World Journal of Otorhinolaryngology-Head and Neck Surgery (2017) 3, 2–8

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.keaipublishing.com/WJOHNS; www.wjent.org

Research Paper

Protective and antifungal properties of Nanodisk-Amphotericin B over commercially available Amphotericin B☆

Do-Yeon Cho [a,b,*,d], Kyle J. Hoffman [a], Gobind S. Gill [a], Dong-Jin Lim [a], Daniel Skinner [a], Calvin Mackey [a], Steven M. Rowe [b,c], Bradford A. Woodworth [a,b,**,d]

[a] *Department of Otolaryngology Head & Neck Surgery, University of Alabama at Birmingham, Birmingham, AL, USA*
[b] *Gregory Fleming James Cystic Fibrosis Research Center, University of Alabama at Birmingham, Birmingham, AL, USA*
[c] *Departments of Medicine, Pediatrics, Cell Developmental and Integrative Biology, University of Alabama at Birmingham, Birmingham, AL, USA*

Received 15 January 2017; accepted 23 January 2017
Available online 7 March 2017

KEYWORDS
Chronic rhinosinusitis;
Amphotericin;
Drug delivery;
Transepithelial ion transport;
Sinusitis;
Sinus epithelium;

Abstract *Objective:* Amphotericin B (AMB), a potent antifungal agent, has been employed as topical and systemic therapy for sinonasal fungal infections. A novel formulation of nanodisc (ND) containing super aggregated AMB (ND-AMB) for the treatment of fungal infections has been recently developed to provide greater protection from AMB toxicity than current, clinically approved lipid-based formulations. The objective of the current study was to evaluate the safety and potency of ND-AMB for sinonasal delivery using an *in vitro* model.
Methods: Human sinonasal tissue was harvested during endoscopic sinus surgery and grown at air–liquid interface until well-differentiated. Cultures were exposed to ND-AMB vs AMB and changes in K^+ permeability and resistance were measured and recorded via Ussing chamber

☆ A portion of submitting manuscript was presented at the American Rhinologic Society Annual Meeting, Dallas, TX, September 26, 2015.

* Corresponding author. Department of Otolaryngology Head & Neck Surgery, University of Alabama at Birmingham, BDB 563, 1720 2nd Avenue S., Birmingham, AL, 35294-0012, USA. Fax: +1 205 934 3993.
** Corresponding author. Department of Otolaryngology Head & Neck Surgery, University of Alabama at Birmingham, BDB 563, 1720 2nd Avenue S., Birmingham, AL, 35294-0012, USA. Fax: +1 205 934 3993.
E-mail address: dycho@uabmc.edu (D.-Y. Cho).
[d] The two authors (DYC and BAW) equally contributed and act as equivalent **co-corresponding** authors of this manuscript.

Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

http://dx.doi.org/10.1016/j.wjorl.2017.01.002

2095-8811/Copyright © 2017 Chinese Medical Association. Production and hosting by Elsevier B.V. on behalf of KeAi Communications Co., Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Mucociliary clearance;
Ciliary beat frequency

