Antifungal-Associated Drug-Induced Cardiac Disease

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The etiology of cardiomyopathies are classified into 4 main groupings (dilated, hypertrophic, restrictive, and idiopathic) and can be mechanistically caused by myocarditis, conduction abnormalities, focal direct injury, or nutritional deficiency. Based on our review of this topic, evidence suggests that echinocandin-related cardiac dysfunction is a mitochondrial drug-induced disease caused by focal direct myocyte injury. With caspofungin or anidulafungin administration into the heart via central line, exposure is likely extreme enough to induce the acute toxicity. Chronic or low-dose exposure may lead to hypertrophic cardiomyopathy; however, only acute exposures have been explored to date.

Keywords. echinocandin; cardiac toxicity; echocardiography; cardiac output.

Drug-induced diseases are commonly associated with antimycotic pharmacotherapy. One could predict such an outcome when treating a eukaryotic pathogen that infects a eukaryotic host. The cellular similarities between the host and invading fungal organism produce a narrower margin of safety for antimycotic agents compared with other antimicrobial agents. The most concerning side effects of antifungal therapy are cardiovascular in nature, especially those leading to significant morbidity or mortality.

The first agents developed to combat fungal infections, the polyenes, have proven to be particularly troublesome for pharmacotherapists and physicians trying to prevent drug-induced problems [1, 2]. The development of the triazole and the echinocandin antifungal agents was anticipated to improve safety and possibly efficacy compared with amphotericin B–containing regimens. The triazole antifungals inhibit the conversion of ergosterol to lanosterol via inhibition of the enzyme 14-α-demethylase, whereas the echinocandins inhibit (1→3)-β-d-glucan synthase in yeast and molds. Although systemically administered antifungal triazoles may prolong the QTc interval, there is no indication that the antifungal mechanism of action of triazoles would cause a possible cardiac-decompensating event. There is microbiologic evidence of echinocandin inhibition of Candida parapsilosis mitochondrial function [3]. This is thought to be an additional, though not commonly considered mechanism of antifungal action, but may result in inadequate energy production in the mitochondria of high-demand organs such as the heart due to the similarities between human and yeast mitochondria [3].

Oligomycin, a cyclic lipopeptide of the echinocandin class, is an antifungal purified from supernatants collected during the growth of Streptomyces diastatochromogenes. This and similar compounds were initially developed for human use, but were found to cause profound mitochondrial toxicity and are no longer used clinically. These agents are known inhibitors of H+-ATP synthase. Minimal exposure to oligomycin (6.3 µM) prevents state 3 respiration. This inhibition is incomplete due to proton leaks (mitochondria uncoupling). Observed metabolic acidosis due to accumulated lactate with oligomycin administration provides leading evidence for mitochondrial toxicity [4]. Based on these historical data, it is reasonable to hypothesize that some observed toxicity of commercially available echinocandins may be associated with mitochondrial damage.
LITERATURE REVIEW OF HUMAN CASES

Cardiovascular adverse events attributed to the antifungal drugs are extremely rare. Historically, amphotericin B is the most commonly reported, commonly leading to hypotensive episodes and concerns about abnormal conduction secondary to hypotension. On rare occasion, polyenes have been demonstrated to induce negative chronotropic effects and abnormal conduction, possibly leading to dilated cardiomyopathy [5, 6]. Dysrhythmias have been reported with amphotericin B, most often in patients who are anuric, those who have previous cardiac disease, or those who have received significant overdoses [7]. These events may be related to rapid effluxes of potassium from mammalian cells to cause high extracellular potassium concentrations, cardiac transmembrane depolarization, and ventricular arrhythmias [8]. Several case reports have also noted congestive heart failure [5]. Significant evidence of cardiovascular events with the newer, safer lipid formulations of amphotericin B has been remote in the literature. However, azole antifungal agents (clofazimazole, econazole, voriconazole) have been reported to induce events ranging from hypokalemia and vasodilation to more serious inhibition of calcium channels with possible negative inotropic or arrhythmic (Torsades de pointes) events [9–12].

Since the release of amphotericin in the 1950s, the most evident signal of severe cardiac toxicity came from recent reports concerning itraconazole. This triazole antifungal agent was approved in 1992 to treat invasive fungal infections. In the late 1990s, several case reports of cardiac toxicity associated with itraconazole inspired a review of the US Food and Drug Administration Adverse Event Reporting System (FAERS) database. From 1992–2001, 94 cases of cardiac toxicity were identified from the postmarketing reports [13]. Of these, 58 were classified as possibly associated with itraconazole. Subsequently, the Food and Drug Administration (FDA) required the manufacturer to issue a black box warning in 2001. Itraconazole package labeling now includes a warning against use in patients with a history of heart failure.

