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A COMPREHENSIVE REVIEW ON AMPHOTERICIN-B AS AN ANTIFUNGAL AGENT IN THE TREATMENT OF MUCORMYCOSIS

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ABSTRACT

Fungal infections (also known as mycoses) are less common than bacteria or viruses, but they have become more common in hospital Settings and among immunocompromised patients. In addition, fungi are more complex than bacteria or viruses. Mucormycosis is also known as black fungus. It is a fungus of the Mucorales type that is the source of the infection. People with low or weak immune systems or those whose bodies are less capable of fighting infection are more likely to experience it. Amphotericin-B is the first-line treatment, it is recommended for invasive mucormycosis infections, The incidence of Mucormycosis has become more common in the last few decades, mostly because there are more people with very weak immune systems. Mucormycosis is more common in developing countries, especially India. Most people who have uncontrolled diabetes mellitus (DM), the number of people with mucormycosis in Europe and the U.S. ranges from 0.01 to 0.2 per 100,000 people, while the number in India is much higher (14 per 100,000 population). Patients with a prior history of diabetes mellitus are more common likely to spread a fungal infection, or mucormycosis. In India, 1–9% of patients with mucormycosis have hematological malignancies (HM) as a risk factor, compared to 38–62% in Europe and the US. The most common clinical manifestations of mucormycosis include nasal and orbital involvement, central nervous system, pulmonary, skin and systemic involvement. One new clinical entity, isolated renal mucormycosis, has emerged in India, joining the more common rhino orbito-cerebral manifestations of uncontrolled diabetes.

KEYWORDS: Mucormycosis, Amphotericin-B, Antifungal agent, Fungi.

Fungal Infection

Fungal infections (also known as mycoses) are less common than bacteria or viruses, but they have become more common in hospital settings and among immunocompromised patients. In addition, fungi are more complex than bacteria or viruses. They have distinct ribosomes and a rigid outer cell wall that is densely packed with polysaccharides. The cell membrane, which contains ergosterol, is located within this cell wall (instead of cholesterol).[1] Most fungal infections are caused by (a) dermatophytes (which cause dermatophytoses, ringworm, or tinea) or candida spp. (which cause candidiasis in the oropharynx, vagina, and skin) or Pityrosporoum orbiculare (which causes Pityriasis versicolor or Tinea versicolor). Sporothrix spp. is the most common cause of mycoses on the skin (causing sporotrichosis). Fungi are living things that use oxygen and they can live as parasites or on their own.[2] There are more fungal infections, which is a growing public health problem. The number of people who die in the ICU because of an invasive fungal infection has gone up to 67%.[3] Standard antifungal treatments may not be able to be used as much because they are toxic, do not work as well, or cause drug resistance. Some of these standard therapies are being made in new ways to make them easier to absorb and work better. Several new antifungals have shown that they could be used to treat fungal infections. This antifungal agent can help to treat more fungal infections than what is currently possible. Still, a lot of work needs to be done to make antifungal medicines that work better and are less harmful.[4]

Factors responsible for fungal infection

The various causes of fungal infection include immobility, mucositis, use of antibiotics, radiation therapy, some immunosuppressive agents, as well as intensive care units.[2]

TYPE OF FUNGAL INFECTION

Superficial Infection

It is an infection that affects the most superficial layer of skin, known as the stratum corneum, as well as the cuticle that covers the hair shaft.[5]

Dermatophyte Infection

Dermatophytes are fungi with more invasive properties than those that cause superficial infections. This type of infection only affects keratinized tissues such as skin, hair, and nails. In most cases, they do not cause systemic disease.[5]

Subcutaneous Mycoses

These organisms get into the subcutaneous tissue through trauma and stay alive by making proteolytic enzymes and living in a microaerophilic environment because the damaged tissue has a lower redox potential.[5]

Systemic Mycoses

The respiratory tract is the primary site of infection in this illness (affecting more superficial tissues as well as internal organs).[6]

