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REVIEW ARTICLE **OPEN ACCESS**

Modern Approach to The Treatment of Opportunistic Mycoses By Lipid Forms of Amphotericin B of HIV-Infected Patients

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ABSTRACT
Infectious diseases caused by pathogenic strains of microorganisms, fungi, and protozoa, in people with low immune status, are considered opportunistic infections. Among fungal diseases, the most common are candidiasis and aspergillosis of various etiologies. These co-infections occur in patients with postoperative complications, hard bacterial, oncological, viral diseases, and immunodeficiency. Thus, these mycoses complicate the course of the underlying disease even more and require timely treatment. The analysis of the application of new, more effective antifungal drugs, lipid-associated forms of the macrocyclic polyene antibiotic amphotericin B in the treatment of candidiasis and aspergillosis in patients with HIV infection was presented in this review.
KEYWORDS: *opportunistic mycoses, candidiasis, aspergillosis, human immunodeficiency virus (HIV), polyene antibiotic amphotericin B, liposomal amphotericin, lipid complex of amphotericin B*

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INTRODUCTION

Fungal infections or mycoses (Latin mycosis-fungi) make up a significant part of infectious diseases. Deep mycoses occur by themselves under the influence of fungal microflora, as well as concomitant factors in some diseases. They are strongly associated with bacterial, viral, and oncological diseases, as well as with postoperative complications. These diseases are called co- infections in medical mycology because they often appear in parallel with the above diseases with low immune status of the body in the case of immunodeficiency. Invasive fungal infection or invasive mycoses are general terms for diseases caused by the invasion of living tissue by fungi. Unlike superficial mycoses, invasive mycoses invade internal organs, can disseminate throughout the body, and are associated with high rates of morbidity and mortality, particularly in the immunocompromised host. Invasive fungal infections are broadly categorized as either primary or opportunistic invasive mycoses. Primary invasive fungal infections are caused by fungal spores or conidia in the soil that, when disturbed, can become aerosolized and inhaled leading to infection, even in an immunocompetent patient. Because these fungi are often endemic to certain soil types and hence geographically restricted, primary invasive fungal pathogens are also known as endemic fungi. Systemic mycoses commonly occur and are increasing in incidence, largely because of human immunodeficiency virus (HIV) infections, the use of immunosuppressant drugs to treat patients with cancer or organ transplants. The action of efficient antibiotics is necessary for the full rehabilitation of the patients and increase of immune status of the body.

For many years the main antifungal pharmaceuticals were macrocyclic preparations with polyene structure of molecules. These drugs have the status of antibiotic. In the range of polyene antibiotics, amphotericin B is a more efficient drug used for candidiasis of different etiologies and mold mycoses[1]. There is the chemical structure of amphotericin B on the fig.1

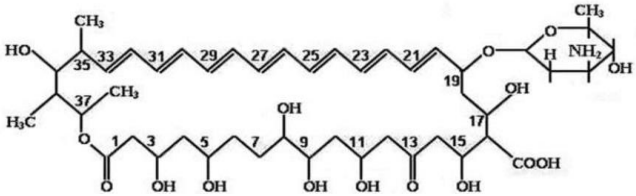


Figure 1. Chemical structure of amphotericin B.

Amphotericin B is active against most types of pathogenic fungi, including those that cause aspergillosis,

blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, and sporotrichosis. The drug is fungicidal or fungistatic depending on the concentration in body fluids and on the susceptibility of the causative fungus. Amphotericin B is highly toxic to humans and is therefore recommended only for serious, potentially fatal fungal infections. Amphotericin B was extracted from microorganism strain Streptomyces nodosus [2]. However, like all products of the vital activity of microorganisms, amphotericin B also loses its effectiveness over the years. Negative factors like toxicity and antibiotics resistance led to the search for new forms of antibiotics. The effect of amphotericin B methyl ether on the human immunodeficiency virus (HIV) was also studied in detail. In this case, the antibiotic contacted cholesterol and suppressed the formation of viral particles of the HIV type HIV-1[3]. Electron microscopic analysis showed that the methyl ester of amphotericin B significantly changes the morphology of virions. It was found that membrane cholesterol plays an important role in the formation of viral particles and the titer of infectivity. The study of the mechanism of action of the cholesterol-binding component showed that this antibiotic inhibits the replication of the HIV isolated from cell lines. Changes in replication caused by the antibiotic are simultaneously associated with high viral infectivity, which affects the formation of viral particles, although in this case, the antibiotic itself does not affect the infectious properties of the virus [3]. Already in the XXI century were developed and tested antibiotics of new generation with improved therapeutic properties against different types of candidiasis and aspergillosis infections. It is shown that it is easy to modify the molecule of amphotericin B. there were developed lipid-associated forms of amphotericin B – lipid complex of preparation and liposomal amphotericin B. These are more effective than initial amphotericin B and its clinical form, deoxycholate of amphotericin B. There is the model of deoxycholate of amphotericin B on the fig.2 and lipid-associated forms of amphotericin B on the fig.3

