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Parenteral systemic antifungal drugs and their clinical drug informations

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Abstract
Invasive fungal infections are an important cause of morbidity and mortality, especially in with patients' immune-compromised conditions such as AIDS, cancer, diabetes and burn patients, neonates, organ transplant patients. Therefore, treatment of fungal infections is still a major problem. The drugs used to treat these infections are very limited due to toxicity or inappropriate pharmacokinetic properties. Nowadays, there are three molecules class used in the clinical for these infections: polyenes, azoles and echinocandins. Amphotericin B and lipid formulations have been used for a long time in the treatment of these infections. The development of new triazole derivatives has provided different treatment options (fluconazole, voriconazole and posaconazole). In addition, three echinocandin derivatives (caspofungin, micafungin, and anidulafungin) have been approved for use in medication. The broad-spectrum triazoles and echinocandin derivative drugs have offer more effective and less toxic alternatives to antifungal therapy. This review provides a brief of the pharmacologic principles and clinical usage involved in treatment of systemic fungal infections.

Keywords: Antifungal, fungus, parenteral, systemic

Introduction

Funguses are eukaryotes that reproduce in single-celled colonies (yeast) or multicellular aggregates (molds). Pathogenic fungus such as Aspergillus, Candida and Cryptococcus cause infections in humans and it's called as mycosis. Fungal infections can be classified as superficial, cutaneous, subcutaneous, and systemic mycoses [1-3]. Fungal infections are opportunistic infections and they cause systemic infections in patients with immune deficiency such as organ transplants, implants, after cancer treatment, AIDS and intensive care patients [4,5]. The drugs should be given intravenously or orally in systemic infections.

Yeast and molds, which are systemic fungal infectious agents, cause primary or opportunistic infections. Pathogenic fungal spores are systemic infections resulting from inhalation and spreading through the internal organs. The most common fungal pathogens in systemic infections are Candida, Pneumocystis, Histoplasma, Aspergillus, Cryptococcus, Mucor, Rhizopus [6]. Invasive fungal infections involve various organs such as blood, heart, brain, bones. Candida is part of the normal microbial flora on mucosal surfaces and can cause local infections such as thrush in the mouth cavity and vaginitis. However, Candida species fungus may also cause fulminant invasive candidiasis and their mortality rate is estimated to be 30-40% [7].

C. krusei, C. glabrata, C. tropcalis, C. parapsilosis and C. albicans which are thought to be responsible pathogens in 50-70% of infections are the most isolated species from the invasive candidiasis [7]. However, in recent years, non-albicans Candida species have also been isolated at increasing rates.

Invasive fungal infections due to Aspergillus species account for 4-5% of all invasive fungal infections. Candida species are the third most common cause of bloodstream infections in intensive care units in the United States and the fourth cause of bloodstream infections [8]. Neutropenia secondary intensive and long-standing cytotoxic chemotherapy, corticosteroid therapy, prolonged antibiotic therapy, organ transplantation, or AIDS are the risk factor for invasive fungal infections [1-3].

Mechanisms of Action

The antifungal drugs are divided into fungicidal and fungistatic according to their effects. While fungicidal compounds kill fungus, fungistatic compounds prevent fungus from multiplying.

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Antifungal chemotherapy is based on biochemical differences between fungus and mammalian cells. Bacterial cells are prokaryote, mammalian and fungal cells are eukaryote. For this reason, the biochemical differences between mammalian and fungus cells are very limited. The biggest difference at the cellular level is that the fungus cell has cell wall on the cell membrane. In mammalian cells, there are only cell membranes. Sterols play an important role on enzyme and ion transport proteins in cell membrane. Fungus cell membrane sterol is ergosterol [9-11]. Azoles inhibit the conversion step of lanosterol to C14-demethyl lanosterol, and thus ergosterol cannot be synthesized. Polyenes bind to the double-layered lipid layer of the membrane and forms complexes with ergosterol. Echinocandins inhibit the enzyme β-(1,3)-D-glucan synthase and this condition leads to fungal cell lysis (Figure 1).

Classification of Parenteral Systemic Antifungal Drugs

Parenteral systemic antifungals that currently using in the market in our country are classified below [12]. Besides, the properties of the antifungal agents are given in Table 1 [13,14].

