Place in therapy review

Anidulafungin: an evidence-based review of its use in invasive fungal infections

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Abstract

Introduction: Anidulafungin is a new echinocandin antifungal agent with indications for use in esophageal candidiasis and candidemia. The mortality and morbidity associated with fungal infections in healthcare facilities necessitates the development of new treatment options for these diseases.

Aims: This review assesses the pharmacology and evidence for the use of anidulafungin in the treatment of serious fungal infections.

Evidence review: There is substantial evidence that anidulafungin is a potent antifungal agent with activity against a broad range of fungal species. Likewise, evidence supports that anidulafungin is a well-tolerated antifungal agent. Clinical studies provide sufficient evidence for regulatory approval for esophageal candidiasis and candidemia, and limited evidence suggests that anidulafungin may be superior to fluconazole for candidemia and invasive candidiasis. The introduction of anidulafungin into clinical practice adds a third option for therapy in the echinocandin class. Research into its efficacy in other fungal infections is ongoing, and further studies into the impact of anidulafungin on economic outcomes will be beneficial.

Place in therapy: Current evidence supports the use of anidulafungin in the management of candidemia, esophageal candidiasis, and invasive candidiasis, as demonstrated by the successful results in large multicenter clinical trials.

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Key words: anidulafungin, candidemia, candidiasis, echinocandins, evidence, review, treatment

Core evidence place in therapy summary for anidulafungin in candidiasis

| Outcome measure                        | Evidence  | Implications                                                   |
|----------------------------------------|-----------|----------------------------------------------------------------|
| Disease-oriented evidence               |           |                                                                |
| Microbiologic response                  | Clear     | Achieved in the majority of patients with few episodes of invasive infection |
| Patient-oriented evidence               |           |                                                                |
| Clinical response                       | Clear     | Effective                                                      |
| Few drug-induced adverse events         | Substantial | Safe and easy to use, and well tolerated, with low discontinuation rates |
| No drug–drug interactions               | Clear     | Safe and easy to use in patients on numerous medications       |
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Scope, aims, and objectives

Anidulafungin is one of several drugs in the echinocandin class of antifungal agents. This evidence-based review focuses on the pharmacology and place in therapy for anidulafungin, the newest of the echinocandin antifungal agents. There have been several prior reviews on anidulafungin within the last few years (Murdoch & Plosker 2004; Pfaller 2004; Raasch 2004; Vazquez 2005; Vazquez 2006a,b; Vazquez & Sobel 2006). Most reviews, however, were published prior to the presentation of the data from the last two clinical trials performed with anidulafungin. In addition, this review utilizes evidence-based medical data in an attempt to identify anidulafungin’s place in the antifungal armamentarium. Anidulafungin is the most recent addition to the echinocandin class of antifungals, which includes caspofungin and micafungin (Table 1).

Methods

Searches of English language medical literature were conducted between May 1 and May 5, 2007, and November 1–9, 2007 in the following databases:

- PubMed, [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi), 1966 to date
- American Society for Microbiology abstract database, [http://www.abstracts2view.com/icaac](http://www.abstracts2view.com/icaac)
- [http://www.antimicrobe.org](http://www.antimicrobe.org)
- [http://www.doctorfungus.org](http://www.doctorfungus.org)
- [http://www.doctorfungus.org](http://www.doctorfungus.org)
- [http://www.doctorfungus.org](http://www.doctorfungus.org)
- [http://www.doctorfungus.org](http://www.doctorfungus.org)
- [http://www.astellas.us/docs/mycamine.pdf](http://www.astellas.us/docs/mycamine.pdf)
- [http://www.merck.com/product/usa/pi_circulars/c/cancidas/cancidas_pi.pdf](http://www.merck.com/product/usa/pi_circulars/c/cancidas/cancidas_pi.pdf)
- [http://www.pfizer.com/pfizer/download/uspi_eraxis.pdf](http://www.pfizer.com/pfizer/download/uspi_eraxis.pdf)
- [http://www.astellas.us/docs/mycamine.pdf](http://www.astellas.us/docs/mycamine.pdf)

The search terms utilized included “anidulafungin,” “caspofungin,” “micafungin,” “Eraxis,” “Cancidas,” “Mycamine,” “echinocandins,” “candidemia,” “candidiasis,” “esophageal candidiasis,” “LY 303366,” and “VER-002.” The literature search results are shown in Table 2.