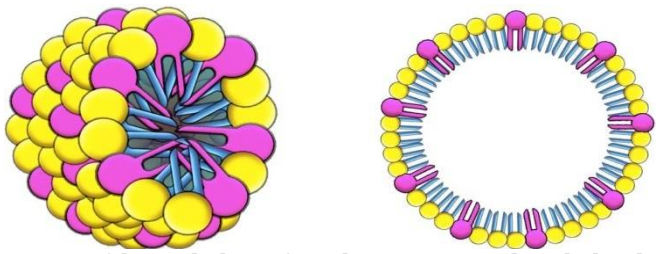
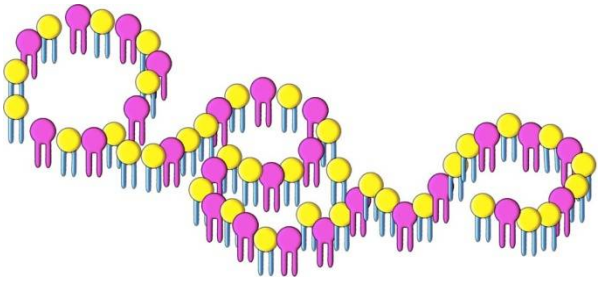
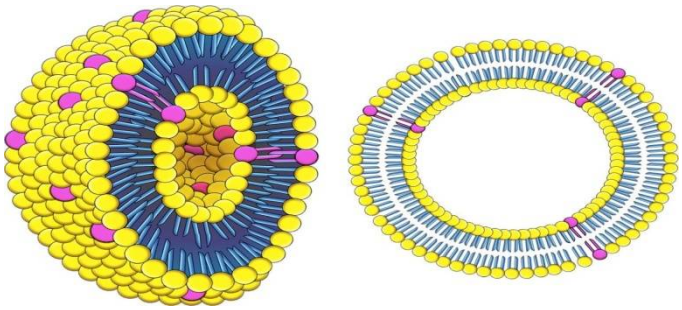


Figure 2. Structure of deoxycholate of amphotericin B in phospholipid membrane.



A. Lipid complex of amphotericin B



B. Liposomal amphotericin B

Figure 3. Lipid-associated forms of amphotericin B

It may be noted that new lipid derivatives of amphotericin B have low toxicity and high activity against candidiasis and aspergillosis. This factor makes it possible to use more appropriate drugs in the treatment of these diseases [4]. In this regard, the use of the liposomal complex of amphotericin B is most

preferable in invasive mycoses, which are a co-infectious pathology in bacterial, viral, and oncological diseases, as well as in postoperative complications. Patients with prolonged or severe neutropenia secondary to treatment with cytotoxic drugs against cancer or AIDs also require hard treatment of fungal infections, because they are at high risk for acute, life- threatening, systemic mycoses such as candidiasis and aspergillosis. In this regard, the use of the liposomal complex of amphotericin B is most preferable in invasive mycoses, which are a co- infectious pathology in bacterial, viral, and oncological diseases, as well as in postoperative complications.

CANDIDIASIS AT THE HIV-INFECTION

Candidiasis is a yeast fungal infection that often occurs in patients with malignant lymphomas, diabetes mellitus, or AIDS, as well as in patients receiving antibacterial, antitumor, corticosteroid, and immunosuppressant drug therapy. The causative agents of candidiasis are yeast- like microscopic fungi from the genus Candida. The photo of fungi Candida is presented on the fig.4