There is currently no vaccine or treatment available for mucormycosis, and it is difficult to avoid breathing in fungal spores due to the prevalence of fungi in the environment. Mucormycosis can be fatal if left untreated. It is possible that there are some strategies that can reduce the risk of mucormycosis in individuals who already have compromised immune systems. These include avoiding activities that involve close contact with soil, avoiding direct contact with water (damaged buildings or flood water after hurricanes and natural disasters), and avoiding areas with a lot of dust such as construction or excavation sites. Through clinical intervention, early detection can prevent abnormalities or deformities such as loss of vision, a crooked nose, or a misaligned jaw.[6]

Anti-fungal agents

These are drugs that are used to treat both mild and severe fungal infections. Most fungal infections are caused by the use of broad-spectrum antibiotics, corticosteroids, anticancer/immunosuppressant drugs, denatures, indwelling catheters and implants, and the spread of AIDS. Since the antiseptic era, there have been many topical antifungals available. This is because the above agents break down the body's defences. Amphotericin B and griseofulvin are two important antibiotics. Amphotericin B is used to treat systemic mycosis, and griseofulvin is used to help with a dermatophyte attack.[7]

Amphotericin-B

It is an antibiotic made by Streptomyces nodosus that kills fungi. It is a polyene macrolide that is amphoteric (polyene: containing many double bonds; macrolide: containing a large lactone ring of 12 or more atoms). When it is put on the skin, it is not absorbed in a good way. Since it is insoluble in water, a collodial preparation is given through an IV injection for systemic use.[8]

Caspofungin

It is the first and the prototype member of the class. It works mostly against Candida and Aspergillus. Candida strains that are not killed by azoles. It can be killed by caspofungin. It works differently than other antifungals because it stops the synthesis of -1, 3-glucan, which is a unique part of the cell wall of fungi. The toughness of the fungal cell wall comes from the way chitin (a fibrillar polysaccharide) and -1, 3-glucan are linked together. Caspofungin weakens the cell wall, which makes fungal cells more vulnerable to osmotic stress. The cells then die. Caspofungin is not taken by mouth; it has to be given through IV route. It moves through the body's tissues but does not get into the Cerebrospinal Fluid (CSF). Metabolism is a long process, and metabolites are passed out of the body in urine and faeces. The plasma half life is 10 hours. Caspofungin can be used to treat deep and invasive candidiasis, candidiasis of the oesophagus, and invasive aspergillosis that does not respond to other treatments. Because it is well tolerated, it is now being used more in patients with neutropenia and low immunity whose fever does not go away with antibacterial antibiotics.[7]

Griseofulvin

Griseofulvin was the first antifungal agent that could be taken orally and still be effective. It is effective against the majority of dermatophytes, such as Epidermophyton, Trichophyton, and Microsporum, among others, but it is ineffective against Candida and other fungi that can cause deep mycosis. Bacteria are also incapable of feeling pain. Dermatophytes actively concentrate it, and this property most likely contributes to the selective toxicity that it possesses. Resistance can be induced in vitro, and this is linked to a reduction in the ability to concentrate.[8]

Flucytosine (5-FC)

5-Flucytosine, also known as 5-FC, is a pyrimidine antimetabolite that can be taken orally to treat fungal infections. 5-FC is taken up by susceptible fungal cells, where it is subsequently converted to 5-FU by cytosine deaminase, which is then further converted to 5-fluoro-2'-deoxyurine-5'-monophosphate. The reason that 5-FC is able to act selectively is because mammalian cells contain relatively lower levels of cytosine deaminase than other cell types.[8]

Clotrimazole

It works well as a topical treatment for tinea infections like ringworm. After 2–4 weeks of applying it twice a day, 60–100% of people have been cured. Over 80% of people who had

athlete's foot, otomycosis, or oral, skin, or vaginal candidiasis saw improvement. It is most often used to treat vaginal vaginitis because a once-a-day application has a long-lasting effect. Most of the time, a 7-day course is used. For oropharyngeal candidiasis, 10 mg troche of clotrimazole is allowed to dissolve in mouth 3 – 4 times a day, or the lotion or gel is put in the mouth and swirled around for as long as possible. It also works well on skin infections caused by Corynebacteria. However, like most topical antifungals do not work well on scalp infections and athlete's foot (nails). Most people can take clotrimazole without any problems. Some people get local irritation that feels like stinging and burning. When used on the skin, there is no systemic toxicity.[7]

