REPORTED CARDIOVASCULAR EVENTS DURING ECHINOCANDIN PHARMACOTHERAPY

John D. Cleary, Pharm.D., FCCP, Kayla R. Stover, Pharm.D. and S. Travis King, Pharm.D.
University of Mississippi School s of Pharmacy & Medicine, Jackson, MS

BACKGROUND

The overall goal of the Mycotic Research Center is to improve the safety and efficiency of antifungal therapy. Cardiac associated adverse events attributed to antifungals have been long recognized. We previously performed two studies in an attempt to elucidate the toxicity of the echinocandin antifungals. Clear decreases in cardiac contractility appear evident in adult male Sprague-Dawley rat hearts infused with caspofungin and anidulafungin in an *ex vivo* Langendorff model. Myocardial toxicity secondary to a depletion in ATP seems a reasonable explanation for the observed events. We hypothesize that the differences in toxicity seen between agents are a result of relative lipophilicity, with the more lipophilic agents (anidulafungin and caspofungin) displaying more toxicity than those that are more hydrophilic (micafungin).

OBJECTIVES

Primary Objective:

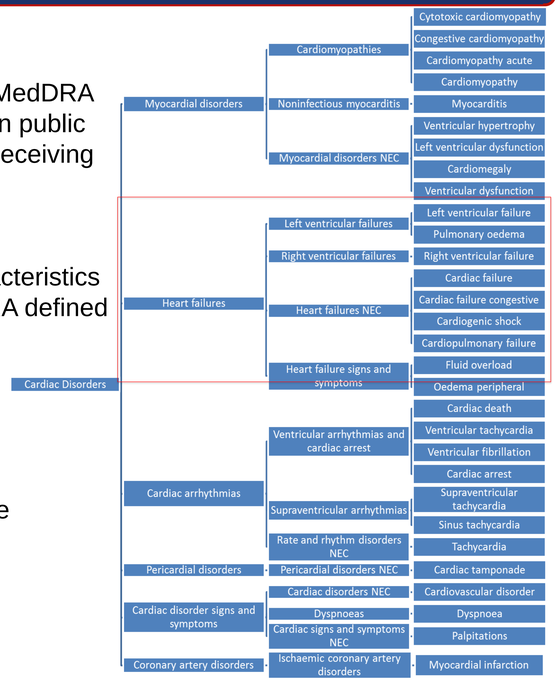
- Elucidate reports of MedDRA defined **heart failures** in public databases for patients receiving antifungal therapy.

Secondary Objective:

- Identify patient characteristics associated with MedDRA defined heart failures.

METHODS

MedDRA Term Structure
Cardiac Disorders



METHODS

- Retrospective Case Review
  - US Food and Drug Administration's Adverse Event Reporting System (AERS) database search was performed.
    - All reports to the AERS database between 2004 and 2012.
    - Cases of acute cardiac or heart failure terms from the Medical Dictionary for Regulatory Activities [MedDRA] related to heart failure or its symptoms were included. Duplicate entries were removed.
    - Misspelled terms & drug name entries were excluded.

  - Data are presented as percentages of total cardiac-related disorders (AERs) and assessed based on years on US market
    - NDA approved:Caspofungin 1/26/01, Micafungin 3/16/05, Anidulafungin 2/17/06, Itraconazole 3/1/97, and Fluconazole 1/29/90.

RESULTS

AERS system query contained 3,419,016 records for the years including 2005 through 2011. Echinocandins (N=11,761) and azole (N=184,843) antifungal ADRs revealed "cardiac disorder" reports in 2,015 and 14,618 cases, respectively. Unique cases presented in table below.