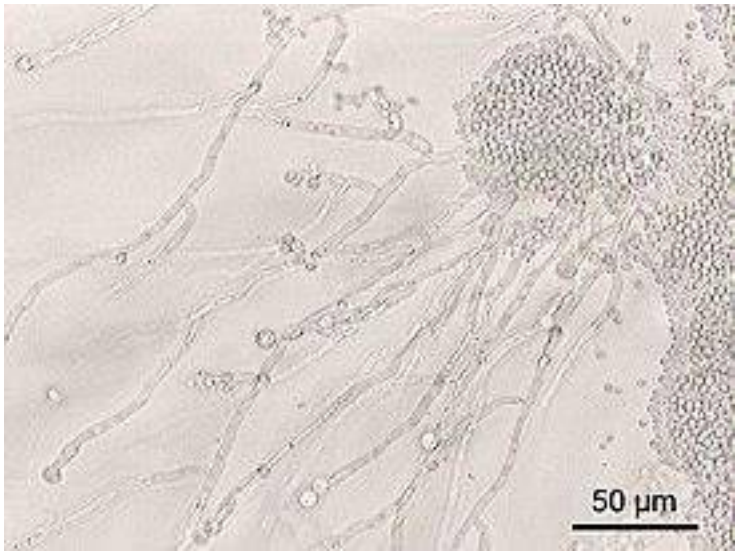


Figure 4. Photo of fungi Candida albicans

It was noted, candidiasis is one of the main opportunistic infections in AIDS patients [5]. These fungi can cause systemic lesions of various epithelial tissues and organs, creating a serious problem for patients with low immunity, including those infected with AIDS, since septic forms of the disease often lead to death [6].

The frequency of candidiasis as co-infectious factors in AIDS patients is 62-70% [5]. It should be noted that the pathogen not only affects the epithelium. Most of the complications of HIV infection are candidiasis, affecting the internal organs - esophagus, pharynx, intestines[5].

The most pathogenic strains are C. Albicans and C. Tropicalis among the existing 100 Candida species. I would like to note that with the creation of new, chemically modified antibiotics of a new generation and testing them on test cultures, the potential use of these drugs in clinical medicine has become possible.

In particular, the chemical modification of amphotericin B, which has the widest range of applications of macrocyclic drugs, was carried out on the initial form of the amphotericin Bmolecule. The modification was carried out using benzoxaboroles on the molecule either by the carboxyl group of the macrolactone ring at the C16 atom or by the amino group of the amino sugar.

A series of compounds were obtained - mono-and dimodified derivatives of amphotericin B. It showed that they exhibit high antifungal activity and in some respects exceed the initial amphotericin B in studying the biological activity of these drugs on Candida yeast cultures in vitro[7,8]. This is especially true for dimodifiedboryl derivatives, in which dimethylaminediethylamide was introduced into the molecule at the C16 atom [7]. Genetic engineering studies were also conducted with the Streptomyces noursei strain, which is the source of the antibiotic. As a result, a low-toxic liposomal drug amphotericin B was obtained by chemical synthesis and genetic engineering.

The study of the molecular-genetic mechanism of action of liposomal amphotericin showed that when liposomal amphotericin incubated Candida albicans biofilms, the MET3 gene responsible for fungal activity was blocked. Thus, it was proved that liposomal amphotericin B is highly effective against the action of Candida albicans fungi. The method of determining the expression of the MET3 gene can be used

for the treatment of candidiasis infections [7,8].
Due to the specifics of HIV-infected patients, the treatment of candidiasis requires the use of new highly effective, and low-toxic drugs. In this aspect, these properties today belong to the lipid forms of amphotericin B.

ASPERGILLOSIS AT THE HIV-INFECTION

Aspergillosis, the most common invasive mold infection worldwide, occurs in debilitated people, including those with leukemia, lymphoma, or acquired immunodeficiency syndrome (AIDS), as well as in people with neutropenia as a result of the disease process or drug therapy. Invasive aspergillosis is characterized by inflammatory granulomatous lesions that can develop in the bronchi, lungs, ear canal, skin or mucous membranes of the eyes, nose or urethra. Photo of Aspergillus fungi is presented on the fig.5.

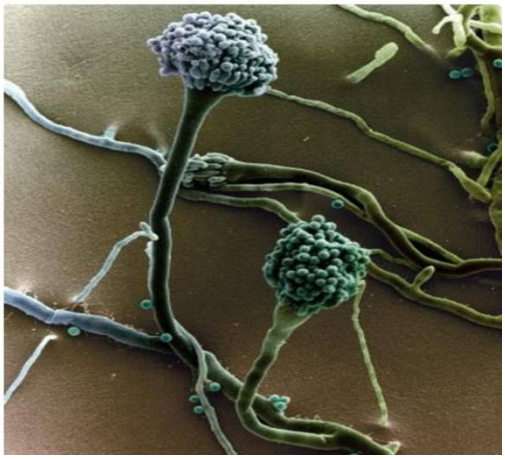


Figure 5. Photo of Aspergillus fungi.