In a more recent, similarly designed study, the FAERS system query from 2004 to 2012 contained 3 419 016 records, including several echinocandin (n = 11 761) and azole (n = 184 843) antifungal adverse events. “Cardiac disorders” were reported in 2015 (17.1%) and 14 618 (7.9%) cases, respectively. Caspofungin had 3.5 cases of heart failure reported per year, whereas anidulafungin and micafungin each had approximately 1 case per year. Reported FAERS cases for caspofungin revealed that 51% of cardiovascular reports were associated with heart failure based on Medical Dictionary for Regulatory Activities (MedDRA version 14.1) classification (MSSO 2014). The reported incidence rate for heart failure/cardiovascular events for itraconazole was 9.8% [14]. These data suggest similar and possibly more threatening cardiac outcomes than initially anticipated.

Recent reports have noted that echinocandin cardiovascular disease cases were mostly male patients ranging in age from 41 to 81 years (62.2 ± 15.8 years) [15–18]. Most individuals were receiving pharmacotherapy by central venous catheter in the intensive care unit. Three of 4 patients had a previous history of both cardiac disease and renal dysfunction. One patient had flash pulmonary edema associated with anidulafungin infusion, suggesting rapid onset of cardiovascular toxicity [15]. The authors hypothesized that histamine release was the underlying etiology. A “red man” syndrome associated with likely histamine release was first reported with anidulafungin in an adolescent during infusion of the first dose [19]. There was no hemodynamic deterioration, and symptoms and signs abated following discontinuation of the infusion. Reinitiation of the infusion at a slower rate was not associated with any subsequent infusion-related toxicity. Life-threatening hemodynamic instability (hypotension and bradycardia) also has been reported during anidulafungin infusion, again supporting a rapid onset. Rapid recovery was obtained after infusion cessation and cardiopulmonary resuscitation [16]. Unfortunately, none of the above reported cases discussed serum or urine lactates.

FDA-approved labeling information for the echinocandins does report a warning for histamine-related reactions seen with infusion [20–22]. Histamine administration has also been associated with a broad range of observations after administration or endogenous release. Literature on histamine administration in humans or rats demonstrates positive inotropic and chronotropic effects along with varying degrees of vasoactive stimulus [23]. However, rat heart is reported not to have histamine receptors, possibly biasing its use as a valid animal model for this research. In rats, the positive inotropic and chronotropic effects elicited by histamine are due to the release of noradrenaline. In Langendorff-perfused rat hearts infused with 0.1–1000 µM of histamine, a maximum increase in left ventricular pressure and coronary flow was observed at 100 µM without significantly influencing heart rate or rhythm. Histamine had a dose-dependent positive inotropic and vasodilatory effect in this isolated rat heart model [24]. Based on current evidence, histamine release as an etiology for heart failure appears to be an unlikely explanation.

LITERATURE REVIEW OF ANIMAL STUDIES

As clinical reports of cardiac events with the echinocandins have only been published with some of the echinocandin antifungals, a difference in echinocandin toxicity may exist. Reported lethal doses (LD50) of these agents in male rats are reported to be 71 mg/kg, 38 mg/kg, and 125 mg/kg for anidulafungin, caspofungin, and micafungin, respectively. Structurally, these agents have differing lipophilicity that could be the basis of observed differences (Figure 1).
An isolated rat heart ex vivo model (Langendorff) is an excellent framework to identify possible mechanisms for possible cardiac toxicity of a pharmaceutical agent. In published Langendorff studies, measured changes in contractility were performed via pressure transducer in the left ventricle after 5-minute infusions of the echinocandin antifungals, negative control (saline), and positive control (itraconazole) [25]. Anidulafungin (8.8–70 µM), caspofungin (5.5–44 µM), and micafungin (5.7–57 µM) were administered representing 1, 4, and 10 times the therapeutic concentrations. Results were considered clinically significant if the decrease in contractility was equal to or greater than that found with itraconazole (−12.4% ± 6.6%), as it is known to cause clinically overt toxicity. Anidulafungin and caspofungin were associated with significantly decreased contractility (average decrease across all doses) compared with negative control (−79.5% ± 12.4% [P < .05] and −40.6% ± 15.6% [P < .05], respectively). At high doses, changes seen with anidulafungin were irreversible. Micafungin infusion was not associated with decreases in contractility (+13.6% ± 2.8% [P = NS]).

