

Anidulafungin: Is There a Place For Another Echinocandin?

Traci White, Pharm.D.

Among the general hospital population, *Candida* is the fourth most common nosocomial bloodstream infection, trailing coagulase-negative staphylococci, *S. aureus*, and *Enterococcus* species.¹ Contributing factors for the rise in candidemia infections include prolonged survival of susceptible immunosuppressed patients, such as patients undergoing solid organ and bone marrow transplantation, prolonged hospitalization of critically ill patients, and the increasing population of patients with HIV infection.² Studies indicate the overall rate of candidemia-attributable mortality to be in the range of 33–47%.^{1,3,4} Although more than half of the *Candida* isolates are identified as *C. albicans*, there is an increased incidence of candidemia caused by non-albicans species such as *C. glabrata*, which has shown reduced susceptibility to the azole antifungals.^{1,2} *Aspergillus*, on the other hand, has become the major cause of morbidity and mortality in many institutions that care for transplant recipients or patients with hematologic malignancies.⁵ Anidulafungin was approved by the FDA in February 2006. It is the third drug of the echinocandin class of antifungals and is indicated for the treatment of esophageal candidiasis, candidemia, and *Candida* infections associated with intra-abdominal abscess and peritonitis. This article will summarize the pharmacology of anidulafungin and review the literature supporting its use in *Candida* and *Aspergillus* infections as well as discuss its potential place in therapy.

Table I: *In Vitro* Susceptibilities of *Candida* spp. to Echinocandins^{6,19,20}

Organism	Caspofungin		Micafungin		Anidulafungin	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>C. albicans</i>	0.015-0.03	0.03-0.06	0.007-0.015	0.015-0.03	0.015-0.03	0.06-0.12
<i>C. glabrata</i>	0.015-0.03	0.03-0.06	0.007-0.015	0.007-0.015	0.03-0.06	0.06-0.12
<i>C. tropicalis</i>	0.015-0.03	0.03-0.06	0.015-0.03	0.03-0.06	0.015-0.03	0.03-0.06
<i>C. krusei</i>	0.06	0.12-0.25	0.03-0.06	0.06-0.12	0.015-0.03	0.03-0.06
<i>C. parapsilosis</i>	0.25-0.5	0.5-1	0.5-1	1-2	1-2	1-2
<i>C. guilliermondii</i>	0.25-0.5	0.5-1	0.25-0.5	0.5-1	0.5-1	1-2
<i>C. lusitaniae</i>	0.12-0.25	0.25-0.5	0.06-0.12	0.12-0.25	0.12-0.25	0.25-0.5
<i>C. albicans</i> *	0.03-0.06	0.03-0.06	0.015	0.03	0.015-0.03	0.03-0.06
<i>C. glabrata</i> *	0.03-0.06	0.06	0.015	0.015	0.03-0.06	0.06-0.12
<i>C. krusei</i> *	0.06-0.12	0.12-0.25	0.03-0.06	0.06-0.12	0.03-0.06	0.06-0.12

* Fluconazole-resistant *Candida* spp. defined as MIC \geq 64mcg/mL

The echinocandins, caspofungin, micafungin, and anidulafungin, are related semisynthetic cyclic lipopeptides with an *N*-linked acyl lipid side chain, subject to different hydroxylation patterns. Anidulafungin, like the other echinocandins, appears to exert its antifungal activity by targeting the FKS1_[dl] gene, which encodes for the components responsible for the catalytic subunit of glucan synthase. This blockade results in the inability of the fungal cell to synthesize β -(1,3)-D-glucan, an essential component of the fungal cell

(Continued on page 46)

A University of Washington Drug Information Center publication
 Distributed monthly by authority of the Pharmacy and Therapeutics Committee
 Editor: Nelda A. Murri, Pharm.D. (206) 598-6612 – Asst. Editor: Elizabeth Rudy, D.V.M., R.Ph.
 Department of Pharmacy Services / School of Pharmacy

Copyright © 2006 by the University of Washington
 Also published at <http://uw.pnrx.org/therapyTopics.asp>
 No material may be reproduced in whole or in part without written permission from the editor.

Invasive fungal infections are associated with high mortality rates. Therefore, aggressive treatment with potent antifungals likely to be effective against causative organisms is essential.

Echinocandins are the newest class of antifungals to be marketed in the United States. Available only as injectable products, the echinocandins are generally better tolerated than amphotericin B, effective against azole-resistant strains of *Candida*, and associated with fewer drug interactions than voriconazole.

Echinocandins appear to be fungistatic against *Aspergillus* spp., thus they are often utilized for their synergistic activity in combination with itraconazole or voriconazole against *Aspergillus*.