Ketoconazole (KTZ)

It is the first orally effective, broad-spectrum antifungal medication that is effective against dermatophytosis and deep mycosis. Gastric acidity facilitates oral absorption of KTZ because it is more soluble at a lower pH. It undergoes extensive hepatic metabolism. It is excreted in urine and faeces. Elimination of KTZ is dose-dependent, with $t_{1/2}$ ranging from $1^{1/2}$ to 6 hours.[7]

Fluconazole

The major benefits of fluconazole are its good penetration into the cerebral spinal fluid (CSF), ocular fluid, vaginal tissue, saliva, and nails, and its higher water solubility compared to ketoconazole. Additionally, the $t_{1/2}$ is approximately 24 hours, which is quite a long time. Oral or intravenous use is viable options for administration.[8]

Mucormycosis

Murcormycosis is also known as black fungus. It is a fungus of the Mucorales type that is the source of the infection. People with low or weak immune systems or those whose bodies are less capable of fighting infection are more likely to experience it. Through ingestion of contaminated food, untreated wounds, or inhalation, this fungus enters the body. Although these fungi are frequently found in soils, decaying matter, and on animal manure, they have no direct effects on people. It poses a risk to those with weakened immune systems. Because it is not easily communicable, it cannot be passed from one person to another through physical contact. Black fungus cases have suddenly increased recently. People who have any age, including premature infants, can be affected by black fungus.[9]

Incidence and Prevelance

The incidence of Mucormycosis has become more common in the last few decades, mostly because there are more people with very weak immune systems. Mucormycosis cases are being reported from all over the world, but the epidemiology of the disease seems to be different in developing & developed countries. In developed countries, the disease is still rare, and it mostly affects people with blood cancers. Mucormycosis is more common in developing countries, especially India. Most people who get it have uncontrolled diabetes mellitus (DM) So, the number of people with mucormycosis in Europe and the U.S. ranges from 0.01 to 0.2 per 100,000 people, while the number in India is much higher (14 per 100,000 population).[10,11,12]

Because diagnostic tests have very low sensitivity and it's difficult to get test samples from deep tissue and it's also difficult to figure out how often mucormycosis happens. Leading International Fungal Education (LIFE), a portal that measures the global burden of serious fungal infections, estimates that there are 10,000 cases of these infections everywhere except in India. If India is counted, there will be 910,000 cases in the world as a whole. Due to a lack of population-based studies, no one knows how often mucormycosis happens in India.[13,14]

Mucormycosis is found in anywhere from 0.005 to 1.7 billion people around the world. In India (0.14/1000), it was nearly 80 times more common than in developed countries. India has the most people with mucormycosis than any other country.[15]

Risk Factors of Mucormycosis

Patients with a prior history of diabetes mellitus are more likely to spread a fungal infection, or mucormycosis. People whose immune systems are vulnerable as a result of chemotherapy or any organ transplant surgery and who are receiving the immunosuppressive steroid medication are more at risk. Antifungal medications are already being used by people to treat the infections. In India, 1–9% of patients with mocormycosis have hematological malignancies (HM) as a risk factor, compared to 38–62% in Europe and the US.[16-19]

Pathogenesis of Mucormycosis

There are many mucorales in the environment because they are so common. Patients with neutropenia due to hematologic or solid malignancy, transplant recipients, iron overload patients, burn victims, and those with poorly controlled or uncontrolled diabetes mellitus (especially ketoacidosis) are at increased risk of contracting the pathogen. Common routes of

infection include inhalation of conidia, ingestion of food contaminated with the pathogen, and traumatic inoculation. Rhino-cerebral disease, for instance, can result from spores being deposited in the turbinates of the nasal cavity; pulmonary disease, when inhaled; gastrointestinal disease, when ingested; and cutaneous disease, when introduced through breached skin. Molds that cause mucormycosis transform into hyphal forms once they colonise environmental tissues. Invasion of fungal hyphae into blood vessels leads to tissue infarction, necrosis, and thrombosis. This leads to a condition known as neutropenia, or neutrophil dysfunction.[20]

