizant of these effects and routinely and continually monitor their patients.

These observations can be optimized by high-level assessments, such as the pulse contour cardiac output monitoring (PiCCO), and clinicians should continue to be vigilant with cardiac monitoring of patients receiving echinocandin antifungals.

Compliance with ethical standards

Conflict of interest None of the authors has any potential financial conflict of interest related to this manuscript.

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