Echinocandins Dosing in Obese Patients: A Systematic Review

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Background

- Echinocandins are a milestone in antifungal chemotherapy given their fungicidal properties with improved toxicity profiles compared to other antifungal agents.
- Echinocandins are used in the empiric treatment of invasive candidiasis and aspergillosis in critically ill, neutropenic, and transplant patients.
- There is emerging evidence that obese patients treated with echinocandins antifungal agents have lower plasma serum concentration and faster clearance.

Purpose

- The objective of this review was to systematically evaluate the available evidence for echinocandins dosing in obese patients.

Methods

- A systematic review of PubMed, Embase, Cochrane library from inception until June 8, 2020 was conducted by 2 authors.

Inclusion and exclusion criteria

- **Included studies:**
  - Studies with data for micafungin, anidulafungin, or caspofungin in obese patients' exposure [body mass index (BMI) 30 or greater]
- **Excluded studies**
  - Studies for patients on renal replacement therapies or extracorporeal membrane oxygenation support
  - Animal studies
  - Review articles and studies in language other than English

Results

- Twenty-five studies met the inclusion criteria; micafungin (n=10), caspofungin (n=7), and anidulafungin (n=8).

Discussion

- Lower echinocandins exposure was consistent in obese patient populations
- High quality studies are needed to evaluate the adequacy of dosing in obese population and the possibility to adjust dosing