Patients with AIDS have a wide range of lung damages of aspergillosis origin, including chronic cavities, invasive and bronchial forms of the disease, which distinguishes them from patients from other risk groups[9,10]. The causative agent of the disease is micellar fungi from the genus Aspergillus. Currently, during the pandemic, aspergillosis is the cause of 30% of the deaths of aspergillosis patients infected with the coronavirus.
As an invasive lung infection, aspergillosis can develop depending on two types of factors: environmental factors and factors related to the patient's condition. Since the 80s of the last century, cases of aspergillosis have become much more frequent. Often invasive aspergillosis is a concomitant factor in cancer patients[9] and, as it turned out, is severe in HIV-infected patients, especially in children. A high mortality rate was recorded in children with pulmonary aspergillosis infected with HIV [10-12]. Clinical studies of children with this diagnosis revealed febrile phenomena, immunosuppression, and infiltration in the lungs. Drug treatment in these cases depends on the toxicity and effectiveness of the drugs used.

THE USE OF LIPID-ASSOCIATED FORMS OF AMPHOTERICIN IN THE TREATMENT OF CANDIDIASIS AND ASPERGILLOSIS

Some derivatives of amphotericin B in liposomal form have been developed. These are lipid complexes and colloidally dispersed forms [4,7,8]. New liposomal derivatives of amphotericin B have low toxicity and high efficacy [4,7,8]. Amphotericin B destroys pathogenic fungi by binding to the ergosterol of the fungus. By modifying the structure of amphotericin B, it is possible to obtain a derivative that would have the ability to bind to ergosterol, but not to cholesterol. Liposomal drugs, such as ambizom, abelset, and amphocil, have been developed based on amphotericin B [4]. Liposomal forms of amphotericin B were formed based on egg lecithin because lecithin is a natural antioxidant and it increases the plasticity of cell membranes. They were studied for Candida at the molecular-genetic level after incubation of biofilms with amphotericin B solution and its experimental liposomal form [7,8].
The microtitration method was used to check the expression of the MET3 gene, which is one of the key genes that control biofilm formation [7,8]. As a result of determining the minimum inhibitory concentration of liposomal amphotericin B, it was found that the use of the liposomal form of amphotericin leads to a decrease in its minimum inhibitory concentration by 8-12 times and more

effective inhibition of Candida albicans fungi compared to the initial amphotericin B [7,8]. The effectiveness of inhibition of activity depended on the composition of liposomes and their charge. Liposomal amphotericin B and the liposomal complex of this antimycotic are the main and most commonly used lipid forms of amphotericin B compared to the colloid-dispersed form of the drug. They are also active against fungal infections as the original drug, but are significantly less nephrotoxic.

From a chemical point of view, these two drugs are completely different. Thus, the lipid complex of amphotericin B consists of amphotericin B and phospholipids and has a size of about 2-5 μm. Liposomal amphotericin B is a capsule of phospholipid liposomes, which contains amphotericin B inside. In this form, liposomes with an antibiotic can remain in the bloodstream for quite a long time [13]. As for the penetration of these drugs, the amphotericin B lipid complex is a ribbon-like structure that is rapidly absorbed by phagocytes, and as a result, higher concentrations of amphotericin in the blood and an increase in the penetration of the amphotericin B lipid complex into tissues, especially lung tissue, are recorded [14].

Pre-clinical researches showed that preparation is concentrated in the liver, spleen, and lungs and in a lesser extent in the bone marrow [14-16]. To compare these two drugs, it should be noted that most of the amphotericin B in the liposomal form of amphotericin at the intravenous injection administration is stored in the liver and spleen, while a smaller part is stored in the lungs and kidneys [16]. That is, the concentration of amphotericin B in the lungs after injection of the amphotericin B lipid complex [13, 15] is higher than after injection of liposomal amphotericin B [4, 15].

RESULTS AND DISCUSSION

The experimental results show that the use of liposomal antimycotics is highly effective against Candida and Aspergillus fungi and make it possible to predict their use to increase the effectiveness of the pharmacological action of antifungal drugs and reduce their therapeutic dose.

The use of lipid-associated forms of amphotericin B significantly reduced the risk of mortality from any cause compared to the initial amphotericin [4]. The advantage of the lipid forms of amphotericin B is to reduce the number and severity of side effects typical of the clinical therapeutic form of the antibiotic, that is, amphotericin B deoxycholate [17]. If it is necessary to prescribe amphotericin B, the choice should be based primarily on clinical efficacy.

CONCLUSION

Due to the effectiveness and low toxicity of the lipid-associated forms of amphotericin B in comparison with the deoxycholate of the original drug, we would like to note the possibility ofusing the lipid complex and liposomal amphotericin in candidiasis and invasive bronchopulmonary aspergillosis.

