Review Article:

Amphotericin B, the Wonder of Today's Pharmacology Science: Persisting Usage for More Than Seven Decades

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ABSTRACT

Background: Despite several available topical and systemic antifungal drugs for the treatment of fungal infections, Amphotericin B (AmB) is still one of the most common first-line choices in treating systemic fungal infection for more than seven decades after its discovery.

Objectives: Amphotericin B which belongs to the polyene group has a wide spectrum of *in vitro* and *in vivo* antifungal activity. Its mechanism of antifungal action is characterized by creating a pore in the fungal plasma membrane leading to cell death.

Methods: In addition to the old formula of deoxycholate-Amphotericin B (D-AmB), three lipid formulas have been developed to reduce the adverse effects of conventional AmB (D-AmB) in the human body and increase its therapeutic efficacy. All of the known available formulas of AmB are administrated via intravenous injection to treat severe systemic fungal infections, while the development of the topical formula of AmB is still under preliminary research. Numerous pharmaceutical formulas of systemic and topical applications with clinical uses of AmB in just humans, not *in vitro* or animals model, against various fungal infections are discussed in this review. Topical AmB formulas are a promising way to develop effective management and to reduce the adverse effects of intravenous formulas of AmB without laboratory monitoring.

Results: The wonderful pharmacological properties of AmB with its prolonged use for about seven decades may help researchers to apply its unique features on other various antimicrobial agents by more understanding about the AmB mechanisms of actions.

Conclusion: Amphotericin B is widely used intravenously for the treatment of systemic fungal infection, while the topical formula of AmB is still under experimental study.

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1. Introduction

Amphotericin B (AmB) is an agent used for several decades in treating various human fungal infections. Opportunistic systemic fungal infection is the most common type of fungal infection mainly treated by AmB [1]. Amphotericin B is one of the most common types of antifungal drugs used for the treatment of various systemic fungal infections in the human body since many decades ago [2, 3].

The most acceptable mechanism of antifungal action of AmB is pore formation in the fungal plasma membrane [4-8]. Deoxycholate-AmB (D-AmB) is an old form of AmB used for the treatment of various systemic fungal infections [8]. It has diverse side effects represented by nephrotoxicity [9]. Thus, new lipid formulas were developed in 1990 [10]. Recently, the main available lipid formulas of AmB are liposomal amphotericin B (L-AmB), Amphotericin B lipid complex (ABLC), and Amphotericin B colloidal dispersion (ABCD) [8, 11, 12].

At present, many studies focus on the topical preparation of AmB as eye drop [13], gel [13], solution [14], or nanoparticles drug [15]. Treatment with topical AmB may not always yield satisfying results as with ordinary forms of this drug in the treatment of fungal infection. However, some topical applications of AmB gave promising outcomes with complete healing, especially in certain cases not responded to conventional therapy. This review is trying to summarize the potential effects of AmB in treating the systemic fungal infection as well as new wonderful topical applications of AmB in humans.

2. Materials and Methods

To conduct a review article of the potential effects of AmB in treating the human systemic fungal infection and its newly topical applications, the databases of Scopus, Embase, PubMed, Google, Magiran, SID, Irandoc, were searched with the keywords of "Amphotericin B", "antifungal agents", "topical formula", and "systemic fungi infection." We searched all the short and extended articles that were scheduled to publish until November 2019.

General features and action mechanisms of AmB

Amphotericin B is naturally produced by soil actinomyces, streptomyces nodosus [16]. The common features of AmB are its yellowish color and aggregation nature with low solubility in water and many organic solvents, but solubility can be increased at pH<2 or >11 [10]. For over five decades, the unique structure of AmB is still useful with high clinical effectiveness to treat numerous fungal diseases in the human body [2, 3] (Figure 1).

Low fungal resistance and broad-spectrum antifungal activities are the most valuable pharmaceutical characters that encourage continuous usage of AmB [17]. Despite the wide clinical use of AmB for more than five decades, fungal resistance has been rarely reported until now compared with other antifungal agents [6, 7, 18, 19]. Like other common drugs, AmB has some side effects that may prevent its use even in the event of dangerous systemic fungal infections. Nephrotoxicity is the major side effect of chronic use of more than 35 mg/d of AmB [9]. It also influences the liver's metabolic capacity through interaction with hepatic cytochrome P450 [20].