Disease overview

Invasive fungal infections are of increasing importance in hospitalized patients, both with and without underlying immunocompromise. Over the past decade the frequency and diversity of invasive fungal infections has dramatically increased. Infections due to Candida species are currently the fourth most common cause of bloodstream infections (Wispelinghoff et al. 2004), while invasive aspergillosis has become the most common serious mold infection in immunocompromised hosts (Denning et al. 1998). While infections with Aspergillus species present significant diagnostic and therapeutic challenges with considerable morbidity, mortality, and cost, it is clear that infections due to Candida spp. are much more commonly observed in hospitalized patents. Serious Candida infections may range from primary bloodstream infections and catheter-related to disseminated candidiasis, where candidemia may not be apparent. The attributable mortality rates are difficult to estimate; crude mortality rates range from 30–60% (Zaoutis et al. 2005).

Current therapy options

Recent literature has shown that early initiation of antifungal therapy can improve patient outcomes, and considerable research is ongoing to define optimal therapy (Garey et al. 2006; Davis et al. 2007).

Table 1 | FDA-approved indications of available echinocandin antifungals (Eraxis®, prescribing information; Cancidas®, prescribing information; Mycamine® prescribing information)

| Category                              | Anidulafungin | Caspofungin | Micafungin |
|----------------------------------------|---------------|-------------|------------|
| Initial search                         |               |             |            |
| records excluded                       | 89            | 33          |            |
| records included                       | 56            | 5           |            |
| Level 1 clinical evidence              | 2             | 0           |            |
| Level 2 clinical evidence              | 2             | 2           |            |
| Level ≥3 clinical evidence             | 4             | 2           |            |
| Trials other than RCT                  | 46            | 1           |            |
| Case studies                           | 2             | 0           |            |
| Economic evidence                      | 0             | 0           |            |

For definitions of levels of evidence, see Editorial Information on inside back cover or on Core Evidence website ([http://www.coremedicalpublishing.com](http://www.coremedicalpublishing.com)).

RCT, randomized controlled trial.
Guidelines for the management of candidemia and candidiasis have been published by the Mycosis Study Group and Infectious Disease Society of the Americas and can be accessed via the website www.idsociety.org (Pappas et al. 2004). For several decades, amphotericin B was the only antifungal agent available for the treatment of systemic fungal infections. However, over the past 10–15 years several new classes of antifungals, specifically the azoles (fluconazole,itraconazole, voriconazole, posaconazole) and the echinocandins (caspofungin, micafungin, anidulafungin) are now available to manage these severe infections. For the past decade, fluconazole has been the main antifungal used to treat candidal infections in most types of patients. Unfortunately, over the past decade, two major changes have occurred that have precipitated a change in the management of candidal infections. The first change has been a well-documented shift in the Candida species causing candidemia and candidiasis, from the susceptible Candida albicans, to the less susceptible nonalbicans Candida (NAC) species. Of the NAC species, C. glabrata, C. parapsilosis, C. tropicalis, and C. krusei constitute the bulk of infections. These NAC species are important because they have varying susceptibilities to azoles and amphotericin B. The second change has been the development of fluconazole resistance in some of the NAC species, especially C. glabrata. The changing epidemiology of fungal infections coupled with the significant mortality and cost associated with the treatment of fungal infection has driven the development of new antifungal agents. Although new guidelines are under development, the current recommendation is to initiate antifungal therapy with either fluconazole, one of the echinocandins, or voriconazole, depending on the species of Candida identified in the patient (Pappas et al. 2004). In patients that are hemodynamically unstable, neutropenic, or infected with either C. glabrata or C. krusei the echinocandins are the preferred antifungal agents.

Unmet needs

Despite the availability of several new antifungal agents, the attributable mortality rates associated with candidemia and invasive candidiasis are generally between 30–40%, and have remained unchanged for the past decade. In addition, because of the extensive amount of fluconazole use in clinical practice over the past 10–15 years, we now have to recognize the increased frequency of azole resistance in the NAC species, especially in C. glabrata. These two reasons are why the echinocandins (caspofungin,micafungin,and anidulafungin) have become the preferred antifungal agents in seriously ill patients with disseminated fungal infections.