Among the echinocandins, caspofungin and micafungin are currently on the UW Medicine Drug Formulary. Anidulafungin is pending consideration by the Pharmacy & Therapeutics Committee.

wall, leading to osmotic instability and eventual cell death.² The three echinocandins have similar spectrums of activity against *Candida* spp. with minimal differences in MIC values (see Table I). The isolates shown in Table I represent species from Asia, Latin America, Europe, and North America and include 315 fluconazole-resistant *Candida* strains.^{6,19,20} All *C. glabrata* and *C. krusei* isolates (N=256) found to be fluconazole-resistant were susceptible to anidulafungin at concentrations ≤ 0.5 mcg/mL, well above the concentration achieved with the IV administration of 100mg/day.⁶ Currently, however, there are no established susceptibility breakpoints for the echinocandins, making the clinical application of this data difficult.⁷ Possessing a broad range of *in vitro* fungicidal activity against *Candida* spp., anidulafungin also has fungistatic activity against several species of *Aspergillus*.⁵ Therefore, echinocandins are often utilized for their synergistic activity in combination with itraconazole or voriconazole against *Aspergillus*.⁵ Synergy was primarily observed in isolates of *A. flavus* and *A. fumigatus* *in vitro*, with no indication of antagonism between anidulafungin and either itraconazole or voriconazole.⁸ The synergistic effect was not seen in *Fusarium* spp. or with the combination of anidulafungin and amphotericin B.⁸ Anidulafungin does not have activity against Zygomycetes or *Cryptococcus*.⁹

Comparison of pharmacokinetic and pharmacodynamic characteristics of the echinocandins in Table II emphasizes that anidulafungin lacks CYP-mediated metabolism, has a large volume of distribution, and exhibits a prolonged half-life. Like the other echinocandins, anidulafungin has poor oral bioavailability and is only formulated as an IV preparation. The recommended dose for candidemia and invasive candidiasis is a 200mg loading dose on the first day of treatment, subsequently followed by 100mg daily. For the treatment of esophageal candidiasis, a 100mg loading dose on day 1 and 50mg daily thereafter is given. No dosage adjustments are recommended for any degree of hepatic or renal impairment, whereas the dose of caspofungin should be reduced in moderate hepatic impairment (Child-Pugh score of 7–9). Elimination of anidulafungin is primarily biliary with degradation products being passed through feces. Anidulafungin has a volume of distribution approximately three times that of micafungin and caspofungin; however, further studies are needed to determine the clinical significance of the differences in tissue penetration between the echinocandins. As a class, the echinocandins are generally well tolerated but increases in hepatic transaminases and infusion-related reactions, such as flushing, rash, and vasodilation have been reported. Reducing the rate of infusion is recommended to prevent histamine-mediated infusion reactions from recurring.²

Rather than undergoing hepatic metabolism, anidulafungin is converted to an open-ring form in the blood and is subsequently degraded by nonspecific peptidases.⁵ Consequently, clearance of anidulafungin is not affected by coadministration of cytochrome P450 inducers, inhibitors, or substrates. Solid organ transplant patients requiring antifungal therapy typically need aggressive monitoring to minimize clinically significant drug interactions between antifungals and cyclosporine, tacrolimus, or sirolimus. As demonstrated by Table II, anidulafungin may be a more favorable option than caspofungin or micafungin when an echinocandin is initiated during long-term management with these immunosuppressants. In a study evaluating the pharmacokinetics of anidulafungin given with cyclosporine, 11 of 12 healthy adults experienced an overall 22% increase in anidulafungin AUC.¹⁰ This increase was deemed clinically insignificant by the authors because the concentrations were consistent with interpatient variability observed in other studies. One subject was withdrawn from the study on day 6 due to a mild increase in liver function enzymes which was reversible upon follow-up.¹⁰ In contrast, a higher incidence of elevated hepatic transaminase levels has been demonstrated in patients receiving caspofungin and cyclosporine concomitantly, with an increase in caspofungin AUC by