Characteristic	Caspofungin	Anidulafungin	Micafungin	Fluconazole	Itraconazole
Sample: Any Cardiac ADR	809	92	263	6584	1004
Demographics					
Age (mean + Sd)	47.1 ± 21.4	54.7 ± 17.3	49.5 ± 20.4	52.8 + 19.7	53.3 + 21.3
Weight (kg)	68.9 + 28	68.9 + 21.8	70.6 + 34.9	87.1 + 28	59.3 + 17.5
Gender (%F)	42.9%	39.1%	36.5%	48%	34%
Therapy					
Duration of Tx (Days)	19.3 + 29.7*	14.7 + 22.3	19.7 + 40.6	8.5 ± 6.9	17.3 ± 16.2
Systemic Candidiasis	9%	33%	21%	3%	2%
Aspergillosis	12%	11%	10%	1%	6%
Adverse Reaction					
Cardiac Failures	N=25	N=1	N=9	N=212	N=44
Heart Failure/Card ADRs (%)	41%	4%	11%	39%	51%
% Cardiac Deaths	3.8%	0.0%	1.5%	1.4%	2.0%
Concurrent History					
Cardiac Related PMH	<1%	<1%	<1%	<1%	1.8%
AML/ALL	12%	15%	5%	3%	9%
Multiple Myeloma	1%	0%	7%	16%	10%

* Excluded 3 cases that received drug > 12 months into therapy.

RESULTS

- Cardiovascular Cases
  - Echinocandins had an onset at 13.5 + 17.1 days excluding 22 that exceeded 3 months therapy.
    - Heart Failure (% of "Cardiac Disorder" Reports)
      - Caspofungin: 97 Cases (41%), 3.5 cases/yr Heart Failure
      - Anidulafungin 10 Cases (~5%), ~1 case/yr Heart Failure
      - Micafungin 26 Cases (~10%), ~1 case/yr Heart Failure
- Cardiovascular Controls
  - Azole adverse events were associated an onset of 10.8 + 18.5 days if one excludes 4 cases that were > 3 months of therapy. The range for all azole ADRs was 0 – 2779 days.
    - Heart Failure (% of "Cardiac Disorder" Reports)
      - Itraconazole 44 Cases (51%), 6.2 cases/yr Heart Failure
      - Fluconazole 212 Cases (39%), 30 cases/yr Heart Failure
- OBSERVATON: Interestingly, cardiac related adverse reactions (ADRs) increased from <10% of reports annually in 2005 to greater 20% by 2012. Greatest increase in reports was observed with fluconazole. Death occurred in 1,496/7,587 (19.7%) in azole treated and 293/1,164 (25.2%) of echinocandin patients.

CONCLUSIONS

- Many antifungals appear associated with:
  - Increased Heart Failure reported in US FDA AERS.
  - Caspofungin and Itraconazole report similar percents.
- Theoretical concern about treating patients with previous cardiac abnormalities and those who are receiving these agents directly into the heart (data from FDA summary of itraconazole):
  - Critically ill patients in the intensive care unit.
  - Central venous/arterial catheters or patients with a peripherally inserted central catheter (PICC Line).
- Further clinical research is required to elucidate this drug induced disease & controls needed for doses dispensed in epidemiological data.

ADDITIONAL REFERENCES OF INTEREST

- Cleary JD, Stover KR, Farley J, Daley W, Kyle PB, Hosler J. Cardiac toxicity of itraconazole. Pharmacology & Pharmacy 2013;4:362-8.
- Hindahl CB, Wilson JW. Flash pulmonary oedema during anidulafungin administration. J Clin Pharm Ther, 2012;37:491-3.
- Fink M, Zerlauth U, Kaulfersch C et al. A severe case of haemodynamic instability during anidulafungin administration. J Clin Pharm Ther, 2013;38:241–242.
- Lichtenstern C, Wolff M, Arens C et al. Cardiac effects of echinocandin preparations – three case reports. J Clin Pharm Ther, 2013. [Epub]
- Stover KR, Farley J, Kyle P, Cleary JD. Cardiotoxicity of some echinocandin antifungals. Exp Opin Drug Saf, 2013 Sept 18. [Epub]