Anidulafungin pharmacology

Chemistry and mechanism

Echinocandin antifungals were first discovered in the 1970s, and named the pneumocandins for their activity against Pneumocystis (Denning 1997). Approved by the FDA in 2006, anidulafungin was the first echinocandin discovered; however, caspofungin and micafungin were introduced into the market in 2001 and 2005, respectively. Anidulafungin is derived from echinocandin B₉, which is produced by A. nidulans. Anidulafungin’s structure consists of an amphiphilic hexapeptide linked to an alloxytriphenyl side chain. It is this N-linked acyl lipid side chain that differs between the echinocandins, and accounts for some of the differences in their properties (Kurtz & Rex 2001). Drugs in the echinocandin class of antifungals inhibit cell wall synthesis, causing cell wall damage through noncompetitive inhibition of beta-(1,3)-glucan-synthase (Douglas 2001). Depletion of beta-(1,3)-glucan, a vital component of the fungal cell wall structure, leads to osmotic cell lysis.

Pharmacodynamics

Anidulafungin demonstrates in-vitro activity against many clinically relevant fungal species including a broad range of Candida species, such as those strains resistant to fluconazole or amphotericin B. In-vitro susceptibility assays reveal a decreased activity against C. parapsilosis, although no direct correlation between minimum inhibitory concentration (MIC) and clinical outcome has been established for echinocandins (Table 3) (Marco et al. 1998; Uzun et al. 1997; Znanel et al. 1997; Wiederhold et al. 2003; Pfaller et al. 2005; Pfaller et al. 2006). Furthermore,

| Anidulafungin | Caspofungin | Micafungin |
|---------------|------------|------------|
| AUC (mcg/h per mL) | 110 | 98 | 66 |
| Candida albicans | | | |
| MIC range | 0.007–2 | 0.007–0.5 | 0.007–0.25 |
| MIC₉₀ | 0.03 | 0.03 | 0.015 |
| MIC₅₀ | 0.06 | 0.06 | 0.03 |
| C. parapsilosis | | | |
| MIC range | 0.015–4 | 0.015–4 | 0.015–2 |
| MIC₉₀ | 2 | 0.5 | 1 |
| MIC₅₀ | 2 | 1 | 2 |
| C. glabrata | | | |
| MIC range | 0.06–0.25 | 0.015–0.8 | 0.007–1 |
| MIC₉₀ | 0.12 | 0.03 | 0.015 |
| MIC₅₀ | 0.25 | 0.06 | 0.015 |
| C. krusei | | | |
| MIC range | 0.125–0.5 | 0.015–1 | 0.015–0.25 |
| MIC₉₀ | 0.25 | 0.06 | 0.006 |
| MIC₅₀ | 0.25 | 1 | 0.12 |
| Aspergillus fumigatus | | | |
| MIC range | <0.03–0.06 | 0.015–2 | 0.007–0.015 |
| A. flavus MIC range | <0.03–0.12 | 0.015–0.12 | 0.007–0.015 |
| A. terreus MIC range | 0.03 | 0.12–2.0 | 0.003–0.007 |
| A. niger MIC range | 0.03–0.125 | 0.12–2.0 | 0.007–0.015 |
andidulafungin also has proven in-vitro activity against fluconazole- and itraconazole-resistant Candida species recovered from HIV-positive individuals (Chavez et al. 1999; Cuenca-Estrella et al. 2000; Pfaller et al. 2005). Anidulafungin has also demonstrated in-vitro activity against Aspergillus species including A. fumigatus, A. flavus, A. niger, and A. terreus, along with activity against many of the emerging molds such as Bipolaris spicifera, Exophiala jeaneselmi, Fonsecaea pedrosoi, Madurella mycetomatis, Penicillium marneffei, Philophora verrucosa, Pseudallescheria boydii, Sporothrix schenckii, and Wangiella dermatitidis (Espinel-Ingroff 1998; Odashi et al. 2004).

In addition, anidulafungin has demonstrated additive effects in combination with amphotericin B against Aspergillus and Fusarium species, and potential synergistic activity in combination with itraconazole or voriconazole against Aspergillus species (Philip A et al. 2005; Vazquez 2007).

The pharmacodynamic activity of anidulafungin (like other echinocandins) differs between organisms. Against Aspergillus, anidulafungin exerts a fungistatic effect in vivo, and demonstrates fungicidal activity against Candida species in vitro and in vivo. Against Candida species, the effect of echinocandins has been shown to be related to concentration and area under the concentration-time curve (Petraitiene et al. 1999; Louie et al. 2005). Additionally, an Eagle-like effect (paradoxical increase in fungal growth at higher concentrations) has been observed in yeast and filamentous fungi; however additional investigation into the mechanism and clinical significance of this relationship is warranted (Clemons & Stevens 2006; Wiederhold et al. 2004). In-vitro assays of anidulafungin in the presence of human serum suggest that serum binding reduces the activity of echinocandins against glucan synthase (Paderu et al. 2007). The clinical significance of the high protein binding is currently not known.

