Cardiac Safety of High-dose Micafungin

Sir,

Pharmacotherapy in patients with systemic fungal infections continues to challenge the heartiest clinicians. The inability of the antimycotic to discriminate the infected eukaryotic host from the pathogen often leads to treatment-limiting adverse events. In our continued efforts to improve the safety of antifungal therapy, we initiated studies to evaluate the dose, onset, peak, and duration of echinocandin-induced cardiomyopathy.

Over the past 5–6 years, a plethora of animal data and case reports has been published that describes this phenomenon.[1] First, we performed *ex vivo* studies in an attempt to elucidate the toxicity of the echinocandin antifungals. Clear decreases in cardiac contractility were observed in adult male Sprague-Dawley rat hearts after infusion of caspofungin and anidulafungin.[2] To determine whether these displayed effects would translate to a live model, we performed *in vivo* studies in live, adult male Sprague-Dawley rats.[3] Blood pressure and echocardiography were evaluated before, during, and after a 10-minute central infusion of caspofungin, anidulafungin, or micafungin. At doses known to replicate human pharmacologic exposures, caspofungin and anidulafungin were associated with significant decreases in cardiac output (CO). No changes were seen with micafungin. In a similar *in vivo* rat model, investigators evaluated the effect of high (8.75–30 mg/kg)- and low-dose (0.875–3 mg/kg) echinocandin administration on cardiac function.[4] Their results were similar to those described above: high-dose anidulafungin and caspofungin showed immediate hemodynamic decreases, while animals treated with micafungin had no impact on cardiac function. Finally, several clinical reports of toxicity associated with these agents, ranging from pulmonary edema to cardiac decompensation, have substantiated this previous research.[5] The purpose of this study was to expand assessments of cardiac toxicity to include a wider array of doses of micafungin to define dose and onset of this adverse event.

Animals were catheterized and prepared as previously described.[3] Micafungin was infused over 20 min into adult male Sprague-Dawley rats (408 ± 43 g) through central line at doses ranging from 1 to 50 mg/kg (equivalent to human doses ranging from 0.17 to 8.3 mg/kg). Saline was used as a negative control, and anidulafungin 11.5 mg/kg and caspofungin 6 mg/kg were used as model validation/positive control agents at doses previously associated with decreases in CO.[3]

The primary outcome associated with antifungal administration was change in calculated CO. In dose-targeted experiments, CO compared between each targeted echinocandin dose and negative controls as discrete experiments were evaluated using a one-sided Student's *t*-test. A drop in normal cardiac index (average 3.35 L/min/m^2; range 2.5–4.2 L/min/m^2) by 30% would represent heart failure or a clinically significant decrease in heart function as previously described.[3] For this report, the remaining variables are presented demonstratively.

This research was approved by the Institutional Animal Care and Use Committee at this institution.

In 5 negative control animals, saline was infused over 20 min with no significant changes in mean arterial pressure (−6.8 ± 7%), heart rate (HR) (−5.0 ± 5.6%), or CO (−17.1 ± 1.3%). Anidulafungin 11.5 mg/kg (n = 4) and caspofungin 6 mg/kg (n = 3) were used as positive controls, and both were associated with significant decreases in CO (−72.2 ± 14.4% and −82.5 ± 24.7%, respectively) and mean arterial pressure (MAP) (−61.0 ± 15.5% and −53.1 ± 3.9%), similar to previously published results.[3]

Micafungin exposures between 1 and 5 mg/kg in these animals should represent the ~0.6 mg/kg administered in humans. At 1 (n = 2) and 5 mg/kg (n = 2), CO changes were not significant (−16.7 ± 2.1% and −18.2 ± 1.9%, respectively). These changes in CO were not associated with substantial changes in HR (3.3 ± 1.3%, −8.2 ± 4.6%) or blood pressure (−2.8 ± 2.0%, −2.1 ± 6.8%). In assessments of higher exposures, micafungin was tested at 10 (n = 3), 25 (n = 5), and 50 mg/kg (n = 4). These exposures were associated with insignificant decreases in CO ($P > 0.05$) when compared to a similarly timed saline control [Figure 1]. Interestingly, as the doses progressed from 25 mg/kg to 50 mg/kg, rats demonstrated an increased mean arterial blood pressure (−9.2 ± 16.8% vs. 34.2 ± 11%) without a change in HR (−4.1 ± 5.5% vs. 6.1 ± 2.7%) and