There is no clear idea 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 adhering activity of AmB to the ergosterol of the fungal cell membrane causing dysfunction by forming pore ion channels [4-8]. Pore formation may inhibit fungal glycolysis and quick efflux of K+ and Mg+ions inside fungal cells which increase the acidity and consequently fungal cell death [16] (Figure 2).

The mechanisms of L-AmB begins when the liposomal vesicle attaches to fungal cells in the infection site, then release of AmB from holding vesicle to adhere to the ergosterol of the fungal cell membrane and damaging it [8].

Another mechanism of Amphotericin B is by the production of free radicals inside fungi [21], thereby leading to oxygen depletion and superoxide anion that affects the cellular pathways of fungi [22]. Moreover, AmB has immunomodulatory properties that induce a pro-inflammatory response that protects immunocompromised persons [6].

History of AmB and formula development

AmB was isolated from Streptomyces nodosus in the soil of the Orinoco River region of Venezuela during the 1950s. Deoxycholate-AmB (D-AmB) is the first form of AmB developed in 1955 to use against systemic fungal infections [8]. It was quickly approved to use clinically by the FDA in 1958 despite its unknown structure due to its broad-spectrum antifungal activity [3]. In 1958, an intravenous formula of sodium D-AmB solution was presented in the markets with the name Fungizone-Squibb [6]. The original formula of AmB that contains deoxycholate-AmB has more side effects (presented by neph-

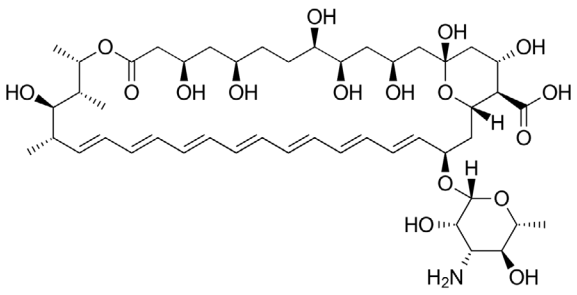

Figure 1. Structure of Amphotericin B

rotoxicity) than the recently developed lipid formula in 1990 which releases low concentrations of AmB in the human serum [10].

Liposomal Amphotericin B (L-AmB) is a developed form of the first AmB formula (D-AmB) to reduce the adverse effect [8]. L-AmB was presented to the markets in 1989 as the first drug to manage leishmaniasis when approved by the FDA in 1997 [10]. When L-AmB is used alone it reduces nephrotoxicity [23]. However, using L-AmB is restricted because of the expensive prices [21], and close monitoring required after 9 days of treatment beginning [24].

Amphotericin B Lipid Complex (ABLC) is sold under the brand name Abelcet® has a ribbon-like structure and 1:1 molar ratio with two phospholipids layers [10]. It was firstly approved by the FDA in 1995. ABLC has risks of hepatic disorders, while risks to kidney and lung are very low compared with other formulas of AmB [10]. It may be related to the large size of the ABLC that can be uptaken by macrophages with a high rate of clearance from plasma. The safe dose required for ABLC is 5 mg/kg/d [16].

Amphotericin B Colloidal Dspersion (ABCD) is another formula of AmB which is sold under the brand name Amphotec®. It has an equal concentration of cholesterol phosphate [10]. The diverse effect of ABCD utilization resembles that of D-AmB, but it differs from it by faster clearance from the plasma due to the macrophage engulfment [16].

Systemic usage of AmB

Recently invasive systemic fungal infections are the major cause of morbidity and mortality in immunocompromised individuals such as those with AIDS, transplant recipients, or tumor patients under immunosuppressive chemotherapy [10].

Systemic mycoses that are mostly treated by AmB, include those caused by opportunistic fungi such as Aspergillus spp., Candida spp., and zygomycetes as well as those caused by primary pathogenic fungi such as Histoplasma capsulatum, Blastomyces spp., Coccidioides immitis, Cryptococcus spp., and Paracoccidioides spp. [10, 25-27].