Clinical Presentation/Signs & Symptoms

The most common clinical manifestations of mucormycosis include nasal and orbital involvement, central nervous system, pulmonary, skin and systemic involvement. One new clinical entity, isolated renal mucormycosis, has emerged in India, joining the more common rhino orbito-cerebral manifestations of uncontrolled diabetes. Two global registers were recently mined for data on paediatric mucormycosis. Rhizopus spp. (39.7%), Lichtheimia spp. (17.5%), Mucor spp. (12.7%), Cunninghamella bertholletiae (6.3%), and unspecified species (6.3%).[21]

For the proper diagnosis of rhinocerebral mucormycosis in diabetic patients, it is important to identify symptoms such as diplopia, sinus pain, proptosis, periorbital swelling, cranial nerve palsy, orbital apex syndrome, tissue necrosis, and ulcers of the palate.[22]

Anti-fungal agents used in the treatment of Mucormycosis

Mucormycosis is treated with antifungal medications and surgery. The cornerstone of the treatment of mucormycosis is early complete surgical removal whenever possible along with systemic antifungal therapy. It is strongly advised to start treatment right away in any immunocompromised patient who has symptoms of suspected mucormycosis.[23,24] Because of its high level of toxicity, amphotericin B deoxycholate should be avoided whenever possible, and alternatives should be used instead. Isavuconazole is recommended with a moderate dosage for the treatment of mucormycosis in patients who have not responded to other antifungal medications. There is also some evidence that suggests posaconazole, in the form of oral suspension, delayed-release tablets, and infusion, could be effective as a first-line treatment. The length of treatment for mucormycosis is unknown and is something that must be determined on an individual basis. The guideline group strongly endorses treatment until the permanent reversal of immunosuppression is achieved and there is a complete

response on imaging. This may be difficult to determine due to scarring and postoperative changes, but the guideline group strongly supports treatment until it is accomplished. In most cases, the duration of treatment ranges from several weeks to several months. The wide range is a reflection of the pattern of organs that are involved, as well as the competing risks posed by underlying conditions. It has been shown that long-term survivors are at risk for late relapse. When switching to an oral treatment, the use of tablets containing either isavuconazole or posaconazole that have a delayed release is strongly supported.[25,26]

Amphotericin-B [chemical name, IUPAC name, chemical structure]

Chemical Name: C_{47} H_{73} NO_{17} [27]

Amphotericin B is a macrolide polyene antifungal that is made by the soil actinomycete Streptomyces nodosus. It has been used in clinics. Since amphotericin B is not soluble in saline at a normal pH, it is made by mixing 50 mg of amphotericin B with 41 mg of the detergent sodium deoxycholate. This makes ribbon-like aggregates that form a mixed colloidal dispersion.[28]

IUPAC Name

(1R, 3S, 5R, 6R, 9R, 11R, 15S, 16R, 17R, 18S, 19E, 21E, 23E, 25E, 27E, 29E, 3 1E, 33R, 35S, 36R, 37S) -13-[(2R,3S,4S,5S,6R)] -4-amino-3,5 dihydroxy-6-methyloxan-2-yl]oxy-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1] nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid.[27]

Chemical structure of Amphotericin - B[27]

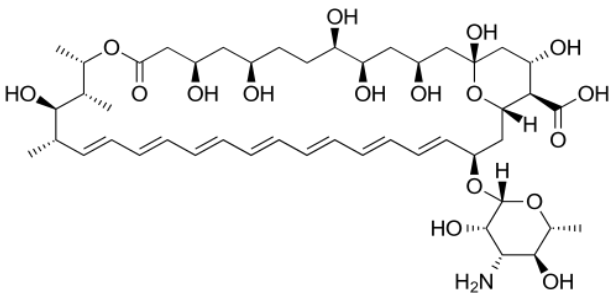

Figure 4: Structure of Amphotericin – B [29]