Table II: Pharmacokinetic/Pharmacodynamic Comparison of Echinocandins^{7,21,22}

Parameter		Caspofungin	Micafungin	Anidulafungin
C_{max} (steady-state)		9.9mcg/mL (70mg load then 50mg daily in healthy adults)	5mcg/mL (50mg) 16mcg/mL (150mg)	7.2mcg/mL (200mg load then 100mg daily)
V_d (steady-state)		0.15L/kg	0.2L/kg	0.6L/kg
Elimination $t_{1/2}$		9-11h	14h	26h
Protein binding		97%	>99%	84%
Metabolism		Hepatic; Non-enzymatic peptide hydrolysis and N-acetylation	Hepatic; arylsulfatase, catechol-O-methyltransferase, some CYP3A4 hydroxylation	No hepatic metabolism; undergoes chemical degradation
Indication & Usual IV Dose	Esophageal candidiasis	50mg daily	150mg daily	100mg load then 50mg daily
	Other	Candidemia, invasive candidiasis, presumed fungal infections in febrile neutropenic patients, invasive <i>Aspergillosis</i> : 70mg load then 50mg daily	- Prophylaxis of <i>Candida</i> infections in patients undergoing hematopoietic stem cell transplantation: 50mg daily; - Candidemia and invasive candidiasis (off-label uses): 100mg daily	Candidemia and invasive candidiasis: 200mg load then 100mg daily
Drug Interactions		- Caspofungin decreases tacrolimus AUC by 20% - Cyclosporine increases caspofungin AUC by 35% (↓ caspofungin to 35mg daily) - CYP450 inducers (i.e. rifampin, efavirenz, phenytoin) decrease caspofungin levels (↑ caspofungin to 70mg daily)	Micafungin increases sirolimus and nifedipine AUCs by 20%	Cyclosporine increases anidulafungin AUC by 22% but no dosage adjustment recommended
Hepatic & Renal Dosage Adjustments		- 35mg IV daily recommended in moderate hepatic insufficiency (Child-Pugh 7-9) - No adjustment necessary for renal insufficiency	None	None

In clinical studies anidulafungin has been well tolerated and has not demonstrated any clinically significant drug interactions.

Anidulafungin may be a more favorable option than caspofungin or micafungin when an echinocandin is initiated for a patient requiring long-term management with cyclosporine, tacrolimus, or sirolimus.

35%. A multi-dose, crossover study evaluating the pharmacokinetic interaction of oral voriconazole given with anidulafungin revealed no significant differences in steady-state plasma concentrations or adverse effects compared with anidulafungin alone.¹¹

With associated mutations in the *FKS1* gene, *Candida* species can develop resistance to echinocandins.² Resistance to caspofungin was seen in a patient with prolonged caspofungin therapy for *C. albicans* esophagitis.¹² Cross-resistance to caspofungin and micafungin has been reported in a patient with prosthetic valve endocarditis due to *C. parapsilosis*, as indicated by increased MICs of both echinocandins.¹³ Interestingly, the MICs of anidulafungin remained low. Additionally, a patient with relapsed acute myelogenous leukemia treated with caspofungin for *C. krusei* candidemia subsequently developed fungal endophthalmitis and severe oropharyngeal thrush after 17 days of caspofungin therapy.¹⁴ Susceptibility testing of the *C. krusei* throat isolate indicated an MIC value of 8mcg/mL for caspofungin and 4mcg/mL for anidulafungin and micafungin. Vitreal fluid cultures remained negative.¹⁴ Preliminary studies have found mutations in the *C. krusei* *FKS1* gene (Marr, unpublished). Additional susceptibility studies along with increased clinical experience of echinocandins will help to determine patterns of resistance to this class.

Anidulafungin is an effective therapeutic option for the systemic treatment of serious *Candida* infections.

For the treatment of candidemia, anidulafungin appears to be superior to fluconazole.

It is postulated that the echinocandins do not reach, or persist in, the esophageal mucosa as well as fluconazole, resulting in higher esophageal *Candida* relapse rates. Higher relapse rates in this setting are thought to represent a class effect of the echinocandins.

Possessing potent activity against a broad range of *Candida* species, anidulafungin has been established as efficacious for the treatment of candidemia and invasive and esophageal candidiasis. Likewise, promising clinical outcomes with combinations of itraconazole or voriconazole and echinocandins against *Aspergillus* spp. may pave the way for increased use of anidulafungin for this indication.

In vivo studies thus far support anidulafungin as an effective therapeutic option for the treatment of serious *Candida* infections. A randomized, double-blind study comparing anidulafungin and fluconazole for the treatment of esophageal candidiasis was performed in 600 patients, the majority of whom had a diagnosis of AIDS.¹⁵ Patients received IV anidulafungin (100mg on day 1, 50mg daily thereafter) or oral fluconazole (200mg on day 1, 100mg daily thereafter). Treatment was continued for 14–21 days with a minimum of 7 days after resolution of symptoms. Of the 504 patients who completed therapy, the anidulafungin-treated group had an endoscopic success rate (cure or improvement) of 97.2%, whereas those treated with fluconazole had a 98.8% success rate at the end of therapy (median 14 days).¹⁵ The treatment difference of –1.6% (95% CI: –4.1 to 0.8) established anidulafungin as being statistically non-inferior to fluconazole. Both groups demonstrated similar clinical cures, as defined by absence of symptoms from baseline, with an average of 5 days to resolution of symptoms. The anidulafungin group, however, experienced statistically significant higher endoscopic recurrence rates at the 2-week follow-up visit (35.6% vs. 10.5%; $P < 0.001$). Additionally, caspofungin and micafungin have been associated with a greater rate of clinical relapse than fluconazole when studied in esophageal candidiasis, although not reaching statistical significance in either study (only the anidulafungin study performed repeat endoscopies after therapy).^{16,17} Currently, the higher rates of relapse are thought to be a class effect; it has been postulated that the echinocandins do not reach or persist in the esophageal mucosa as well as fluconazole.¹⁵