Study name	Population	Effect of obesity in echinocandin exposure
Anidulafungin		
Dowell, JA 2004	Mixed patient population from multiple phase II/III anidulafungin clinical studies for esophageal candidiasis, invasive candidiasis, and invasive aspergillosis.	Anidulafungin clearance increased with increasing body weight in males, especially in patients with invasive candidiasis
Liu 2013	Mixed ICU population with invasive candidiasis. Patients who had any of the following were included: neutropenia, abdominal surgery, solid organ transplant, renal or hepatic insufficiency, or aged > 65 years. One patient with BMI of 33 kg/m^2 was excluded as culture was negative. Only one patient with BMI of 83 kg/m^2 (240 kg) had her pharmacokinetics determined.	The authors used a higher maintenance dose of 150 mg/day which resulted in a $AUC_{0\text{-}24}$ (55.3 mg · h/liter) that fell within the range of other ICU patients who received 100 mg maintenance dose. The author concluded that increasing the maintenance dose by 50% may be required but more data is needed.
Liu 2013	Mixed ICU patient population from multiple phase II/III anidulafungin clinical studies for invasive candidiasis and candidemia	The author recommended that the same dose can be administered to all patients regardless of bodyweight; however, caution should be exercised in patients with body weight >150 kg.
Wanrooy 2014	Mixed ICU patient population who had suspected or confirmed invasive candidiasis or candidemia	Using linear regression model, no correlation between anidulafungin exposure and body weight was observed (r_s = −0.282, P = 0.229); however, the highest BMI was 36 kg/m^2.
Liu, P 2014	Adult patients with invasive Aspergillosis infection	As the body weight increases, anidulafungin area under the time concentration curve decreases
Lempers 2016	Obese patients (BMI >40) undergoing gastric bypass or sleeve surgery (no fungal infection) were included	There was a strong, yet, not statistically significant correlation between body weight and anidulafungin exposure (r_s = −0.6429, p = 0.096). The AUC following a single dose was 32.5% lower compared with general population.
Brüggemann, RJ 2017	Mixed ICU patient population	None of the covariates (including body weight) were associated with anidulafungin pharmacokinetics parameters (BMI ranged between 17-33 kg/m^2)
Wasmann 2018	Healthy subjects with employment of Monte-Carlo simulation	Both anidulafungin clearance and volume of distribution were increased with increase in body weight. Additionally, the $AUC_{0\text{-}240}$ was lower than 99 mg · h/liter compared to normal weight individuals. The authors suggested increasing the loading as well as the maintenance dose by 25%.
Caspofungin		
Nguyen, TH 2007	Surgical intensive care unit patients with suspected or proven Candida or Aspergillus infection	Caspofungin exposure was predicted to be higher in patients with body weight less than 75 Kg
Ryan, DM 2011	Phase II/III adult clinical trials for caspofungin use in esophageal candidiasis, invasive candidiasis, salvage treatment of invasive Aspergillosis, and empirical therapy of suspected invasive fungal infections in patients with persistent fever and neutropenia	The proportion of patients with favorable clinical response in obese and non-obese patients were similar
Wurthwein, G 2012	Adults immunocompromised patients with invasive fungal disease and evidence of proven or probable invasive Aspergillosis	Increasing in body weight more than 80 Kg was correlated with increased clearance of caspogungin
Hall, G 2013	Healthy volunteers	When body weight exceed 66.3 Kg, the systemic clearance of casnpfungin increase
Muilwijk, E 2014	Mixed ICU population in patients with suspected or conformed fungal infection	Body weight didn't affect caspofungin exposure; however, the heaviest patient in this study was 99 kg only. Additionally,
Ferriols-Lisart, R 2017	Case report of ICU patient admitted for anastomotic leak following elective laparoscopic bariatric surgery	Caspofungin was dosed at 100 mg/day, the AUC was 115.9 mg*h/L after first dose, and 140.4 mg*h/L on day 3. Authors recommended using higher caspofungin dose in critically ill and obese patients.
Elst, KC 2017	Adult intensive care unit patients with invasive Aspergillosis	Increase in body weight was significantly correlated with increased systemic clearance of caspofungin
Micafungin		
Tabata, K 2006	7 phase I-III trials conducted in Japan for healthy volunteer and patients for micafungin use in fungal infections	Micafungin clearance was influenced by increased body weight in pediatric patients. However, the relationship was not observed in adult patients.
Hope, WW 2007	Children aged 2 to 17 years with micafungin for empirical treatment of febrile neutropenia	Micafungin exposure is predicted to be lower with increasing body weight.
Gumbo, T 2008	Adult patients underwent bone marrow or peripheral stem cell transplantation	Micafungin serum clearance increased by approximately 50% when body weight is greater than 66.3 Kg.
Zomp, A 2011	40 years old African American morbidly obese patient with disseminated Candida glabrata infection	Serum micafungin concentrations were lower in this patient than previously reported concentrations
Hall, RG 2011	Overweight, obese, and extremely obese adults' healthy volunteers	Systemic micafungin clearance continues to increase as body weight increase beyond 66 Kg
Lempers 2015	Mixed ICU population with suspected or confirmed fungal infection	Using linear regression model, the authors didn't observe that body habitus was an independent risk factor for altered micafungin pharmacokinetics (BMI ranged between 16.3 – 47.5 kg/m^2
Garcia-de-Lorenzo, A 2016	Critically ill adult patients with severe burn injuries with proven or suspected fungal infection	There was no difference in micafungin concentration between burn patient and patients with intra-abdominal infection although burn patients have statistically significantly higher body weight
Boonstra 2017	Mixed ICU population with suspected or confirmed invasive candidiasis or candidemia	There was a negative correlation between body weight and micafungin AUC (r_s = −0.488, p = 0.034); however, there was no correlation between BMI and micafungin exposure.
Jullien, V 2017	Intensive care unit patients with sepsis and mechanically ventilated with suspected candidiasis	When the body weight increases, the probability for target attainment decrease proportionally
Maseda 2018	Mixed ICU and non-ICU population with empirical or directed treatment for invasive candidiasis with Monte-Carlo simulation	Using the Fractional target attainment ($AUC_{0\text{-}24}$/MIC) of >90%, the 100 mg dose of micafungin was associated with inadequate exposure regardless of the patient weight in candida albicans species. Increasing the dose to 150 mg and 200 mg resulted in improvement in the FTA in candida species but not to other nonalbicans species.

Limitations

- Outcomes of treatment is lacking in this study
- Patient populations in the study are heterogenous, and could have different outcomes

Conclusion

- Evidence is consistent regarding lower exposure of echinocandins in obese patient population

Disclosures

- All authors have nothing else to disclose