Review Article

Pulmonary Mycoses Treated by Topical Amphotericin B

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Abstract

Since its discovery, amphotericin B (AmB) became a key management because it is the most common antifungal drug with activity to disrupt the fungal cell wall. Furthermore, it is the first-choice treatment in pulmonary mycoses that may consider lethal infection; the difference in lipid structure between fungal and mammalian cell membranes determines the effect of AmB. However, some fungal pulmonary diseases such as aspergillomas are partially contact with the blood and narrow touch the walls of the lung cavities, thus administration of systemic antifungal agents may be ineffective to eliminate these infections. Tissue penetration of systemic antifungal agents must be evaluated to get a proper appreciation of their antifungal activity, which may differ even within the same antifungal class. So, topical administration considered necessity in these situations. AmB belongs to the polyene group has a wide-spectrum *in vitro* and *in vivo* antifungal activity. All of the known available formulas of AmB are administrated through intravenous injection to treat severe systemic fungal infections, while the development of the topical formula of AmB is still under preliminary development, including topical pulmonary AmB. Due to the revealing of antimicrobial-resistant fungi in recent years and ineffective systemic management of pulmonary fungi, this study explains the role of topical AmB in treating refractory lung fungi that not response to other drugs that may help researchers to develop an effective topical formula of AmB regarding pulmonary mycosis.

Keywords: Antifungal agents, fungal treatment, pulmonary mycosis, topical amphotericin B, topical treatment

Introduction

Formulations of the amphotericin B (AmB) remain the first-choice agents for the management of pulmonary fungal diseases.[1] AmB is an ancient agent used over many decades in treating various fungal infections clinically in the human.[2] Low fungal resistance and broad-spectrum antifungal activities are the most valuable pharmaceutical characters encourage continuous usage of AmB.[3]

AmB isolated from *Streptomyces nodosus* in the soil of the Orinoco River region of Venezuela in the 1950s. Deoxycholate AmB (D-AmB) is the first form of AmB developed in 1955 to use against systemic fungal infections.[4] It quickly approved to use clinically by the Food and Drug Administration in 1958 in spite of unknown its structure due to its broad-spectrum antifungal activity.[5] In 1958, an intravenous formula of sodium D-AmB solution was presented in the markets at the name Fungizone Squibb.[6] The ancient formula of AmB that contains D-AmB has more side effects presented by nephrotoxicity than recently developed lipid formula in 1990, which releases low concentrations of AmB in the human serum.[7]

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Systemic drugs distribute in tissues at different concentration that may differ from their concentration in bloodstream, hence, the knowledge of systemic antifungal drug tissue penetration is important to understand the efficacy of drug to treat fungi, some pulmonary mycosis are located in balls at lung cavity with few contacts to blood vessels, thus, these systemic antifungal drugs are ineffective. Hence, using a topical antifungal drug is required.[1]

This study highlights the topical efficacy of AmB to treat pulmonary mycosis depending on searches and case report studies.

Topical Usage of Amphotericin B

Topical modern applications of AmB provide a promising way of fungal treatment to reduce the adverse effects of intravenous usage of AmB.[2]

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There are many advantages to using AmB as a topical treatment of dermatophytosis. First, discover new drugs or modification old one will participate to increase the available limited number of antifungal drugs.[8] Second, topical preparations are much less costly than systemic administration of antifungal drugs and cause minimal adverse side effects.[9,10] Third, the application of the topical formula of AmB considers more safety to use and will not produce clinically relevant serum levels of AmB.[10,11]

AmB is used over many decades in the management of different fungal infections in the human as pulmonary mycosis. Opportunistic systemic fungal infection considered the most common type of fungal infection mainly treated by AmB.[2] At present, many studies focused on the topical preparation of AmB as eye drop[12] or gel[12] or solution[13] or as nanoparticles drug.[14] However, treatment with topical AmB may not always give satisfying results as with ordinary forms of this drug in the treatment of fungal infection, while some topical applications of AmB gave performing outcomes with complete healing, especially in certain cases not responded to conventional therapy that considered life-threatening danger as lung and bronchial mycosis. The topical formula of AmB to treat fungal respiratory tract give good results as mentioned in the previous studies, hence, developing this formula is necessary due to the appearance of drug-resistant fungi.

Mechanisms of Action of Amphotericin B

There is no clear vision about the mechanism of action to explain the antifungal effect of AmB although it has been used for many decades. The most accepted one is the activity of AmB adheres to the ergosterol of the fungal cell membrane causing dysfunction by forming pore ion channels.[4,15-17] Pore formation may lead to inhibition of fungal glycolysis and quick efflux of K^+ and Mg^+ ions inside fungal cells which increase the acidity consequently fungal cell death occurs.[18]

The mechanisms of liposomal AmB (L-AmB) began when the liposomal vesicle become attached to fungal cells in the infection site, then release AmB from holding vesicle to adhere to the ergosterol of fungal cell membrane and damage it.[4]

Another mechanism of action of AmB presented by production of free radicals inside fungal cell,[17,19] this leads to oxygen depletion and superoxide anion formation that effects on the cellular pathways of fungi.[20] Moreover, AmB has immunomodulatory properties that induce pro-inflammatory response and this gives protection to the immunocompromised persons.[17]

Topical Amphotericin B in Treatment Lung Fungi

Mitomo *et al*. 2018[21] were studied the endobronchial instillation of AmB as a pulmonary topical formula. Lung chromomycosis due to *Scedosporium prolificans* that appeared after lung transplantation failed to be treated by systemic itraconazole [Table 1].