Resistance

The definition of echinocandin resistance is yet to be defined, but recent Clinical and Laboratory Standards Institute guidelines define a susceptible isolate with an MIC of <2 mcg/mL as susceptible, and isolates with MICs to echinocandins of >2 mcg/mL as nonsusceptible. To date, reduced echinocandin susceptibility remains uncommon, although most of the research to date has evaluated caspofungin susceptibility and reduced susceptibility. There have been several reports describing cross-resistance of echinocandins in different Candida species after prolonged exposures to echinocandins (Hakki et al. 2006; Laverdiere et al. 2006). In addition, in one series, although the activity was compromised, anidulafungin retained greater activity among C. glabrata isolates with reduced caspofungin susceptibility (Cota et al. 2006). In a recent case report by Moudgal et al., the authors described the first case of a multiechinocandin-resistant C. parapsilosis infection in a patient with refractory prosthetic valve endocarditis (Moudgal et al. 2005). Interestingly enough, all of the isolates that demonstrated reduced susceptibility to caspofungin and micafungin remained susceptible to anidulafungin. More recently, Chen et al. (2005) described 31 isolates of C. parapsilosis recovered from burn unit patients that displayed reduced susceptibility to micafungin and or caspofungin, but retained their susceptibility to anidulafungin. The mechanism of this cross-reduced echinocandin susceptibility is currently unknown.

Although the mechanisms of resistance to the echinocandins are not yet fully understood, there are several mechanisms that have been recently elucidated and reported. The most commonly described mechanisms involve the FKS1 and FKS2 genes that encode for the catalytic subunit of beta-(1,3)-glucan synthase (Douglas 2001; Douglas et al. 1994). Several investigators have already described mutations in two different “hotspots” of the FKS1 gene that have been shown to confer resistance to caspofungin in C. albicans, C. glabrata, and C. guilliermondii (Park et al. 2005; Balashov 2006; Katiyar 2006; Miller 2006). Other purported resistance mechanisms are the overproduction of beta-(1,3)-glucan synthase and the expression of efflux pumps (Osherov et al. 2002; Ghannoun 2005). Echinocandins have no activity against Cryptococcus neoformans, possibly related to impaired binding to a variation of glucan synthase in this organism (Maligie & Sellgrenniff 2006).

Pharmacokinetics

Like other echinocandins, oral bioavailability of anidulafungin is less than 10%, and thus is only available for parenteral administration. Protein binding was originally reported to be 84% (Wiederhold & Lewis 2003); however, it is now believed to be approximately 98%, which is consistent with the other agents in the class (Eraxis prescribing information). Anidulafungin demonstrates a large volume of distribution of 30–50L, and a terminal elimination half-life of 25 hours, following a biexponential decay. Steady-state concentrations are achieved on the first day of therapy after administration of a loading dose twice the normal daily dose. Anidulafungin is not metabolized by the liver, but undergoes slow chemical degradation by peptidases. An intermediate metabolite is formed by the opening of the hexapeptide ring, and this is then metabolized in plasma to tertiary degradation products. Approximately 10% of anidulafungin is eliminated unchanged via the biliary system. Since the drug is not degraded by hepatic enzymes, there are no interactions with the cytochrome P450 system.

Few data exist on anidulafungin in pediatric patients; however, an evaluation of safety and pharmacokinetics was conducted in a group of neutropenic children 2–17 years of age. A total of 24 patients were administered 0.75 mg/kg per day or 1.5 mg/kg per day anidulafungin based on total body weight, and pharmacokinetic parameters were determined. The study excluded children with hepatic or renal disease. The investigators determined that pediatric patients receiving 0.75 mg/kg per day or 1.5 mg/kg per day achieved similar anidulafungin concentrations to adults receiving 50 or 100mg/day, respectively (Benjamin 2006).
Clinical evidence with anidulafungin