Intravenous injection of 3.39 mg/kg/d of ABLC in 23 patients with paracoccidioidomycosis resulted in a 100% curative rate [27]. Synergism with other antifungal agents could also increase AmB activity against pathogenic fungi as the combination with flucytosine against melanized

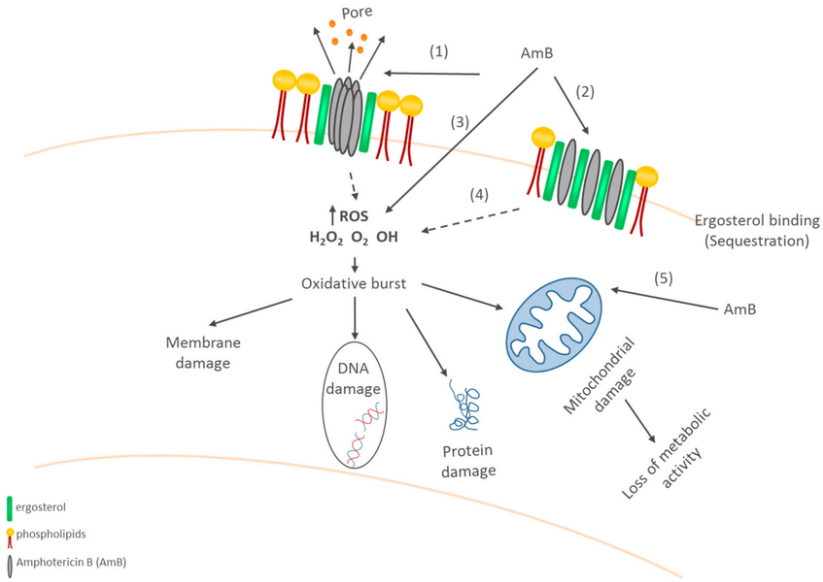

Figure 2. Action mechanism of Amphotericin B

Table 1. Topical usage of Amphotericin B (AmB) against fungi in human

Ref.	Fungi Type	Location of Fungi	AmB Dose	AmB Formula	Treatment Duration	Result	Year
[15]	Lichtheimia ramose	Postoperative rhinomaxillary mucormycosis	5 mg every 2 days	ABLC solution	5 weeks	Efficacious management	2012
[29]	Rhizopus spp.	Soft tissue infection	0.1% in D5W (0.1 g/100 mL)	D-AmB	8 weeks	Clear resolution	2014
[34]	Sporotrichosis	Cutaneous	AmB (0.1% w/w)	L-AmB jelly	8 weeks	Full recovery	2015
[35]	Scedosporium prolificans	Lung chromoblastomycosis	Three instillations once every 3 months	D-AmB Bronchial installation	2 year	Improvement was noticed	2018
[36]	Non-albicans Candida	Vagina	50 mg nightly	AmB vaginal suppositories	14 days	70% of women treated	2005
[37]	Scedosporium apiospermum	Corneal ulcers	0 .15 %	AmB eye drops	4 months	Good curative result	2013
[38]	Non-dermatophytes molds	Onychomycosis	2 mg/mL, 1 to 3 drops once daily	D-AmB drops	12 months	All patients treated except 1	2011
[39]	Different cutaneous fungi	Fungal cutaneous	0.1% twice daily	The gel of lipid-based AmB	2 weeks	All patients cured	2014
[40]	Scopulariopsis brevicaulis	Corneal ulcers	2 mg/mL hourly by day and 2 hourly by night,	AmB drops	15 days	Resolved ulcer	1994
[41]	Candida krusei	Vagina	3% daily	AmB vaginal gel	14 days	Symptoms are resolved	2016
[42]	Aspergillus fumigates	Bronchial aspergilloma	1%	Liposomal AmB	4 weeks	Aspergilloma disappeared	2014
[43]	Mucor species	vagina	3% 5 g daily	AmB	7 weeks	Disappearing of symptoms, culture-negative	2001
[44]	Candida glabrata	Vagina	100 mg once daily	AmB lubricating jell	2 weeks	Significant improvement	2001
[45]	Different fungal keratitis	Corneal ulcers	0.5 mg	AmB eye drops	31 days	corneal ulcers resolving	2010
[46]	Candida glabrata	Vagina	100 mg once Nightly	AmB vaginal applicator	14 days	Negative culture after 2 weeks	2003

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fungi of Chaetothyriales order that cause primary cerebral infections [28].