The efficacy of anidulafungin compared to IV fluconazole for the treatment of candidemia was assessed in a Phase III clinical trial involving 256 patients.¹⁸ The study included patients with at least one positive blood culture for *Candida* and analyzed the global success rate of each group at the end of IV therapy. Global success was defined as the resolution of signs and symptoms of fungal infection, evidence of fungal eradication, and lack of toxicity or tolerability issues. Beginning at day 11, patients were permitted to switch to oral fluconazole 400mg daily when clinically indicated (IV antifungal therapy for at least 10 days, afebrile for >24 hours, able to tolerate oral therapy, reduction in signs and symptoms, and last blood culture negative). The average duration of IV therapy was 14 days in the anidulafungin group (range 1–33 days) and 11 days in the fluconazole group (range 1–36 days). At the end of IV therapy, anidulafungin, given as 100mg once daily following a 200mg loading dose on day 1, had a 15.4% higher global success rate than IV fluconazole given as 400mg once daily following an 800mg loading dose on day 1 (75.6% vs. 60.2%; 95% CI: 3.9 to 27). Although not statistically significant, endpoints assessing global success rates 6 weeks after the end of therapy also favored anidulafungin with a 6-week success rate of 55.9% vs. 44.1% (95% CI: –0.6 to 24.28) in the fluconazole group. Importantly, this study was able to demonstrate superiority of anidulafungin over fluconazole, which previously has not been shown between any other antifungal comparators for the treatment of candidemia.^{5,18}

Echinocandin	UW Medicine Acquisition Costs*	Drug Cost for 14 Days of Candidemia Treatment
Caspofungin	\$198/50mg \$198/70mg	\$2772
Micafungin	\$79/50mg \$187/100mg	\$2618
Anidulafungin	\$90.00/50mg	\$2700

* Contract prices currently under negotiation.

Possessing potent activity against a broad range of *Candida* species, anidulafungin has been established as efficacious for the treatment of candidemia and invasive and esophageal candidiasis. Likewise, promising clinical outcomes with the combination of triazoles and echinocandins for the treatment of *Aspergillus* infections may pave the way for increased use of anidulafungin for this indication. In the meantime, the lack of drug-drug interactions, favorable pharmacokinetics, and minimal side effect profile of anidulafungin distinguishes it among the echinocandins as a reasonable therapeutic option for the treatment of invasive fungal infections.

Note: The author and editor gratefully acknowledges the assistance of Kieren Marr, M.D., Doug Black, Pharm.D., and Jeannie Chan, Pharm.D., M.P.H., in reviewing this article.