Esophageal candidiasis

The efficacy of anidulafungin in treating esophageal candidiasis was studied in a randomized, double-dummy, controlled clinical trial that included 601 patients with endoscopically proven esophageal candidiasis (Krause 2004a) (Table 4). A total of 300 patients received an intravenous loading dose of anidulafungin 100 mg, followed by 50 mg/day, and 301 patients received oral fluconazole 100 mg/day. Treatment was continued for 14–21 days (a minimum of 7 days after resolution of symptoms). Of the 504 patients who completed therapy, 242 out of 249 (97.2%) who received anidulafungin and 252 out of 255 (98.8%) who received fluconazole demonstrated endoscopic evidence of cure or improvement, indicating that anidulafungin is at least as efficacious as fluconazole in the treatment of esophageal candidiasis. The one difference between treatment groups was the relapse rate. At the 2-week follow-up, the relapse rate was 35.6% for anidulafungin and 10.5% for fluconazole. Although the relapse rate was high with anidulafungin, a similar relapse rate was also seen in patients with oropharyngeal candidiasis (OPC) and/or esophageal candidiasis treated with caspofungin (Arathoon et al. 2002). The cause of this higher relapse rate associated with echinocandin use when compared with fluconazole is unknown.

Anidulafungin is also effective in managing patients with fluconazole-refractory mucosal candidiasis. Anidulafungin was evaluated in a small, open-label clinical trial in patients with refractory oropharyngeal or esophageal candidiasis who had failed at least 14 days’ treatment with fluconazole >200 mg/day (Vazquez et al. 2007). In an interim analysis of 18 patients enrolled in the study, 17 had a diagnosis of AIDS (CD4 cell count <50 cells/mm³). At the end of therapy, 17 out of 18 patients had a successful clinical response, and 10 out of 11 patients with esophageal candidiasis were considered endoscopic successes. Clinical response was defined as cure (absence of symptoms and requiring no additional therapy), improvement (decrease in severity when compared to baseline and no further need for antifungals), or failure. In addition, at the end of therapy, if patients had esophageal candidiasis at baseline, the endoscopic response was also evaluated and classified as cure, improvement, or failure. Furthermore, anidulafungin was well tolerated with only one serious adverse event (rash). Anidulafungin appears to be a promising treatment regimen for azole-refractory mucosal candidiasis.

Candidemia and invasive candidiasis

A phase II, open-label, dose-ranging study was conducted in 123 patients with candidemia and signs or symptoms of active infection (Krause et al. 2004b) (Table 4). Participants received anidulafungin at dosages of 50, 75, or 100 mg/day. Success was defined as both a clinical and microbiological success, as documented by resolved clinical manifestations and sterilization of blood cultures. Anidulafungin was successful in 73 out of the 83 evaluable patients at the end of antifungal therapy (84%, 90%, and 89%, respectively, for the different dosage regimens). At the 2-week follow-up period, the corresponding success rates in these very ill patients were 72, 85, and 83%, favoring the two higher dosages. Anidulafungin was well tolerated at all dosages and adverse events were uncommon. Adverse events considered to be treatment-related were reported in <5% of patients in any dose group, with the exception of hypokalemia, which was reported in 10% of patients in the 50 mg dose group. Overall, the most commonly reported events were hypotension (13%), vomiting (13%), constipation (11%), and nausea (11%). There was no dose–response relationship with respect to the frequency of adverse events.

Table 4 | Clinical trials evaluating anidulafungin in candidemia and esophageal candidiasis

| Disease                                 | No. patients enrolled | Treatment and dosage regimen | Outcome                                      | Adverse events | Level of evidence | Reference          |
|-----------------------------------------|-----------------------|------------------------------|---------------------------------------------|----------------|-------------------|--------------------|
| Esophageal candidiasis                  | 36                    | Afgn 50 mg LD, followed by 25 mg/d | Endoscopic response rates 81% vs 85%       | N/A            | 3                 | Brown et al. 2000  |
|                                         |                       | Afgn 70 mg LD, followed by 50 mg/d                                            |                                                                                     |
| Esophageal candidiasis                  | 601                   | Afgn 100 mg LD, followed by 50 mg/d                                           | Endoscopic response rates: 242/249 (97%) vs 252/255 (98.8%)      | 9.3% vs 12%   | 2                 | Krause et al. 2004a|
|                                         |                       | Flz 100 mg LD, followed by 100 mg/d                                           |                                                                                     |
| Candidemia and invasive candidiasis     | 123                   | Afgn 50 mg/d                     | Global response rates 72% vs 85% vs 83%     | <5% in all three groups | 3                 | Krause et al. 2004b|
|                                         |                       | Afgn 75 mg/d                     |                                                                                     |
|                                         |                       | Afgn 100 mg/d                    |                                                                                     |
| Candidemia and invasive candidiasis     | 245                   | Afgn 200 mg LD, followed by 100 mg/d                                           | Global response rate at end of i.v. 75.6% vs 60.2%                     | Comparable in both groups | 2                 | Reboli et al. 2007 |
|                                         |                       | Flz 800 mg LD, followed by 400 mg/d                                           |                                                                                     |
| Antifungal-refractory mucosal candidiasis| 19                   | Afgn 200 mg LD, followed by 100 mg/d                                           | Clinical response 18/19 vs Endoscopic response 11/12 | Nausea/vomiting -20% vs Hypokalemia -10% | 3                 | Vazquez et al. 2007|

