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Poster Session VI
PK/PD of antifungals and miscellaneous antibacterials

TOXICITY AND EFFICACY DIFFERENCES BETWEEN LIPOSOMAL AMPHOTERICIN B FORMULATIONS IN UNINFECTED AND ASPERGILLUS FUMIGATUS INFECTED MICE

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Objective: Previous studies with liposomal amphotericin B formulations, AmBisome® and Anfogen®, which have the same chemical composition, but are prepared using different production conditions, showed that the drugs were not the same in their toxicity and efficacy profiles in both uninfected and infected mice indicating that safety and antifungal activity for these two drugs were not comparable. In this study, we examined particle size, *in vitro* and *in vivo* toxicity, efficacy and tissue distribution of AmBisome (AmBi) and another liposomal amphotericin B preparation, Lambin (Lamb).

Methods: Particle sizes were compared using dynamic light scattering. *In vitro* toxicity was measured using a RBC potassium release assay (K50). Uninfected C57Bl/6 mice (5/group) were given single iv doses of 20 or 50 mg/kg drug and monitored daily for survival and morbidity. Other groups of C57Bl/6 mice (7/group) were given daily, iv doses of 5, 15 or 25 mg/kg drug for 14 days and tissues were then collected for histopathology. Immunosuppressed Swiss Webster mice were challenged intranasally with 5.9x10^6 *Aspergillus fumigatus* and treated daily iv with 10 or 15 mg/kg drug or 5% dextrose beginning 2h post-challenge. After 2 treatments, lungs and BAL (7/group) were collected for histopathology, fungal burden (Log10 CFU/g), and drug concentration. Remaining mice (10/group) were treated for 4 more days and monitored for survival to day 21.

Results: The median particle sizes were not the same (Lamb = 122.2nm; AmBi = 77.8nm). Lamb was also more toxic than AmBi based on RBC sensitivity (K50 value = 1.4ug/ml Lamb versus (vs) 7.4ug/ml AmBi), iv single dose toxicity (80% mortality Lamb vs 0% mortality AmBi at 50 mg/kg) and renal tubular changes in uninfected mice given 5 mg/kg Lamb, but not 5 mg/kg AmBi, after iv daily dosing for 14 days. Survival following *A. fumigatus* challenge was 10% for D5W, 30% for 10 mg/kg Lamb, 50% for 15 mg/kg AmBi, and 60% for both 10 mg/kg AmBi or 15 mg/kg Lamb. Although after 2 treatments AmBi and Lamb were equally effective in lowering lung fungal burdens, both AmBi doses and 15 mg/kg Lamb were better than 10 mg/kg Lamb for lowering BAL fungal burden ($P \leq 0.05$). Lung histopathology after 2 treatments also showed that AmBi resulted in fewer fungal elements and less tissue damage than Lamb and mean BAL drug concentrations were higher for AmBi vs Lamb (10 mg/kg Lamb = undetectable levels, 10 mg/kg AmBi = 0.9 ug/mL, 15 mg/kg Lamb =0.04 ug/mL, 15 mg/kg AmBi= 3.8 ug/mL).
Conclusions: Given the differences in size, toxicity, efficacy and drug distribution of these two amphotericin B liposomal formulations, the results show that AmBi and Lamb are not functionally comparable and underscores the need for adequate testing when comparing liposome formulations.