This review provides a comprehensive analysis of these drugs based on the most up-to-date experimental data of interest to HIV-infected patients because such opportunistic infections complicate the course of the disease and their treatment. Lipid-associated forms of amphotericin B can be recommended and used as more effective and low-toxic drugs in the fight against opportunistic infections.

REFERENCES

1. Baghirova A.A., Ragimov N.R. (2020) // J. of Integrated OMICS, Portugal, v.10, issue 1, pp. 31-34. doi: 10.5584
2. Gold W., Stout H.A., Pagano J.F., Donovick R. (1956) // In vitro studies. Antibiot. Annu., pp.579-586
3. Waheed A.A., Sherimay D. Ablan, FerriSoheilian, KunioNagashima, Akira Ono, Carl P.Schaffner,Eric O. Freed. Inhibition of human immunodeficiency virus type 1 assembly and release by the cholesterol-binding compound amphotericin B methyl ester: evidence for Vpu Dependence // J. Virol., 2008, v.82, №19, pp.9776–9781
4. Cavassin F.B., Bau-CarneiroJ.L Vilas-Boas R.R.,Queiroz-Telles F. Sixty years of Amphotericin B: An Overview of the Main Antifungal Agent Used to Treat Invasive Fungal Infections //Infect Dis.Ther., 2021, doi.org/10.1007/s40121-020-00382-7
5. Rakhmanova A.G., Bubochkin A.B., Vinogradova A.N., Dmitriyeva M.I., Agamaliyeva A.D. Candidiasis of HIV-infected patients // "ÄIDs and immunosuppression", 2015,т.7, №1, pp. 60-68. https://doi.org/10.22328/2077-9828-2015-7-1-60-68 (In Russian)
6. Sepkowitz K.A. Opportunistic Infections in Patients with and Patients without Acquired Immunodeficiency Syndrome Clin Infect Dis., 2002, v. 34, № 8, pp. 1098-107. doi: 10.1086/339548
7. Tevyashova A.N., Korolev A.M., Trenin A.S., Dezhenkova L.G., Shtil A.A., Polshakov V.I., Savelyev OY, Olsufyeva EN. New conjugates of polyene macrolide amphotericin B with benzoxaboroles: synthesis and properties // J.Antibiotics, 2016, v. 69, № 7, pp. 549–560.
8. Tevyashova A.N., Olsufyeva E.N., Preobrashenskaya M.N. Design of dual action antibiotics as an approach to search for new promising drugs // Russ Chem. Rev., 2015, v. 84, №1, pp.61-97.
9. Klimko N.N. Invasive aspergillosis of oncological and hematological patients // Oncohematology, 2006, № 1-2, pp. 98-107 (In Russian).
10. Agamaliyeva A.D., Karayev Z.O. Invasive aspergillosis of HIV-infected patients. Proceedings of the IV National

Congress of Azerbaijan on Allergology, Immunology and Immunorehabilitation- Baku, 2012, pp. 36-37.
11. Pursell KJ, Telzak EE, Armstrong D. Aspergillus species colonization and invasive disease in patients with AIDS. ClinInfect.Dis. 1992;14(1):141-48.
12. Zeichner S.L. Textbook of Pediatric HIV Care / ZeichnerS.L.,Read J.S. — USA: Cambridge University, 2005. — 600 p.
13. Smith P.J., Olson J.A., Constable D. et al. Effects of dosing regimen on accumulation, retention and prophylactic efficacy of liposomal amphothericin B. // J. AntimicrobChemother 2007, v.59, pp.941–51.
14. Clark J.M., Whitney R.R., Olsen S.J. et al. Amphothericin B lipid complex therapy of experimental fungal infections in mice. // Antimicrob. Agents Chemother. 1991, v. 35, pp. 615–21.
15. Olson J.A., Adler-Moore J.P., Schwartz J.et al. Comparative efficacies, toxicities and tissue concentrations of amphothericin B lipid formulations in a murine pulmonary aspergillosis model. // Antimicrob. Agents Chemother. 2006, v.50, pp. 2122–2131.
16. Paterson P., Seaton S., Prentice H.G. et al. Treatment failure in invasive aspergillosis: susceptibility of deep tissue isolates following treatment with amphothericin B. //J.Antimicrob. Chemother,2003,v. 52,pp.873–876.
17. Cordonnier C, Bresnik M, Ebrahimi R. Liposomal amphotericin B (AmBisome R) efficacy in confirmed invasive aspergillosis and other filamentous fungal infections in immunocompromised hosts: A pooled analysis. // Mycoses , 2007, № 50, pp. 205–209

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