Afgn, anidulafungin; d, day; Flz, fluconazole; i.v., intravenous; LD = loading dose; N/A, not available.
In a recently completed phase III, multicenter, double-blind, randomized clinical trial, a 100 mg dose of anidulafungin was compared with a 400 mg dose of fluconazole in patients with candidemia and/or invasive candidiasis (Reboli et al. 2007) (Table 4). A total of 261 patients were enrolled in this pivotal clinical trial, 256 were included in the intent-to-treat population, and 245 in the modified intent-to-treat population. In the study 127 patients received at least one dose of anidulafungin while 118 patients received fluconazole. The primary analysis was performed at the end of intravenous therapy (day 10). Success was defined as both a clinical and microbiological success, as documented by resolved clinical manifestations and sterilization of blood cultures. A successful outcome was achieved in 76% of patients who received anidulafungin compared with a 60% success in patients who received fluconazole. The difference between groups was 15.4%, with a 95% confidence interval of 3.9 to 27.0. Additionally, at the 2-week follow-up period, a similar treatment difference in response was observed, with a success rate of 65% and 49%, respectively. Compared with those subjects who received fluconazole, anidulafungin recipients had a higher rate of success for every Candida species except for C. parapsilosis. However, the total number of patients with C. parapsilosis was only 24 (10%) of the total population (10 patients in the anidulafungin arm and 14 patients in the fluconazole arm), thus making it difficult to make any definitive comments regarding the treatment differential. In addition, it was not a statistically significant difference. One of the limitations to this study was associated with the fact that the evidence for superiority of anidulafungin over fluconazole was decreased when data from the highest enrolling site were excluded from the analysis. However, statistical analysis was not able to demonstrate a “center effect,” and global success rates were 73% in the anidulafungin arm compared with 61% in the fluconazole arm (treatment difference of 12.1%; 95% CI –1.1, 25.3).

Overall, the adverse event and tolerability profiles were similar between the two treatment groups. Treatment-related adverse events were only observed in two patients in each arm, with one case of seizures and one case of atrial fibrillation in the anidulafungin arm. In general, most of the adverse events reported were due to the underlying disease state and not the study drugs. In addition, the mortality rate from all causes was found to be 31% in the fluconazole arm compared with 23% in the anidulafungin arm. Although it was an 8% difference, it did not reach statistical difference.

### Safety

In clinical studies documenting over 600 patients, anidulafungin has been well tolerated compared with adverse effects seen with other antifungals. The most common adverse effects reported include headache and nausea. In a few cases mild, reversible elevations of liver function tests have been seen. With rapid intravenous administration some flushing, nausea, and dyspnea were reported; however, infusion-related reactions quickly subside and can be greatly reduced with slower infusion rates. No specific monitoring parameters are routinely recommended in patients receiving anidulafungin (Krause et al. 2004ab; Reboli et al. 2007).

### Drug Interactions

In studies performed to date, anidulafungin has not been associated with any significant drug–drug interactions. Concurrent dosing with cyclosporine (a CYP3A4 substrate) following anidulafungin 100 mg/day demonstrated no significant alteration in pharmacokinetics of either drug (Dowell et al. 2005). No changes in disposition were observed with concomitant administration of anidulafungin and voriconazole (Dowell et al. 2005) and liposomal Amphotericin B. Similarly, no interactions have been identified between anidulafungin and any substrates, inhibitors, or inducers of cytochrome P450 enzymes, including rifampin, efavirenz, or nevirapine.