The patient was a female, after 8 years of the lung transplantation, chest radiography X-ray appeared an abnormal shadow in the right lung, the pulmonary chromomycosis diagnosed in bronchoscopic aspirate, and *S. prolificans* was detected as the causative agent.

Topical AmB instillation is used. About 5 mg of AmB was topically prepared. After three topical instillations, the bronchial obstruction is highly cleared; endobronchial topical AmB instillation was used one time every 3 months. After six instillations, the abnormal shadow disappeared, and the bronchial obstruction is improved. This study revealed that endobronchial topical AmB instillation is a therapeutic required when systemic antifungal management is ineffective to treat pulmonary mycosis.[21]

Takeda *et al*., 2014[22] presented a case report study of a 72-year-old male suffering from recurrent hemoptysis and dyspnea, with 28-mm fungus ball in a pulmonary cavity, aspergilloma was diagnosed. A biopsy examination of which detected *Aspergillus fumigates*, a yellow fungus ball was observed in the cavity.

Systemic voriconazole among 2 months followed by itraconazole for 4 weeks was ineffective, the patient was poor pulmonary functions, and surgical was not possible.

L-AmB clinically administered locally into the bronchial instillation of yellow fungus ball, 2.5 mg/kg of 1% L-AmB

Table 1: Topical amphotericin B against pulmonary mycosis

Reference	Fungi type	Location of fungi	Number patient	AmB dose	AmB formula	Treatment duration	Result	Years	Study type
[21]	*S. prolificans*	Lung chromomycosis	1	3 instillations once every 3 months	D-AmB bronchial installation	2 years	Improvement was noticed	2018	Case report
[22]	*A. fumigatus*	Bronchial aspergilloma	1	1% L-AmB	L-AmB bronchial instillation	4 weeks	Aspergilloma disappeared	2014	Case report
[23]	*A. fumigatus*	Bronchial aspergilloma	3	2-3 mg (0.5 mg/ml) aqueous solution once a week	L-AmB administrated bronchoscopically	4-8 months	Successfully treatment	2000	Case report
[24]	*A. niger* and *A. fumigatus*	Aspergilloma	7	AmB in 10-20 ml of 5% dextrose	D-AmB endobronchial or percutaneous	3.6 months	Effective topical treatment	1993	Original article

A. fumigatus: *Aspergillus fumigatus*, *A. niger*: *Aspergillus niger*, *S. prolificans*: *Scedosporium prolificans*, AmB: Amphotericin B, L-AmB: Liposomal-AmB, D-AmB: Deoxycholate-AmB

administrated every treatment by dissolving L-AmB in distilled water at 10 mg/mL. The procedure was conducted once a week in the outpatient department for 4 weeks, the L-AMB dose was increased to 200 mg/body, by the sixth stage of management, the fungus ball decreased in size, after the seventh treatment stage, the diameter had diminished to 14 mm. In the end, the aspergilloma disappeared at 2 months after the ninth round of topical L-AmB treatment. This treatment strategy is suitable for patients with pulmonary complications.[22]

Boettcher *et al*., 2000,[23] reported three patients with invasive aspergillosis, who got combined antifungal management with systemic, aerosolized, and topical AmB, administrated bronchoscopically. In the first case, *Aspergillus fumigatus* was detected and 50 mg of conventional AmB used. In case two, *Aspergillus flavus* was isolated.

In the third case, a 46-year-old male developed necrosis 2 weeks after bilateral lung transplantation, 5 weeks later, culture showed *A. fumigatus* from bronchoalveolar lavage The patient received 2–3 mg L-AmB (0.5 mg/ml) aqueous solution administrated bronchoscopically once a week for a total of 4 weeks, resulting in a progressive reduction of secretions at each control bronchoscopy, successfully treatment achieved at 4–8 months after lung transplantation.[23]

Yamada *et al*.[24] demonstrated that 12 patients with aspergilloma treated with intracavitary antifungal agents from 1988 through 1992 by endobronchial or percutaneous approach. The AmB management performed in seven patients by dissolving AMB in 10–20 ml of 5% dextrose.

Persons with effective topical treatment had a shorter mean period of the disease course (3.6 months) than the less effective group (44.4 months). This study suggested that the old mycetoma was not effective to antifungal agents, so early diagnosis and therapy are demanded to achieve a better treatment effect.[24]

Conclusion

Pulmonary mycosis is one of the most common lethal problems that make patients under serious risks of life-threatening. Topical AmB formulas are a promising way to develop effective management of the refractory fungal lung mycosis. Using AmB in modern branches and new applications is demanded, because AmB is a potential antifungal agent with rare resistance, as well as its broad-spectrum activity toward many fungal infections, more studies about topical AmB pulmonary formulas are recommended.

Topical treatment of pulmonary fungi is urgent when systemic drugs are ineffective, for patients with fungal pulmonary complications, and when the operation is inappropriate for patients.

Some formulas of AmB utilized in the treatment of pulmonary mycosis as D-AmB and L-AmB, the topical application of these formulas are promising as additional therapeutic options in the management of bronchial mycosis as aspergillosis and other fungal infections in the lung. Anyway, this branch of treatment demanded more accurate information as dose frequency and adjustment of bronchoscopic administration need to be evaluated.

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Conflicts of interest

There are no conflicts of interest.

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