1. Polyenes antibiotics
Amphotericin B conventional, Ampothericin B liposomal

2. Azole derivatives
Fluconazole, Voriconazole, Posaconazole

3. Echinocandins
Caspofungin, Anidulafungin, Micafungin

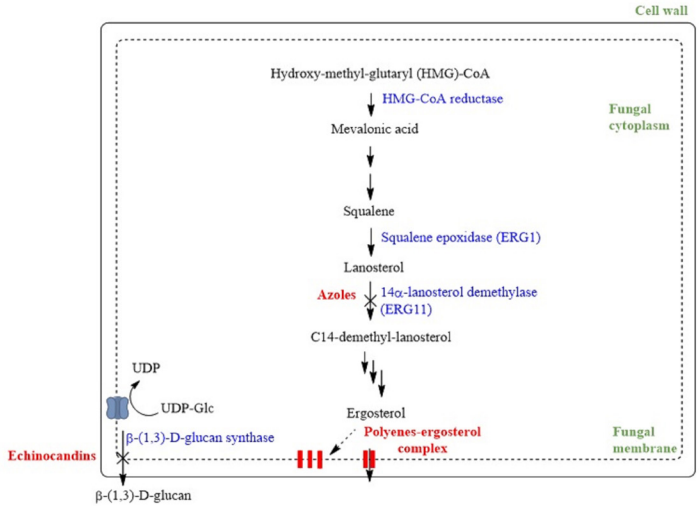

Figure 1. Antifungal agent targets

Amphotericin B

Amphotericin B is an antifungal antibiotic originally produced by Streptomyces nodosus. Amphotericin B is prepared as a colloidal suspension of sodium deoxycholate in order to use as injectable form since it is not water soluble [9]. It targets ergosterol in fungal membranes and binds to the double-layered lipid layer of the membrane and forms complexes with ergosterol. This complex leads to form pores, leak out the cytoplasm, and the oxidative damage results death of the fungal cell [15]. Amphotericin B cannot not be absorbed orally, so intravenous administration is essential. The comparisons of amphotericin B formulations have shown Table 2 [13-18].

Table 1. Antifungal agents

Generic name	Dosage forms	Dose	Elimination
Amphotericin B(conventional)	IV	0.5-1 mg/kg q24h	Unknown
Amphotericin B (liposomal)	IV	3-7 mg/kg q24h	Unknown
Caspofungin	IV	70 mg once and then 50 mg q24h	Hepatic
Micafungin	IV	100 mg q24h	Hepatic
Anidulafungin	IV	200 mg once and then 100 mg q24h	Chemical degradation
Fluconazole	IV, po	100-800 mg q24h	Renal
Voriconazole	IV, po	200 mg po q12h; 6 mg/kg IV q12h 2 doses, then 4 mg/kg IV q12h	Hepatic
Posaconazole	IV, po	200 mg qid initially and then 400 mg bid	Hepatic

IV: intravenous, po: per oral, q12h: every 12 hours, q24h: every 24 hours, bid: two times a day, qid: four times a day

Table 2. Comparison of Amphotericin B formulations

Property	AmBd	L-AmB
Molecular Structure	Micelles	Liposome
Size (nm)	0.035	80
Cmax (µg/mL)	1.5-2.9	83±35.2
AUC (µg.h/mL)	17.1-36	555±311
Half-life (h)	24	8.6±3.1
Infusion-related toxicity	+++	+
Nephrotoxicity	+++	+
Hepatotoxicity	+	++

AmBd: Conventional amphotericin B, L-AmB: Liposomal amphotericin B, AUC area under the concentration–time curve, Cmax peak plasma concentration. ±indicates range of values, Plus signs indicate degree of toxicity: +, mild; ++, moderate; and +++, severe.

Amphotericin B (Conventional)

Infusion-related side effects of amphotericin B are fever, chills, hypotension, pain, thrombophlebitis and anaphylaxis. To prevent these side effects, 1 mg of amphotericin B may be administered by intravenous infusion for 20-30 min. Nephrotoxicity is the major toxicity that limits the dose. Liposomal formulations has been developed to reduce toxicity and allow higher doses to be given. In addition to renal dysfunction, hypokalemia, hypocalcemia and hypomagnesaemia may occur, but these effects usually reverse when the drug is discontinued. It should be avoided concomitant drugs which have nephrotoxic side effects (13,17).

Reducing the production of erythropoietin may cause normocytic and normochromic anemia. Elevation of ALT, AST, ALP and bilirubin levels may be occur (14).

Amphotericin B can reconstituted only with dextrose solutions such as 5% dextrose, 10% dextrose. It is incompatible with 0.9% NaCl. After dilution in the form of 0.1 mg/ml dilution, it should administered as IV infusion for 2-6 hours (13).

For systemic fungal infections, after administering 0.25-0.5 mg/kg loading dose, It is used at a dose of 0.25-1 mg for 24 hour interval. (13,18).