While few postmarketing data have been published on the safety of anidulafungin, a small study provides information on the potential for disulfiram-like reaction when anidulafungin and its alcohol-containing diluent is administered with concomitant metronidazole. A prospective cohort was followed for potential disulfiram-like reaction, defined as having at least one symptom from each category of general disorder, gastrointestinal, and neurologic symptoms. Of 44 patients receiving the combination of agents, none experienced a disulfiram-like reaction (Hurren et al. 2007).

### Economic evidence and resource utilization

The treatment of candidemia has been associated with an attributable cost of nearly US$40 000 per case and greater than 10 additional days of hospitalization (Zaoutis et al. 2005).

There is no economic evidence for the use of anidulafungin over other echinocandins or azoles in the treatment of candidemia and or invasive candidiasis. However, the fungicidal activity in vitro of anidulafungin compared with the fungistatic activity of the azoles, and the fact that the pivotal candidemia trial demonstrated statistical superiority of anidulafungin over fluconazole along with a decrease in mortality, suggest that the use of anidulafungin over fluconazole in patients with candidemia may prove beneficial. Cost-benefit and cost-effectiveness studies still need to be done comparing these two classes of antifungals.

### Dosage, administration, and formulations

The FDA-approved dose of anidulafungin is based on the indication. For esophageal candidiasis, it is given as a 100 mg intravenous loading dose, followed by 50 mg intravenously once daily. For the treatment of candidemia and systemic candidiasis, a 200 mg loading dose is given on day one, followed by 100 mg daily. Clinical need for dose escalation has not been reported, but a one-time dose of 260 mg, the maximum dose studied, was well tolerated (Thye et al. 2001). The maximum cumulative dose in studies without additional adverse effects reported was daily doses of 100 mg continued over 90 days (Dowell et al. 2004). Unlike other echinocandins, no adjustments of anidulafungin doses are necessary for either renal or hepatic insufficiency. The drug is a large molecule and is not well dialyzable; however, specific dosing recommendations in dialysis or continuous renal replacement therapy have not been established.
Like other currently available echinocandins, anidulafungin is available only in intravenous preparations, owing to its large molecular weight and low oral bioavailability. Anidulafungin is insoluble in water, and is reconstituted in 20% w/w dehydrated alcohol in water for intravenous administration. After reconstitution in the manufacturer-provided solution, it can be diluted with either 0.9% sodium chloride or 5% dextrose and should be administered within 24 hours. A maximum infusion rate of 1.1 mg/minute is recommended to reduce the likelihood of infusion-related reactions.

**Place in therapy**

The safety and efficacy of anidulafungin, plus its novel pharmacokinetics, make it a suitable alternative antifungal for therapy of mucocutaneous candidiasis, candidemia, and invasive candidiasis. It provides a broad spectrum of activity with proven efficacy against a wide array of Candida species, including those that are azole- or polyene-resistant, and has also demonstrated activity against *Aspergillus* species.

Anidulafungin appears to have several advantages over other antifungal drugs. For example, it does not require dosing adjustments in patients based on age, gender, weight, disease state, concomitant drug therapy, or renal or hepatic insufficiency. In addition, because of its lack of hepatic metabolism and lack of P450 interaction, it does not have any drug–drug interactions. Furthermore, because of its unique mechanism of action, anidulafungin does not induce cross-resistance with other classes of antifungals.

It is the first antifungal agent that has demonstrated statistical superiority in a comparative clinical trial evaluating therapy for candidemia. Results of current studies warrant further clinical trials evaluating the use of anidulafungin as either primary or preemptive therapy for invasive fungal infections, such as candidemia and invasive candidiasis and aspergillosis. Moreover, because of its lack of adverse drug interactions and the possibility of *in-vitro* additive or synergistic activity with other antifungals, the role of anidulafungin in combination with other antifungals should be further explored in the management of some of the high mortality-associated mold infections, such as aspergillosis.

In summary, anidulafungin shows excellent promise and should be a valuable new antifungal agent with a novel mechanism of action. Completed clinical studies have demonstrated that anidulafungin should prove useful as a first-line agent for treating a range of serious fungal infections, including mucocutaneous candidiasis, candidemia, invasive candidiasis, and azole-refractory mucosal candidiasis. However, although it has *in-vitro* activity against *Aspergillus* species and other molds, its usefulness against serious mold infections such as aspergillosis, either as monotherapy or in combination, is currently unknown.

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