Streptomycetes and related actinobacteria are the main sources of polyenes, which are made of macrolactone cores with 3–8 conjugated double bonds.[29]

MOA of Amphotericin-B

Amphotericin B binds to ergosterol, a component of the fungal cell membrane, pores in the membrane are created, allowing monovalent ions (K^+, Na^+, H^+, CI^-) to leak out and killing the fungus. Amphotericin B "primary effect" as an antifungal agent is referred to as this. Van der Waals interactions control the Amphotericin B/ergosterol complex, which creates the pore on the membrane of fungal cells. Amphotericin B causes oxidative stress in the fungal cell, according to research, though it is unclear to what extent this is the case. Amphotericin A and B are the two types of amphotericin, but only B is used because it exhibits superior anti-fungal properties. Although Amphotericin A exhibits very little antifungal activity, it is almost identical to Amphotericin B.[30]

Amphotericin-B dose and dosage forms available in India

There are currently three different drug forms on the market. The AMB molecule itself is not soluble in pH 7 normal saline and thus is not absorbed when taken orally. Several formulations have been developed to increase its bioavailability when administered intravenously.[31]

Conventional amphotericin B (C-AMB)

Because Pure AMB cannot be dissolved in water, it is made with bile salt deoxycholate and administered intravenously. It is offered as an injection-ready lyophilized powder. A colloid of C-AMB particles mostly less than 0.4 m in diameter forms in water. Significant amounts of drug are removed by filters in intravenous infusion lines that catch particles larger than 0.22 m in diameter. Infusion solutions with electrolytes can make the colloid aggregate.[26]

Liposomal amphotericin B (L-AMB)

A small, unilamellar liposomal vesicle is used as a vehicle for the incorporation of AMB in this formulation. It is possible to achieve blood levels that are comparable to those achieved with C-AMB. Because LAMB can be administered in higher doses, it has been shown to produce blood levels that are higher than those obtained with C-AMB.[26]

Amphotericin B lipid complex (ABLC)

AMB is combined in a 1:1 ratio with two phospholipids, dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol, to create this structure, which has the appearance of a broad ribbon. When compared to C-AMB at the same dose, blood levels of AMB are significantly

lower with ABLC. A few mycoses, possibly with the exception of cryptococcal meningitis, are resistant to ABLC. The medication is authorised for deep mycoses salvage therapy.[26]

Oral Route

Amphotericin B can be taken orally to treat intestinal moniliasis, and it can also be applied topically to treat vaginitis, otomycosis, and other fungal infections. There is a formulation of amphotericin B that can be taken orally, but it is not very widely available. Oral preparations both have very less availability and very less solubility in the body.[32]

Intravenous

The bioavailability when administered intravenously is 100%. Patients are given a variety of formulations, including lipid-based formulations, which are thought to have fewer side effects and are more well-tolerated by patients.[32]

Pharmacological actions of Amphotericin-B

The AMB (amphotericin-B) has a strong affinity for ergosterol, which is found in fungal cell membranes. It forms pores that increase membrane permeability, resulting in rapid ion leakage and fungal cell death. Furthermore, it sequesters ergosterol from the lipid bilayer, causing fungal cell death. Polyenes also bind to cholesterol in host cell membranes, which is similar to ergosterol. As a result, AMB's selectivity of action is low, and it is responsible for systemic toxicity. Bacteria do not have antibacterial properties because they lack sterols. The AMB is active against a wide variety of fungi, including Candida spp., Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Sporothrix schenckii, Coccidioides spp., Paracoccidioides braziliensis, Aspergillus spp., Penicillium marneffei, Fusarium spp., Tor It is fungicidal at low concentrations and fungistatic at high concentrations. Dermatophytes are inhibited in vitro, but skin concentrations are ineffective.[7,26,32]

Adverse effects of Amphotericin-B [7,26,32,33]

Amphotericin B is well-known for its severe side effects, which can be fatal in some cases. As a result, proper medication administration must be taken care of and under the supervision of a doctor. It can cause mild to severe side effects such as fever and chills, as well as kidney damage in some cases.