3. Results

A combination of both systemic and topical utilization of AmB was used in a 6-month-old infant with chemotherapy who suffered from bilineal leukemia, presented with a soft-tissue fungal infection due to Rhizopus spp. The successful result was obtained by systemic liposomal amphotericin B administration (10 mg/kg/d) and local 0.1% deoxycholate-AmB formula in D5W (0.1 g/100 mL). He completed the 8 weeks course of treatment with complete cure [29]. Topical modern applications of AmB provide a promising way of fungal treatment to reduce the adverse effects of intravenous usage of AmB [1].

4. Discussion

There are many advantages to using AmB as a topical treatment. Firstly, discovering new drugs or modification of old ones will increase the available limited number of antifungal drugs [30]. Secondly, topical preparations are cheaper than orally administered antifungal drugs and cause minimal adverse effects [31, 32]. Third, the application of the topical formula of AmB is considered safer to use and will not produce clinically high serum levels of AmB [32, 33]. Fourth, the failure of other antifungal agents to treat cutaneous fungal infection will be resolved as noticed when used topical AmB (0.1% w/w) against sporotrichosis [35]. Fifth, the quality of patient life will increase if new drugs are introduced to cure infectious lesions in a short time [30] (Table 1).

Compresses soaked in a solution of 5 mg ABLC was successfully used every 2 days until 5 weeks as a topical treatment during the postoperative period of a patient with rhinomaxillary mucormycosis caused by Lichtheimia ramosa [15]. Bronchial instillation is another type of tropical use of AmB. A person with lung chromoblastomycosis due to Scedosporium prolificans that appeared after lung transplantation failed to treatment by systemic itraconazole. However, the improvement

of bronchial obstruction was noticed after 3 instillations by AmB which was continuous as once every 3 months for 2 years [37]. Moreover, vaginal suppositories of 50 mg AmB showed successful management of 70% of 10 women with non-albicans candida vaginitis after given nightly for 14 days. Suppositories had also less local side effects and were well-tolerated [36]. Providing eye drop from topical AmB is successfully developed. Liposomal AmB (AmBisome®) as a 0.5% (w/v) eye drop is suggested to be an alternative to Fungizone® of 0.15% (w/v) D-AmB which cause cornea irritation. The stability of L-AmB new drop is quite good for 6 months at room temperature or temperature from +2°C to -8°C [13].

In some situations, topical AmB as eye drop may fail to treat fungal eye infection. So, a combination of AmB with another agent may enhance its therapeutic activity. Topical voriconazole and AmB eye drop for 6 weeks showed successful results in the treatment of women with keratitis caused by Scedosporium apiospermum after AmB failed alone to yield a positive curative result [37].

The efficacy of topical AmB solution was evaluated on the mold of non-dermatophyte onychomycosis. D-AmB was reconstituted in a 50:50 (v/v) mixture of dimethylsulphoxide and 2-propanol to be 2 mg/mL. One to three drops once daily applied topically to the infected nails and surrounding tissue. After 12-month management, onychomycosis was clinically treated in all patients, a mycological cure was detected except one patient [38].

Topical gel formulation of lipid-based amphotericin B (0.1%) was developed to treat adult patients with fungal cutaneous and or mucocutaneous infections. One hundred patients with recurrent cutaneous and or mucocutaneous infections after failure to respond to the standard therapy for fungal infection were treated with amphotericin B gel. The amphotericin B gel was used twice daily for two weeks in patients with cutaneous fungal infection and 7 days in patients of mucocutaneous fungal infection. At the end of the management, all patients with mucocutaneous infections were cured [39].

A combination of topical AmB and chloramphenicol was used to treat Scopulariopsis brevicaulis that was resistant to all antifungal drugs such as miconazole, AmB, clotrimazole, nystatin, and fluconazole. AmB was used as a single drug but without any cure. Management changed to topical amphotericin B 2 mg/mL plus chloramphenicol 1%, hourly by day, and 2 hourly by night, while other antibiotics were stopped. On the following day, the ulcer size was reduced. On day 11, the patient was asymptomatic and the ulcer had been resolved. On day 15, the amphotericin B and chloramphenicol drops were discontinued. The fungal culture of toe and fingernail clippings was negative [40].

The topical formulation of amphotericin 3% to treat Candida krusei vaginitis was developed by combining amphotericin B deoxycholate with lubricating jelly Aquagel®. Propylene glycol was used for lubricant with the intravaginal formulation daily for 14 days and the patient's symptoms were resolved [41].