References

1. Pappas PG, Rex JH, Lee J, et al. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. *Clin Infect Dis* 2003;37(5):634-43.
2. Morris MI, Villmann M. Echinocandins in the management of invasive fungal infections, part 1. *Am J Health Syst Pharm* 2006;63(18):1693-703.
3. Morris MI, Villmann M. Echinocandins in the management of invasive fungal infections, part 2. *Am J Health Syst Pharm* 2006;63(19):1813-20.
4. Gudlaugsson O, Gillespie S, Lee K, et al. Attributable mortality of nosocomial candidemia, revisited. *Clin Infect Dis* 2003;37(9):1172-7.
5. Vazquez JA, Sobel JD. Anidulafungin: a novel echinocandin. *Clin Infect Dis* 2006;43(2):215-22.
6. Pfaller MA, Boyken L, Hollis RJ, et al. In vitro activities of anidulafungin against more than 2,500 clinical isolates of *Candida* spp., including 315 isolates resistant to fluconazole. *J Clin Microbiol* 2005;43(11):5425-7.
7. Theuretzbacher U. Pharmacokinetics/pharmacodynamics of echinocandins. *Eur J Clin Microbiol Infect Dis* 2004;23(11):805-12.
8. Philip A, Odabasi Z, Rodriguez J, et al. In vitro synergy testing of anidulafungin with itraconazole, voriconazole, and amphotericin B against *Aspergillus* spp. and *Fusarium* spp. *Antimicrob Agents Chemother* 2005;49(8):3572-4.
9. Denning DW. Echinocandin antifungal drugs. *Lancet* 2003;362(9390):1142-51.
10. Dowell JA, Stogniew M, Krause D, et al. Assessment of the safety and pharmacokinetics of anidulafungin when administered with cyclosporine. *J Clin Pharmacol* 2005;45(2):227-33.
11. Dowell JA, Schranz J, Baruch A, et al. Safety and pharmacokinetics of coadministered voriconazole and anidulafungin. *J Clin Pharmacol* 2005;45(12):1373-82.
12. Hernandez S, Lopez-Ribot JL, Najvar LK, et al. Caspofungin resistance in *Candida albicans*: correlating clinical outcome with laboratory susceptibility testing of three isogenic isolates serially obtained from a patient with progressive *Candida* esophagitis. *Antimicrob Agents Chemother* 2004;48(4):1382-3.
13. Moudgal V, Little T, Boikov D, et al. Multiechinocandin- and multiazole-resistant *Candida parapsilosis* isolates serially obtained during therapy for prosthetic valve endocarditis. *Antimicrob Agents Chemother* 2005;49(2):767-9.
14. Hakki M, Staab JF, Marr KA. Emergence of a *Candida krusei* isolate with reduced susceptibility to caspofungin during therapy. *Antimicrob Agents Chemother* 2006;50(7):2522-4.
15. Krause DS, Simjee AE, van Rensburg C, et al. A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. *Clin Infect Dis* 2004;39(6):770-5.
16. Villanueva A, Gotuzzo E, Arathoon EG, et al. A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. *Am J Med* 2002;113(4):294-9.
17. de Wet NT, Bester AJ, Viljoen JJ, et al. A randomized, double blind, comparative trial of micafungin (FK463) vs. fluconazole for the treatment of oesophageal candidiasis. *Alimentary Pharmacology & Therapeutics* 2005;21(7):899-907.
18. Clinical study report: anidulafungin, VER002-9. A phase 3, double-blind, randomized, multi-center study on the safety and efficacy of anidulafungin vs. fluconazole in the treatment of patients with candidemia and other forms of invasive candidiasis and prevention of complications. Pfizer Inc. [Data on File] 2005.

(Continued on page 50)

Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost [‡]	Therapeutic Classification	Use	Usual Adult Starting Dose*
Ibandronate (Boniva)	Tablet: 2.5mg, 150mg IV: 5mg/5mL	Bisphosphonate	Treatment of osteoporosis and postmenopausal prevention of osteoporosis	2.5mg po daily or 150mg po once monthly
	The Committee voted to limit IV formulation to use by Dr. Ott and Dr. Chestnut.			
Papain/Urea (Accuzyme)	Topical ointment: papain 830,000 units and 100mg urea/g (6g, 30g)	Proteolytic enzyme	Debridement of acute and chronic lesions	Applied topically daily or BID
Other Actions				
Mycophenolate sodium (Myfortic)	The UW Medicine P&T Committee voted to competitively bid mycophenolate sodium (Myfortic) and mycophenolate mofetil (Cellcept) as therapeutic equivalents with the lower-priced agent to be made the preferred formulary oral mycophenolate product.			

* Refer to product labeling for full prescribing information. † Contact pharmacy for information on drug costs.

Anidulafungin: Is There a Place For Another Echinocandin?

(continued)

19. Pfaller MA, Boyken L, Hollis RJ, et al. Global surveillance of in vitro activity of micafungin against *Candida*: a comparison with caspofungin by CLSI-recommended methods. *J Clin Microbiology* 2006;44(10):3533-8.
20. Messer SA, Diekema DJ, Boyken L, et al. Activities of micafungin against 315 invasive clinical isolates of fluconazole-resistant *Candida* spp. *J Clin Microbiology* 2006;44(2):324-6.
21. Stone JA, Holland SD, Wickersham PJ, et al. Single- and multiple-dose pharmacokinetics of caspofungin in healthy men. *Antimicrob Agents Chemother* 2002;46(3):739-45.
22. Black T. Study of Micafungin in Patients with Invasive Candidiasis or Candidemia [Personal Communication]. Astellas Pharma Inc. September 2006.

Vol. 35, No. 11

Newsletter:

Anidulafungin: Is There a Place For Another Echinocandin? 45-50

October P&T Committee Actions, 50



DRUG INFORMATION CENTER
Box 354735
Seattle, WA 98195-4735

drug therapy topics