ABSTRACT

Background: Amphotericin B (AmB), due to its fungicidal efficacy, broad spectrum and limited resistance, can be considered the "gold standard" antifungal treatment. However, use of AmB is limited by toxicity and intravenous administration. CaMB is a lipid-crystal, nanoparticle formulation designed for targeted oral delivery of AmB to the infected tissue without the associated toxicity.

Methods: BALB/c mice (n=24) were infected on Day 0 with 5 x 10^8 CFUs of Candida albicans. After infection mice were treated for 14-days with control, DAMB (Amphotericin B deoxycholate) 2 mg/kg intraperitoneal, or CaMB 10 mg/kg oral. Untreated and untreated mice were used as blank controls. Free mice from each treatment group were sacrificed on days 1, 3, 5, 7, 11, and 15. Plasma and tissues were collected for analysis of AmB concentrations.

Results: Concentrations of AmB in plasma were undetectable in 61% of the CaMB and 44% of DAMB samples with no significant difference in plasma levels between groups. In the tissues however, quantifiable AmB levels were seen in all samples (See Figure), with CaMB reaching the MIC of 0.25 μg/ml in 1-2 days whereas DAMB takes 3-5 days to reach the MIC level. All efficacious dose, tissue levels for CaMB stay at 2-3 μg/ml whereas DAMB causes tissue levels to increase to 4-40 μg/ml.

Conclusions: CaMB-infected mice, orally administered CaMB is taken up from the GI tract resulting in significant tissue concentration above the MIC level. Contrary to DAMB, concentrations of AmB from CaMB accumulate rapidly in the tissues without escalating to extremely high levels during the second week of treatment, potentially mitigating side effects and toxicities.

COCHLEATE TECHNOLOGY

How Cochleates Encapsulate Drugs

Cochleate delivery vehicles have been shown to mediate oral bioavailability for injectable drugs, reduce toxicity, and significantly enhance intracellular drug delivery. Cochleates are stable, lipid-crystal, nano-particle compositions of simple, naturally occurring phospholipid-outer and calcium. They have a unique multilayered structure consisting of a large, continuous, solid, lipid-crystal sheet rolled up in a spiral or as stacked sheets, creating an impermeable structure that resists degradation by the body. These vehicles provide protection from degradation for "encapsulated" molecules. Cochleates within the interior of the cochleate remain intact even though the outer layers of the cochleate may be exposed to harsh environmental conditions or enzymes.

Cell-Targeted Delivery

Microscopic readily engulf cochleates and their cargo

Once inside the macrophage, the low calcium level in the cytoplasm causes the cochleate to open, releasing the cargo molecule.

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RESULTS

Oral Dosing of Encocochleated Amphotericin B (CaMB): Rapid Drug Targeting to Infected Tissues in Mice with Invasive Candidiasis

R. MANNINO* and D. PERLIN*

Oral administration of AmB-cochleates has been shown to result in very efficacious, replicable doses of the leading AmB formulation (Fungizone) in mouse models of systemic candidiasis and aspergillosis.

- AmB-cochleates also demonstrate substantially lower toxicity than existing commercial AmB products.
- AmB-cochleates showed good safety in rats and dogs in 7 and 28 day toxicity studies.
- A commercially viable and cost-effective manufacturing process for AmB-cochleates has been developed.
- Scale-up 100 liter GMP batches of AmB-cochleates have been produced.
- An NCI-52 for AmB-cochleates is open, and a phase II human clinical trial was supportive of further studies.
- A phase 3a- efficacy study is targeted to begin in October, 2015.

Oral delivery of AmB-cochleates is efficacious in a mouse model of disseminated candidiasis.

- Oral administration of AmB-cochleates, but not DAMB, prevented dissemination of C. albicans in a mouse model of disseminated candidiasis.
- Plasma AmB levels were at or below the limit of quantitation (50 ng/ml).

Oral delivery is efficacious in a mouse model of invasive candidiasis.

- Oral dosing of Encochleated Amphotericin B (CaMB): Rapid Drug Targeting to Infected Tissues in Mice with Invasive Candidiasis.
- In infected mice treated with oral CaMB at 10 mg/kg, the liver, lung, and kidneys showed reproducible and quantifiable levels of AmB that achieved their maximal levels (~2 mg/kg tissue) early in the treatment schedule.
- Fungizone-treated mice showed lower tissue concentrations at early times, but nearly two-fold higher AmB levels in liver and lung which were achieved by day 11.
- Plasma AmB levels at oral CaMB were at or below the limit of quantitation (50 mg/ml).
- In infected mice treated with CaMB at 2 mg/kg, tissue concentrations were 100% survival in 30% and a 4 log reduction in CFU in both the lung and kidney. AmB levels in plasma and tissue are not detectable.
- Oral administration of CaMB to mice resulted in 100% survival in 30% and a 4 log reduction in CFU in both the lung and kidney. AmB levels in plasma and tissue are not detectable.
- Rapid tissue penetration to the lung, shell, and spleen achieved 100% survival in 30% and a 4 log reduction in CFU in both the lung and kidney. AmB levels in plasma and tissue are not detectable.

SUMMARY AND CONCLUSIONS

- Oral Administration of Drugs Formulated into Cochleates Can Change the Pharmacokinetics, Biodistribution and Tolerability of the Drug