assay. Ciliary beat frequency (CBF) was analyzed in parallel as well as cytotoxic assay. Potency was assessed using real-time PCR measurement of the *Aspergillus fumigatus* 18S rRNA.
Results: Ussing chamber studies revealed K^+ currents that increased rapidly within 30 s of adding AMB (10 μg/mL) to the apical side, indicating apical membranes had become permeable to K^+ ions. In contrast, negligible induction of K^+ current was obtained following addition of ND-AMB [AMB = (107.7 ± 15.9) μA/cm^2 AMB vs ND-AMB = (2.3 ± 0.7) μA/cm^2 ND-AMB; $P = 0.005$]. ND-AMB also protected nasal epithelial cells from cytotoxicity of AMB ($P < 0.05$). There was no difference in ciliary beat frequency between the two groups ($P = 0.96$). The expression of *A. fumigatus* 18S rRNA with exposure of lower dose of ND-AMB was significantly lower compared to that with AMB ($P < 0.05$).
Conclusions: Data from the present study suggests ND-AMB protects human nasal epithelia membranes from AMB toxicity by protecting against apical cell K^+ permeability while maintaining uncompromised antifungal property compared to AMB. ND-AMB could provide a novel topical therapy for sinonasal fungal diseases.
Copyright © 2017 Chinese Medical Association. Production and hosting by Elsevier B.V. on behalf of KeAi Communications Co., Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Since fungi are present throughout the environment, human exposure is inevitable and normal respiration routinely deposits fungal elements within the nose and paranasal sinuses.[1] In most instances, the presence of fungal elements in the nose has no consequences. However, fungi can contribute to the pathogenesis of rhinosinusitis (fungal rhinosinusitis) in tissue-invasive or noninvasive conditions. Regional variation in incidence has been reported, with the southern part of United States particularly endemic.[2] Fungal rhinosinusitis (FRS) has been categorized primarily based on whether the fungus invades local tissues or not, a characteristic intimately associated with the status of the host's immune system. Patients who are immunocompromised are highly susceptible to invasive fungal sinusitis (IFS), and despite prophylactic treatment, mortality due to fungal infections remains high. With the use of newer and more potent chemotherapeutic agents and regimens, more patients are now susceptible to fatal invasive fungal sinusitis.[3]

Amphotericin B (AMB) is a potent antifungal agent and topical delivery of AMB may have significant advantages over systemic intake (either intravenous or oral) including the avoidance of systemic and infusion-related toxicities. However, AMB affects the integrity of apical cell membranes in human nasal epithelial cells and can be toxic at higher doses.[4,5] Oda et al[6–8] have developed a novel formulation of NanoDisk (ND) containing super aggregated AMB for the treatment of fungal infections. NanoDisk amphotericin B (ND-AMB) provided greater protection from AMB toxicity than current clinically approved lipid-based formulations of AMB in pulmonary tissue and highly efficacious treatment for invasive candidiasis in a mouse model. This drug also has important applications in topical or inhaled therapy for fungal-related respiratory diseases. The objective of the present study is to determine whether a novel nanoparticle delivery platform for AMB, ND-AMB, is less disruptive to human nasal epithelium than existing formulations of AMB and maintains similar antifungal property. We hypothesized that AMB would cause minimal damage to the nasal epithelium with similar potency when formulated within the ND.

Methods

Amphotericin

Amphotericin (AMB; Sigma-Aldrich, St. Louis, MO) was prepared according to manufacturer's instructions. ND-AMB was provided as a gift from the Oda laboratory and preparation of ND-AMB has been described previously by Michael Oda.[8]

Primary cell culture

Institutional Review Board and Institutional Animal Care and Use Committee approval were obtained prior to initiating these studies. Human septonasal epithelial cells (HSNE) were harvested, grown on Costar 6.5-mm diameter permeable filter supports (Corning Life Sciences, Lowell, MA), and submerged in culture medium as previously described.[9–12] Media was removed from the monolayers on day 4 after the epithelium reached confluence, and cells fed via the basal chamber. Differentiation and ciliogenesis occurred in all cultures within 10—14 days. Cultures were used for experiments when well-differentiated with widespread ciliogenesis with transepithelial resistances (Rt) > 100 Ω cm^2.

Ussing chamber analysis

Transwell inserts (Costar) were mounted in Ussing chambers to investigate pharmacologic manipulation of vectorial ion transport as previously described.[13–15] Transepithelial current measurements were performed with Easy Mount Ussing chambers (Physiologic Instruments, San Diego, CA) with an apical-to-basolateral directed gradient for K^+.[6,16] High K^+ buffer in the apical reservoir was (in mmol/L): 120 KCl, 20 $NaHCO_3$, 5 $KHCO_3$, 1.2 NaH_2PO_4, 5.6 glucose, 2.5 $CaCl_2$, and 1.2 $MgSO_4$. The basolateral reservoir buffer was (in mmol/L): 120 NaCl, 20 $NaHCO_3$, 5 $KHCO_3$, 1.2 NaH_2PO_4,

Download English Version:

https://daneshyari.com/en/article/5670703

Download Persian Version:

https://daneshyari.com/article/5670703

Daneshyari.com