Random histopathologic assessments were reported from echinocandin-exposed hearts used in Langendorff studies. Exploration into pathologic evidence for observed ex vivo cardiac changes were conducted initially via hematoxylin and peroxidase staining and review by a single blinded pathologist. No macroscopic abnormalities could be identified. Heart tissue sections further fixed with buffered glutaraldehyde and osmium tetroxide and evaluated by transmission electron microscopy revealed alarmingly enlarged mitochondria, disintegrating myofibrils, swollen sarcoplasmic reticulum, and excess secondary lysosomes in samples exposed to high-dose anidulafungin and caspofungin, and all doses of oligomycin (Figure 2). Anidulafungin-exposed tissue also displayed dense cellular matrix and large vacuoles in the cell while high-dose micafungin showed some enlarged mitochondria and sarcoplasmic reticulum but no substantial evidence of disintegrating myofibrils, excess secondary lysosomes, or abnormal myocardial tissue [25]. There have not been confirmatory reports published on these histopathologic changes, but these observations appear to have been validated by investigations into functional mitochondria changes.

Focused studies on mitochondria have reported altered electron transfer from reduced nicotinamide adenine dinucleotide (NADH) to O2 in isolated, intact Sprague-Dawley rat heart and liver mitochondria [26]. The isolated mitochondria were exposed to echinocandin antifungal agents at concentrations 0.1–100 times the known achievable human serum concentrations. A sigmoidal dose response was observed when modeling measured electron transfer and energy production for caspofungin and micafungin. Anidulafungin was not tested. Caspofungin and micafungin inhibited NADH 2O2 production (Figure 3). The investigators reported concentrations for 50% inhibition (IC50) values of 10–20 µM whether using intact mitochondria or washed inner mitochondrial membranes. These IC50 values are close to serum concentrations achieved after drug administration, although the exposure concentration

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**Figure 1.** Structural differences between the major echinocandins. The primary sites of substitution are identified (“R”) on the cyclic lipopeptide ring. Two prospective lipopeptides (aculeacin A and aminocandin) are also represented. Oligomycin is not shown due to the large number of dissimilarities (absence of nitrogen) in the ring structure. Surfactin structure is substantially larger and could not fit in the figure.
must be lower in intact cells due to plasma membrane protection. In addition, the echinocandins appear to each interact with >1 electron transfer complex. Using inner mitochondrial membranes, caspofungin primarily inhibited complex III (IC₅₀ = 7 µM; 50% inhibition) and complex IV (IC₅₀ = 20 µM; 80% inhibition). Micafungin primarily inhibited complex III (IC₅₀ = 20 µM; 80% inhibition). Conversely, micafungin also stimulated electron transfer activity at complex IV up to 250% at 100 µM drug, with a half maximal effective concentration of 13 µM. This observation would suggest increased inotropic activity. Inhibition of complex III and IV appears to correlate with observed decreases in mitochondrial energy production.

The assimilated published clinical and ex vivo studies have driven investigators to evaluate echinocandin antifungal direct cellular toxicity. In an in vitro evaluation of the effect on isolated ventricular cardiomyocytes, caspofungin, anidulafungin, and micafungin were tested at concentrations ranging from 0.09 µM to 90 µM [27]. Cells were exposed to the experimental agents for 90 minutes, and contractile responses as a result of electrical stimuli were measured at 5 intervals of 15 seconds and reported as a mean contractile responsiveness. With caspofungin, cells exposed to 0.09–3 µM were not different than controls. At exposures of 9 µM, there was a significant decrease in contractile responsiveness. Cells exposed to anidulafungin at 2.9 and 8.9 µM showed a significant increase in contractility compared to controls, whereas lower doses showed no difference. At exposures of 30 µM and 90 µM for both caspofungin and anidulafungin, cardiomyocytes changed shape and contractility was unmeasurable. With micafungin, exposures of 3–30 µM also produced cell shortening. However, the elimination of contractions was only achieved with the 90-µM dose.

Degradation of the echinocandins was hypothesized to lead to a toxic byproduct resulting in increases in myocardial damage.

