13. Antimycotic Drugs

FUNGI

Fungi are unique in the world of microbiology for a variety of reasons. They are larger than bacteria/viruses and have membrane bound organelles. They share the same ribosomal structure as human eukaryotic cells. But it is in their wall and membrane that fungi become truly inimitable. Composed of ergosterol the membrane of fungi is an important target for antimycotic drugs (fig. 13.1). Not only are some of the most potent drugs directed at the membrane, but inhibiting the synthesis of this barrier is also another excellent target in eradicating fungi. The complex carbohydrate cell wall, composed of chitin, glucans, and mannans is a further location in the fungal cell, which offers a chink in the otherwise formidable fungal armor. This discussion will begin with the outermost components of the fungal wall and gravitate inwards to provide a better understanding of the arsenal of antimycotic drugs at a physician's disposal.

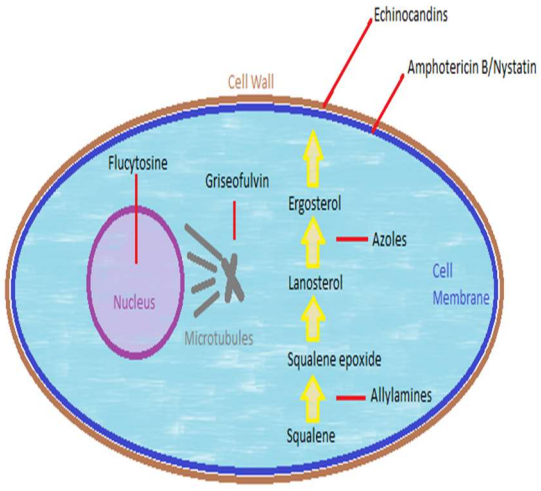


Fig. 13.1. Mycotic drugs and schematic diagram of their mechanisms of action.

ECHINOCANDINS

Echinocandins act via inhibition of cell wall synthesis (β-glucan). They accomplish this by inhibition of β-(1,3)-D-glucan synthase. By crippling the production of glucans the fungal cell is exposed to osmotic forces and subsequently dies (fungicidal effect). Caspofungin is the prototypical representative with anidulafungin and micafungin serving more specific roles. The main indication is candidaemia. Additionally, they can be used for treament of refractory oesophageal and systemic candidosis or in prophylaxis. The drugs are given IV due and also do not possess high CNS penetration thus making them virtually useless in CNS invasion of fungi.

Adverse effects:

The drugs tend to be low on the adverse effect spectrum when compared to other antifungals due to the lack of glucan in human cells. GI upset and flushing are the most commonly encountered side effects. The most severe, albeit rare, side effect is hepatotoxicity (especially with caspofungin) and thus liver function test should be conducted to ensure that liver damage is minimized.

AMPHOTERICIN B

When it comes to the most powerful antifungal drug, look no further than Amphotericin B (hereto referred as ampho B). Ampho B (a member of the polyene group) binds to ergosterol and creates pores in the membrane of fungal cells. These pores create channels in the cellular membrane that allow the leakage of components. This powerful effect renders it fungicidal across most clinically relevant concentrations. The indications of Ampho B are indicated in severe candida infections. It is a drug reserved for serious systemic mycosis, Cryptococcal meningitis, Candida and Mucormycoses. The drug can be given by a variety of routes (IV, aerosolized, etc.) but cannot

be readily given via oral route due to poor bioavailability.

Adverse Effects:

Despite its wide spectrum of activity the administration of amphotericin B comes at great cost. Cross reactivity with sterols in human cells make the drug very toxic. Fever, chills, and hypotension are among the least of the worries. The drug also causes nephrotoxicity leading to electrolyte imbalances (especially K and Mg), anemia, IV phlebitis and can even cause liver toxicity. The main solutions to decrease toxicity are hydration and a liposomal formulation. The liposomal formulation is of particular note as it not only decreases renal toxicity, but it can actually increase the potency of the drug as well.

NYSTATIN

Nystatin is a very similar drug to Amphotericin B. Both are members of the polyene family and both have the same mechanism of action. Nystatin proves to be an ever more toxic drug to the human body and as such is found only for topical use. The main indications are "swish and swallow" formulations for oral candidiasis (oral thrush), vaginal candidiasis or for diaper rash treatment. The drug can exhibit some hypersensitivity reactions (contact dermatitis) but these are extremely rare when topical or swish and swallow formulations are used.

ALLYLAMINES

The allylamines are one of two groups of drugs which act directly on ergosterol synthesis (the other being azoles). Allylamines inhibit the conversion of squalene to squalene epoxide by competing with squalene epoxidase. This action halts the production of ergosterol and thus creates osmotic damage to the fungal cell along with the buildup of squalene which is toxic to mycotic elements. The main representatives are terbinafine, naftifine and butenafine (each having a similar spectrum of activity). The drugs can be administered topically or orally for systemic use. The main indications are tinea infections for topical use and systemic use for onychomycosis and rarely systemic tinea infections.

Adverse Effects:

Effects are minor compared to some of the previously mentioned drugs. The main concerns are GI upset, headaches and hepatotoxicity, which should warrant further inspection with liver function tests. A rare taste and even visual disturbance have been noted but these are usually transient. Should they appear chronically then further workup, especially with an ophthalmologist is required.