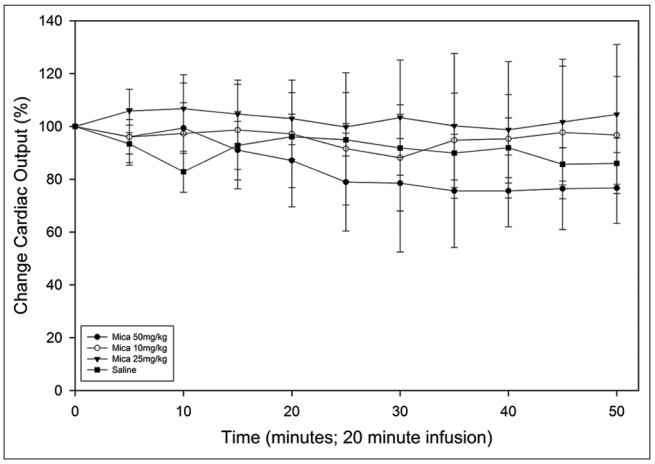

Figure 1: Cardiac output with high-dose micafungin (10–50 mg/kg) compared to saline control. Preventilation measurements of cardiac output are represented as a percent change from baseline relative to time (20 min antifungal infusion and 30 min observation period). Values represent mean cardiac output decrease from baseline ± standard deviation

with a clinically insignificant decrease in CO (−1.3 ± 0.3% vs. 24.4 ± 3.2%). The 50 mg/kg exposure in the rodents corresponds to an approximate 8.5 mg/kg (~600 mg dose) in humans. No chronotropic effects were observed during medication administration.

If one accepts the definition of clinical significance, doses of caspofungin (6 mg/kg) and anidulafungin (11.5 mg/kg) that are known to replicate human pharmacologic doses were associated with significant decreases in CO in an *in vivo* model, while micafungin at doses ranging from 1 to 50 mg/kg were not. Compared to the previous study (10 min infusion), a longer infusion time (20 min) was used in this trial to account for the increased doses and volumes of drug. The use of the control agents over this same infusion with no changes led to the conclusion that this extension of infusion time had no impact on the results.

When conducting an assessment of the cardiovascular response to micafungin, supra-therapeutic doses (50 mg/kg) led to hypertension in both our model and in human published reports.[6] If one evaluates the physiologic relationship (equation) for blood pressure (blood pressure = total peripheral resistance (TPR) × CO, where CO = HR × stroke volume), it would appear that an increase in TPR would be anticipated in response to micafungin based on measured parameters. There have not been published literature assessing or reporting this phenomenon. These investigators used central arterial blood pressure monitoring over tail vein cuff or other methods to improve the quality and accuracy of the readings. In the model's live, anesthetized rodents, changes in blood pressure should have been evident.

As we embark on an effort to ever improve the treatment and care of patients with invasive fungal infections, these results are very important. In one center, Gumbo *et al.* are evaluating the utility of micafungin single- or two-dose regimens for the treatment of invasive candidiasis, utilizing higher doses of micafungin to achieve more rapid results.[7,8] As we evaluate dosing strategies such as these to take advantage of the pharmacokinetics and pharmacodynamics of the antifungal agents, it is important to know which of the echinocandins will be able to be safely dosed at a higher level. The studies completed to date suggest that micafungin alone will be an effective, high-dose regimen that is free from the cardiac toxicities that have occurred with anidulafungin and caspofungin.

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Conflicts of interest

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