Amphotericin B (Liposomal)

The infusion-related reactions and side effects, and those to protect against these side effects are the same as for conventional Amphotericin B (13,17).

It is prepared by diluting not exceeding 1-2 mg/ml in adults and 0.2-0.5 mg/ml in pediatric patients. It is prepared solution by diluting 1-2 mg/ml and 0.2-0.5 mg/ml for adults and pediatric patients, respectively. The duration of the infusion should be at least 2 hours [13,18].

Azole Antifungals

Azoles are the most common using antifungals in the clinic practice. Azol antifungals inhibit ergosterol synthesis and their target locus is cytochrome P450 lanosterol 14α-demethylase, encoded by the ERG11 gene which is part of the ergosterol biosynthetic pathway [19]. Sterol 14α-demethylase (14DM, CYP51) is an important microsomal cytochrome P450 for the biosynthesis of sterols required for membrane formation in eukaryotes and for the survival of numerous organisms [20].

They carry an imidazole or triazole ring as a pharmacophore azole group. These group compounds have broad spectrum of action, good oral bioavailability and low toxicity. Triazole derivatives have some advantages over imidazoles, such as their less effect on human sterol synthesis and their faster metabolization [21].

Drug interactions are important in the azole group of antifungal drugs. Since systemic azoles which inhibitors of various CYP450 isoforms, they interact with a large number of drugs, the result of which is the duration and toxicity of their own or other drugs [22,23]. For example; potential interactions between fluconazole and warfarin extend the duration of action of warfarin. The interaction of itraconazole and statins increases the potential toxicity of statins [10,11].

Fluconazole

Fluconazole which is a synthetic triazole antifungal is a fungistatic agent. It's using for invasive Candida infections, but it is resistant to C. krusei, C. glabrata and C. lusimiatae [14].

Their gastrointestinal side effects are nausea, vomiting, abdominal pain and diarrhea as well as cholestasis, AST, ALT, GGTP elevation, hepatic necrosis and liver failure. Liver enzymes should be checked regularly during the treatment. Regular blood count should be done in order to check leukopenia, neutropenia, thrombocytopenia and anemia. The other rare, side effects are dizziness, headache, drowsiness, seizures, coma can also be seen [14].

Dose adjustment is necessary for patients with renal insufficiency. If creatinine clearance is 50 ml/min or less of patients are required to be use 50% of the appropriate dose. After dialysis on dialysis patients, the appropriate dose should be applied immediately, and on days without dialysis dose adjustment should be made according to creatinine clearance [13,18].

If fluconazole is used more than 400 mg/day in women with fertility potential, birth control should be applied and should be continued until 1 week after the last dose of the drug [14].

The infusion rate should not exceed 200 mg/h and should be infused within 1-2 hours [13,18].

Voriconazole

It has been approved for use in Aspergillus and invasive Candida infections, including fluconazole resistant isolates [25].

Side effects such as hepatitis, cholestasis, fulminant liver failure as well as visual disturbances and hallucinations can also be seen. Dermatological side effects such as pruritus, rash, anaphylactoid reactions, Stevens Johnson syndrome, and photosensitivity may occur [14].

The dose used in invasive aspergillosis and severe fungal infections is 6 mg/kg, which is to be used intravenously for the first 24 hours, 12 hours interval. After first dose, 4 mg/kg is used with a 12 hours interval. The dosage is 6 mg/kg intravenously administered in the first 24 hours, with 12 hour intervals and then 3-4 mg/kg for 12 hour interval for invasive Candida infections. The average duration of IV therapy for aspergillosis is 10 days (2-90 days) [13,18,24].

Dose adjustment is required for kidney and liver failure. Patients with creatinine clearance below 50 ml/min should be avoided IV route, oral forms should be preferred. In patients with Child Pugh score A or B, the maintenance dose should be reduced by 50% by keeping loading dose. There are no dose-adjusted study data in Score C patients and hepatitis B or C patients [13,18]. In drug administration, infusion rate should not exceed 3 mg/kg per hour; infusion time should be over 1-2 hours [13,24].

Posaconazole

It has been approved for Aspergillus and invasive Candida infections. In vitro activity is shown in Zycomycetes and Aspergillus strains, which are highly resistant to other azoles and amphotericin B [25].

Gastrointestinal side effects such as nausea, vomiting, diarrhea and abdominal pain, as well as dermatological side effects such as pruritus and rash can be seen. Regular ECG follow-up should be done as it may cause prolonged QT interval and ventricular dysrhythmia. Other medications that prolong QT interval (levofloxacin, citalopram etc.) should be avoided. It may cause cholestasis or elevation of liver function tests. It can cause headache, dizziness, confusion [14,18].