AZOLES

Azoles are the largest group of antifungals currently in medical use. Their mechanism of action is similar to the allylamines but the ergosterol block is further. The drugs inhibit the action of 14-α-demethylase, a crucial step of converting lanosterol to ergosterol. The effects are similar to allylamines with osmotic damage and toxicity of previous constituents playing a big factor. The main group of azoles is split up into imidazoles (ketoconazole) and triazoles (the rest). Ketoconazole is used in blastomycoses/ histoplasmosis and is also used orally in mucocutaneous candidiasis and dermatophytoses. Fluconazole is 1st line for esophageal/invasive candidiasis. It is also used as suppressive therapy after amphotericin B/flucytosine is used for 10 weeks in cryptococcal meningitis. Itraconazole and voriconazole are used in a wide variety of candidiasis but especially for aspergillosis and sporotrichoses. Posaconazole is one of the newest azoles and has the broadest spectrum of action, including members of. Finally, Clotrimazole and miconazole are used topically for dermatophytic infections and candidal skin infections. Azoles are given topically and systemically as they have decent bioavailability.

Adverse Effect:

Due to the inhibition of 14-α-demethylase, a P450 enzyme, azoles have a wide spectrum of adverse effects. The strongest inhibitor is ketoconazole, a fact which makes it a seldom used antimycotic. This inhibition can cause liver dysfunction, toxicity and also decrease the metabolism of many drugs, causing their serum concentration to rise, sometimes to dangerous levels. Other side effects include testosterone synthesis inhibition (gynecomastia in men). Overall the azoles can cause QT prolongation and hepatotoxicity of varying degrees necessitating liver function test and EKG follow-up.

FLUCYTOSINE

Flucytosine is a peculiar antimycotic in that its origins arise from fluorouracil, a cytostatic cancer drug. Like its kin, flucytosine acts by inhibiting thymidylate synthase via conversion to 5-fluorouracil. This inhibits DNA and RNA synthesis in fungal cells. It can be used in systemic fungal infections but its most important use is alongside amphotericin B. As a combination the two drugs act synergistically and are first line treatment for Cryptococcal meningitis. The treatment lasts for 10 weeks and is switched over to fluconazole once the patient is afebrile. The dual combination should be used due to the propensity of fungi to develop resistance if flucytosine is used as monotherapy.

Adverse Effects:

Owing to its inhibition of DNA and RNA synthesis it is not surprising that flucytosine can also cause those effects in human tissue. When this occurs the resulting effect is bone marrow suppression which present as anemia, thrombocytopenia, leukocytopenia or any combination of the three. Caution has to be taken as the suppression may be irreversible. Even with cessation of the drug

GRISEOFULVIN

Griseofulvin is another specialty antimycotic. It acts by interfering with microtubule function to disrupt mitosis. This function is fungistatic in nature and thus is not preferred in immunocompromised patients. The drug concentrates in keratin containing tissues (like nails, hair, etc.) and is thus well suited for fungal infections arising in them. The drug is actually not active topically and must be taken orally for full effect. It is used to inhibit the growth of dermatophytes.

Adverse Effects:

Griseofulvin does not readily differentiate between human and fungal tissue and thus has a host of adverse effects. On the more benign side effects are headaches and slight confusion. More serious side effects are teratogenicity and carcinogenicity. Of special note is the activation of the P450 system. In an action opposite that of many azoles, griseofulvin can actually decrease the action of many drugs (warfarin, oral contraceptives, etc.) and thus should not be prescribed with them.

ANTIFUNGAL SUSCEPTIBILITY TESTING

The fungus is cultered on specific media with the antifungal antibiotic, the inhibition of the fungal growth can be assessed, and in this way susceptibility to the antimycotic agents can be determined. Fungi that are susceptible to a specific drug will not grow, and there will be a zone of inhibition of growth or no growth where this drug is present in high enough concentration.

The drug can be applied evenly on small disks, with the active compound oozing out into the culturing media. The media right below the disc will carry the highest concentration of the active compound, and then a concentration gradient will form around the disc. If there is a ring without fungal growth, a **zone of inhibition**, the cultured fungi are susceptible to the agent. The diameter of the zone of inhibition is then used as a measure of antifungal activity. This test is called **disc diffusion test**, and is only used in screening (figure 13.2 A).

The drug can also be applied onto stripes with descending concentration of the active agent. The lowest concentration that still inhibits fungal growth, the **minimal inhibitory concentration,** seen at the tip of the teardrop shaped inhibition zone can then be assessed. This test is called an **E-test** (figure 13.2 B) but minimal inhibitory concentration also can be determined by broth dilution method.

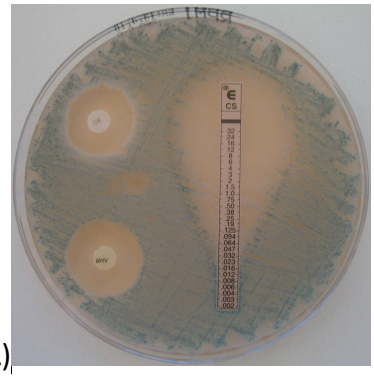
(A)  (B)

Figure 12.8. ***Susceptibility testing of antifungal drugs****. The molds on these pictures are growing freely on agar into which antifungal agents have not diffused. The two small rings on picture (A) represent the disk diffusion test, while the strip on the left (B) shows the E-test used in determination of the minimal inhibitory concentration.*

References

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