Long-term side effects

Nephrotoxicity

Amphotericin B nephrotoxicity is extremely common, and there is reason to be cautious. The lipid formulation is far less toxic to the kidneys than C-AMB. Reduced glomerular filtration rate, renal tubular acidosis, hypokalemia (supplemental K+ is required in one-third of patients), magnesium loss, and inability to concentrate urine are all possible complications. After stopping therapy, nephrotoxicity often returns slowly and incompletely.

Anemia

During C-AMB treatment, hypochromic, normocytic anaemia is common. Lipid formulations reduce anaemia. It is caused by bone marrow failure and is largely reversible. It frequently responds to erythropoietin administration.

CNS toxicity

It only occurs after intravenous administration of C-AMB; headache, vomiting, arachnoiditis, nerve palsies, and other symptoms may occur. Intrathecal administration of 10 to 15 mg of hydrocortisone may reduce these reactions. Other common side effects include malaise, weight loss, and thrombophlebitis at peripheral infusion sites.[34]

Therapeutic uses of Amphotericin-B

As a first-line treatment, it is recommended for invasive mucormycosis infections, as well as those caused by rapidly progressing histoplasmosis, blastomycosis, coccidioidomycosis, penicilliosis, cryptococcal meningitis (in combination with 5-flucytosine), and certain aspergillus and candidal infections. Patients with invasive aspergillosis, extracutaneous sporotrichosis, fusariosis, alternariosis, or trichosporonosis who have not shown improvement while taking an azole antifungal should consider salvage therapy. Treatment of presumed fungal infection in immunocompromised hosts, febrile, and/or neutropenic patients is based on clinical judgement. (Due to their low toxicity, azalides and echinocandins are frequently prescribed.) Healing from Visceral Leishmaniasis Fungal endophthalmitis has been treated with intraocular injections following pars plana vitrectomy. Topical uses (otomycosis, keratitis, vaginitis, rhinomaxillary mucormycosis, and cutaneous leishmaniasis).[26,35,36]

Role of Amphotericin-B in Management of Mucormycosis

The first-line treatment for mucormycosis is a lipid formulation of amphotericin-B (liposomal AMB). Patients who are intolerant or unresponsive to Am-B can be given an oral suspension

of posaconazole. Despite liposomal Amphotericin-B pharmacokinetic and pharmacodynamic activity, doctors are turning to surgery to save patients lives due to the drug's poor pharmacoeconomic status. Liposomal Amphotericin-B limitations may be its high cost and limited market availability. It is effective treatment for mucormycosis. Isavuconazole is the first triazole drug to be approved by the US Food and Drug Administration (FDA) for the treatment of mucormycosis. It inhibits the fungal cell membrane CP450-dependent 14-lanosterol demethylase. As a result, cytotoxic sterols accumulate and reduce ergosterol production, which is required for the development of fungal cell membranes. It prevents fungal growth and replication, resulting in cell death. The main disadvantage of this drug, as with other azoles, is resistance. Resistance develops after repeated drug exposure. Overexpression of ABC transporters (ATP binding cassettes), mutation of the gene encoding the target enzyme (ERG11), and mutation of the ERG3 gene, which impairs azole-mediated cell membrane disruption, are examples of azole resistance mechanisms. As a result, it is a viable treatment option for mucormycosis patients who have other refractory disorders as well as posaconazole intolerance. Azoles primarily target ergosterol, which ensures membrane fluidity, permeability, and proper membrane protein function.[37]

Surgical Management

The high cost and limited availability of liposomal Amphotericin-B have prompted doctors to perform life-saving surgeries. Surgical debridement to remove all necrotic lesions continues to be the cornerstone of effective mucormycosis treatment . As soon as possible, extensive surgery should be performed, with an MRI or CT scan used to determine the extent of the tissues in question and the involvement of tissue margins. Surgical removal of necrotic lesions multiple times has shown to improve patient outcomes.[37]

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