Figure 2. Transmission electron microscopic (TEM) images of cardiac tissue after exposure to buffer negative control (A); anidulafungin 8.8 µM (B); caspofungin 11 µM (C); and micafungin 7.9 µM (D). Oligomycin is not shown, but was similar to anidulafungin in appearance. Specific features of normal tissue identified on TEM. One can readily identify changes in mitochondria and damage to surrounding sarcomeres in plates (B and C). More extensive discussion may be found in the text.
Echinocandins undergo spontaneous degradation into an open-ring peptide [20–22] at physiologic temperatures and pH leading to a microbiologically inactive compound. The in vitro degradation half-life is about 24 hours. Ex vivo live-heart (Langendorff) studies using Harlan Sprague-Dawley rats compared 2.7 µM freshly reconstituted caspofungin with degraded drug (aged 60–90 days under sterile conditions). Investigators observed a significantly longer duration of time to a >50% reduction in contractility with degraded vs fresh echinocandin (24.51 ± 16.97 vs 8.03 ± 4.86 minutes, \( P < .05 \)). These authors concluded that degraded caspofungin was associated with a time delay in the loss of contractility, illustrating a reduced potential for cardiotoxicity [28].

To validate the results found in the ex vivo and in vitro studies, researchers have recently initiated in vivo studies in male Sprague-Dawley rats. Echinocandins were infused over 10 minutes via central line to otherwise healthy, isoflurane-anesthetized animals. Cardiac measurements (cardiac output, heart rate, and stroke volume) were made using a high-resolution in vivo imaging system while blood pressure was continuously monitored via carotid central venous catheter [29,30]. These data were collected during infusion and for 30 minutes after infusion ended. Positive (itraconazole) and negative (saline) controls were performed and compared to echinocandins. All agents were infused at 2 doses known to bracket concentrations similar to serum concentrations in humans (caspofungin 3 mg/kg and 6 mg/kg, anidulafungin 5 mg/kg and 11.5 mg/kg, and micafungin 1 mg/kg and 5 mg/kg). Investigators considered cardiac output decreases \( \geq 30\% \) from baseline to be clinically significant, based on clinical definitions of heart failure and published itraconazole data. At the higher doses administered, both caspofungin and anidulafungin were associated with clinically significant decreases in cardiac output (−62.6% ± 13.0% [\( P < .05 \)] and −62.7% ± 19.4% [\( P < .05 \)]) respectively) (Figure 4). One can see in these curves for cardiac output that no significant recovery is noted during the time monitored. Mean arterial pressure also decreased with both agents through administration and observation periods (43%–47% and 21%–39% in caspofungin and anidulafungin, respectively). Micafungin was not associated with significant changes in blood pressure or cardiac output at either dose (−2% and −18% [\( P = NS \)], respectively). Subsequently, European investigators have validated the cardiac failure observations when higher echinocandin (caspofungin 8.75 mg/kg, anidulafungin 25 mg/kg) exposures were used in a similar model [31]. However, no correlation was found between mitochondrial enzyme activity and hemodynamic failure. No cardiac toxicity was observed in micafungin-treated animals.

One could hypothesize that the differences in echinocandin toxicity are a result of the degree of lipophilicity, with the more lipophilic agents (anidulafungin and caspofungin) displaying...
more toxicity than those that are more hydrophilic. Another hypothesis could be based on the fact that the structures of echinocandins are similar to that of surfactin. Surfactin is a slightly larger (23-member ring) lipopeptide ring with similar numbers of nitrogen, oxygen, and side chains. Similar to surfactant, one could speculate increased solubilization of cardiac cell membranes with echinocandins based on their strong detergent-like activity.

As novel alternate daily or weekly dosing regimens are evaluated for echinocandins for treatment and prevention of invasive candidiasis, the potential differential cardiotoxicity of the different echinocandins should be considered. Based upon these data, micafungin would have the lowest propensity for causing cardiotoxicity when infused at higher doses for extended-interval dosing strategies.

A conservative approach to echinocandin administration is warranted based on these data. Critically ill or hemodynamically unstable individuals in critical care environments receiving central venous administration simulate these experimental models. We suggest only peripheral administration should be considered in these scenarios. Although there are no reports in the literature of chronic toxicity such as that observed with itraconazole, it could hypothetically occur with the prolonged administration of echinocandins. Clinicians should be alert for this potential side effect.

Notes

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