Invasive Aspergillus and Candida infections are administered 300 mg intravenous infusion on the first day of 12 hours interval and 300 mg on the following days each 24 hours. The duration of treatment depends on the development of neutropenia or immunosuppression [13,18,26].

Patients with impaired renal function should be followed up regularly creatinine levels. Patients with GFR less than 50 ml/

min should avoid I.V. administration and should prefer oral administration [13,18].

It should be diluted with only 5% dextrose and 0.9% NaCl solution and stored in the refrigerator at 2-8 °C after preparation. Bolus injection should be avoided; duration of the infusion is 30 minutes for the peripheral venous and 90 minutes for the central venous [13,24].

There are no safety studies for tablets and oral suspensions under 13 years of age, and for IV form under 18 years [13].

Echinocandins

There are many components in the fungus wall that are unique to the fungus cell that are not found in mammalian cells. β-[1,3]-D-glucan forms more than 50% of the cell wall and is responsible for the structural integrity of the cell wall. Echinocandins are large cyclic peptides linked by a long chain fatty acid. They inhibit the β-(1,3)-D-glucan synthase. Inhibition of β(1,3)-glucan synthase leads to fungal cell lysis with cell wall destabilization and leakage of intracellular components [6,9].

Caspofungin, micafungin and anidulafungin are compounds of the echinocandin group approved in 2001, 2005 and 2006, respectively. Echinocandins are effective against many funguses, including Candida and Aspergillus. Because of their high molecular weight, these drugs are poorly absorbed from the gastrointestinal tract and are therefore only using intravenously. The toxicity of these molecules is low, slowly degraded, a daily injection is sufficient, and unlike other antifungal drugs, the interaction of echinocandins with other drugs is rare [6, 27-32].

Anidulafungin

It has been approved for use in invasive Candida infections [14]. There is no need for dose adjustment in kidney and liver failure [13,18].

It may cause hypersensitivity reactions such as itching, rash, and anaphylaxis. Depending on the rate of infusion, side effects such as fever, thrombophlebitis, nausea, vomiting, and myalgia may occur [14].

Administered at a dose of 50 mg for 24 hour interval after 100 mg IV administration on the first day for esophageal candidiasis is. 100 mg IV is administered as an infusion after a loading dose of 200 mg, with an interval of 24 hours sufficient for the other indications. The bolus should not be administered and the IV infusion rate should not exceed 1.1 mg/min [13,18].

Caspofungin

It has been approved for use in resistant Aspergillus and invasive Candida infections [14].

The loading dose is 70 mg for patients with invasive candidiasis, aspergillosis and febrile neutropenia and subsequent dose was determined as 50 mg/day i.v. every day at the same time [13,18].

There is no need for dose adjustment in renal failure. However, dose adjustment is required for liver failure. While dose adjustment is not required at Child Pugh 5-6, for level 7-9 following a 70 mg loading dose, 35 mg daily dose should be administered intravenously in the same hour every day. If Child Pugh is above 9, safety studies are not enough [13,18].

When caspofungin is prepared, it should not be mixed with solutions containing dextrose. The prepared infusion solution can be stored at room temperature for 24 hours and in the refrigerator for 48 hours. The duration of the infusion should be at least 1 hour [13,18,24].

Micafungin

It has been approved for treatment of invasive Candida infections [14].

There is no need for dose adjustment in kidney and liver failure. It may cause ALT and AST elevation and hypersensitivity reactions such as itching, rash, and anaphylaxis [13,18].

It may cause increase of BUN and creatinine. Depending on the rate of infusion, it may cause side effects such as fever, thrombophlebitis, nausea, vomiting, and myalgia [14,18].

150 mg is given as a 24-hour interval for the esophageal candidiasis, and 100 mg I.V. is infused as a 24-hour interval for other indications. The bolus should not be applied and the duration of the infusion should be at least 1 hour [13,18,24].

Conclusion

For the treatment of systemic infections, clinicians can use a large number of antifungal agents. However, in the selection and application of antifungal therapy, the selection of antifungal drugs and the properties of the drug should be accurately assessed. Since the pharmacokinetic and pharmacodynamic properties of each drug are different, the concurrent disease, the drugs used for these diseases, the clinical condition of the patient and the laboratory results should be considered in the treatment regimen. For an effective and accurate treatment, it is necessary to evaluate all the parameters together to achieve the patient-specific treatment regimen.

Competing interests

The authors declare that they have no competing interest

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