Liposomal amphotericin B is clinically administered locally into the bronchial instillation of yellow fungus ball due to aspergilloma caused by Aspergillus fumigates. Systemic voriconazole for 2 months followed by itraconazole for 4 weeks was ineffective. The patient had a poor pulmonary function, so surgery was not possible. Eventually, 2.5 mg/kg of 1% L-AmB was administrated by dissolving L-AmB in distilled water at 10 mg/mL. The aspergilloma disappeared after the ninth dose of treatment [42].

Topical 3% amphotericin B 5 g daily has been used to treat a rare case of vaginitis caused by Mucor species in a healthy woman. Mucor vaginitis appeared refractory and resistant to flucytosine as well as an azole. The treatment outcome was the disappearing of symptoms and the patient became culture-negative [43].

Flucytosine (1 g) and AmB (100 mg) prepared in lubricating jell were used per vagina once daily to treat vaginal Candida glabrata. The patient had failed to respond to antifungals therapy. However, significant improvement, clinical resolving, and negative microbiological culture were observed after 2 weeks of treatment [44].

The topical formula of AmB 0.5 mg eye drops, plus a subconjunctival injection of fluconazole 2 mg was used for the treatment of fungal keratitis in 48 eyes. The eyes were divided into two groups: group one included 24 eyes treated with combination therapy and another group managed with topical AmB alone. Of 48 eyes, just 36 eyes had a positive spore result. Combination treatment was more effective than the use of topical AmB alone. Management by combination treatment in group 1 revealed the statistically significant result of corneal ulcers resolving in 20 eyes (83%), in comparison to group 2 with mono-therapy, which revealed healing in 16 eyes (67%) after 31 days treatment [45].

Candida glabrata resistant to antifungal drugs isolated from vaginal swabs was treated by using a vaginal ap-

plicator nightly, for 14 days of amphotericin 100 mg plus flucytosine 1 g in Aquagel. Her symptoms resolved and culture results for Candida glabrata were negative [46].

A total of 27 patients suffering from burn wounds were enrolled. Topically 5% mafenide acetate/amphotericin B (2 mcg/mL) solution was applied every 4 h to the excised burn wounds for at least five days. Serum amphotericin B level was detected every five days through treatment. The result was a topically prepared solution, applied to grafted burn wounds, which did not produce clinically high serum levels of amphotericin B. Based on this outcome, this topical regimen was considered safe [47].

Topical amphotericin B (3%) has extensively been used to treat visceral leishmaniasis, which was shown to be safe and efficacious in an animal model. In an open-label study, topical amphotericin B was used two or three times per day for 28 days, for the treatment of non-complicated cutaneous leishmaniasis in Colombia. The final cure was observed in 13 (32.5%) out of 40 subjects [48].

Experimental liposomal Amphotericin B was prepared with commercial components and tested *in vitro* in the mycological laboratory to determine efficacy, stability, and potential for topical application on burn patients. Data showed equivalent or superior *in vitro* activity of liposomal Amphotericin B versus unbound drug against Aspergillus fumigatus and superior physical and pharmacologic effect stability over time [49]. Another study described the case of a patient with an invasive aspergillus-associated postoperative wound infection. Successful treatment was achieved with a combination of surgical debridement and a novel approach involving the use of topical amphotericin B in addition to intravenous anti-fungal therapy [50].

A topical nano-liposomal formulation of 0.4% Amphotericin B was developed against Leishmaniasis. The new formulation was safe and worth to be tested in further studies and there was no adverse effect with twice a day application twice a day [51, 52].

5. Conclusions

Amphotericin B is widely used intravenously for the treatment of systemic fungal infection, while the topical formula of AmB is still under the experimental study. Using AmB in modern areas and new applications are required to discover new formulas or modify old ones to increase the available limited number of antifungal drugs. Topical AmB formulas are a promising way to develop effective management. They are cheaper, reduce the adverse effects of intravenous AmB, do not require the monitoring of AmB serum levels, and increase the quality of patient's life.

The wonderful pharmacological properties of AmB despite its prolonged use for about seven decades may help researchers to apply its unique features in other various antimicrobial agents. Because AmB is a potent and broad-spectrum antifungal agent, the researchers must know about its new applications and develop safer formulas with lower side effects that do not require laboratory monitoring.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article.

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Conflict of interest

The authors declared no conflict of interest.

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