Abstract

Efficacy of Liposomal Amphotericin B for the Treatment of Systemic Candidiasis in a Murine Model of Type II Diabetes

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Introduction

Diabetes is the third most widespread disease after heart disease and cancer (Diabetes UK, 2016). Type 2 diabetes mellitus (T2DM) is associated with obesity and the progressive development of complications, including cell insulin production and/or glucose intolerance (Borenstein et al., 2006; Skovso, 2014). This chronic disease status affects numerous metabolic pathways and organ systems including the gastrointestinal tract, the pancreas and the kidneys, which contributes to the immune system dysfunction (Blodd, 2006). T2DM increases the susceptibility to infections and other organ damages such as systemic candidiasis (Cecquini et al., 2012).

Although the efficacy of liposomal amphotericin B (AmBisome) used to treat systemic candidiasis is well documented in both clinical and animal models and in humans (Adler-Moore and Profioli, 2002; Adler-Moore et al., 2006; Tettamanti et al., 2012; Della Perga et al., 2010), reports of its efficacy in diabetic animals is limited. In this study, we present the effects of escalating doses of AmBisome on diabetic mice given a lethal systemic candidiasis infection.

Materials and Methods

Background: Limited studies have been done to determine how Type 2 diabetes mellitus (T2DM) affects the efficacy of antifungal drugs. It has been reported that T2DM changes host susceptibility to systemic candidiasis in mice. The objective of this study was to evaluate the antifungal activity of liposomal amphotericin B (AmBisome) in diabetic mice following a lethal systemic candidiasis infection.

Methods: C57BL/6 mice were maintained on a high (55%) fat diet beginning at 2 weeks prior to intraperitoneal treatment with 106 CFU/mL yeast inoculum and amphotericin B (5 mg/kg) to induce T2DM by pre-existing hyperglycemia. Mice were challenged with a lethal systemic infection of Candida albicans (2 x 107 CFU) and divided into 2 treatment groups: 3.0 mg/kg AmBisome or 5 mg/kg AmBisome. Mice were monitored for survival, weight loss and disease signs. Blood glucose levels monitored (p < 0.02).

Results

- Treatment with AmBisome significantly reduced fungal burden in all tissues examined vs. D5W control, p = 0.0022.
- Tissue concentrations of amphotericin B were significantly higher in all tissues examined vs. D5W control.
- Blood glucose levels were significantly reduced in mice treated with 3 or 5 mg/kg AmBi, p = 0.0411.
- Pro-inflammatory cytokines (IL-1α, IL-1β, TNF-α) were significantly higher in mice treated with 3 or 5 mg/kg AmBi, p = 0.0022.

Conclusions

- AmBisome was effective in treating systemic candidiasis in mice with Type 2 diabetes mellitus (T2DM) based on prolonged survival, minimal weight loss and minor disease signs and significantly reduced fungal burden in the spleen, liver, kidney, fat and pancreas.
- The significant decrease in Blood Glucose Levels in T2DM mice following yeast challenge was likely a result of yeast utilizing the high glucose levels in the blood, which was reversed following AmBisome treatment which markedly reduced the yeast growth; BGL remained low in DSW control mice which continued to have high yeast growth in their tissues.
- Drug distribution and concentration of amphotericin B in the AmBisome treated mice with T2DM was similar to previous results reported in non-T2DM mice (Moore and Profioli, 2003), indicating that the T2DM status did not alter tissue drug distribution and concentrations.
- AmBisome therapy in the T2DM mice modulated the immune response to this infection by significantly reducing the amount of pro-inflammatory cytokines (IL-1α, IL-1β and IL-6) in the kidneys (target site of systemic candidiasis in mice) while increasing the production of tissue 1 and 2 cell cytokines.

References

Borenstein J, Badger J, Goldenberg S, Rade S, Raiber and Akash, 2016. The hygienic environment in T2DM increases the susceptibility to infections and other organ damages such as systemic candidiasis (Cecquini et al., 2012).

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