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**Antifungal drugs**

Fungal infection is called mycoses involving skin and subcutaneous tissue and rarely may cause systemic infection which are life-threatening. The fungi contains rigid cell wall consist of N-acetylglucosamine rather than peptidoglycan. Also fungal cell membrane contain ergosterol rather than cholesterol found in mammalian membrane.

**Antifungal for subcutaneous and systemic infection:**

* **Ketocanazole:**
* Fungistatic, block demethylation of lanosterol to ergosterol (inhibit cell membrane formation) so inhibit cell growth.
* Ketocanazole also inhibit cholesterol synthesis so inhibit cortisol and testosterone synthesis.
* It enzyme inhibitor, so ↓metabolism of other drugs.
* Teratogenic.
* Absorbed at acidic pH, so drug that ↑ pH like anti-ulcer agent ↓ absorption of Ketocanazole, so administration of acidifying agent like cola improve absorption of Ketocanazole.
* Not cross BBB.
* High plasma protein binding and short T 1/2 = 6 hours.
* Excreted by bile.
* Narrow spectrum anti-fungal.
* **Uses:**

1. Mucocutanous candidiasis.
2. Systemic infection except aspergillosis.
3. Hirsutism (due to ↓ testosterone synthesis).
4. Androgenic baldness.
5. Cushing syndrome.

* **Side effects:**

1. GIT disturbances.
2. Gynecomastia, ↓ libido, impotence and menstrual disturbance due to ↓ testosterone and adrenal steroid.
3. Hepatitis.
4. Drug interaction because it enzyme inhibitor.

* Note: the inhibition of testosterone and cortisol is a dose dependent (i.e. at higher doses inhibit these steroids).
* **Fluconazole:**
* Similar mechanism to Ketocanazole.
* Cross BBB.
* Less plasma protein binding.
* Not depend on gastric pH in its absorption.
* Excreted by kidney.
* Not enzyme inhibitor.
* Less side effect and longer T 1/2 (30 hours).
* Not block cortisol and testosterone synthesis.
* Teratogenic.
* Broad spectrum antifungal.
* **Uses**:

1. Candidemia.
2. Cryptococcus Neoformans.
3. Coccidiodomycosis.

* **Itracanazole:**
* Similar to Fluconazole but **differ by:**

1. Not cross BBB.
2. Long T1/2 (40 hours).
3. Excreted by bile.

* **Voriconazole:**
* Broad spectrum antifungal.
* Cross BBB.
* Used for invasive aspergillosis.
* Excreted by bile.
* Inhibit ergosterol synthesis.
* Not enzyme inhibitor.
* Not block cortisol and testosterone synthesis.
* **Caspofugin:**
* Its echinocandin class of antifungal.
* Inhibit cell wall synthesis by blocking the synthesis of D-glucan.
* Used for aspergillosis and candidiasis.
* Not absorbed orally.
* Highly plasma protein binding.
* It very expensive, as used as second line for treatment of systemic infection.
* Cause flushing due to histamine release.
* **Amphotercin B:**
* Its polyene macrolide antibiotic.
* Bind to plasma membrane ergosterol leading to formation of cell membrane pores so ↑ ion entrance and leakage of cellular molecules leading to cell death.
* It fungistatic and fungicidal depends on the organism and drug concentration.
* Not absorbed orally so given I.V. only.
* Highly bind to tissue protein.
* Less cross BBB.
* Excreted by urine and bile.
* **Uses:**

1. Systemic fungal infection.
2. Leishmaniasis.
3. Topical for fungal arthritis and corneal fungal ulcer.

* **Side effects:**

1. Toxic due to low therapeutic index and nephrotoxicity.
2. Fever and chill, so premedication by corticosteroid ↓ this side effects.
3. Hypokalemia and hypotension, these require K+ supplementation.
4. Anaphylaxis and convulsion.
5. Thrombophlebitis, this can be prevented by heparine.

* **Flucytosine:**
* Pyrimidine antimetabolite .
* It enter the cell membrane via specific permease enzyme (not found in human cell membrane), converted to 5-FdUMP (5-flurodeoxyride monophosphate) that inhibit Thymidylate synthetase so inhibit DNA formation.
* It fungistatic, it combined with amphotercine B for systemic fungal infection.
* Absorbed orally, cross BBB, excreted by urine.
* **Side effects:**

1. Pancytopenia and hepatitis.
2. Enterocolitis (due to conversion of 5-flucytosine to 5-flurouracil by bacterial flora).

**Antifungal for cutanous infection only**

Superficial skin infection caused by candida and dermatophyte (ring worm).

* **Terbinafine:**
* Potent antifungal for dermatophyte.
* ↓ Synthesis of ergosterol by inhibition of squalen expoxide enzyme.
* Higher concentration inhibits human cholesterol synthesis.
* Fungicidal for dermatophyte and candida.
* Absorbed orally, high plasma protein binding.
* T 1/2 200-400 hours.
* Excreted by urine.
* **Side effects:**

1. Hepatitis.
2. Visual disturbance**\***.

* **Griseofulvin:**
* Fungistatic, derived from penicillinium.
* Inhibit fungal microtubule and mitosis.
* Absorbed orally, this enhanced by fatty food.
* It enzyme inducer.
* It causes disulfarm like reaction with alcohol.
* It accumulated in newly synthesized keratinized cell.
* **Uses:**

1. Dermatophyte of skin and nail.
2. Cancer, because it ↓ mitosis of malignant cell, not the normal cell.

* **Side effects:**

1. Drug interaction.
2. Potentiate porphyria.

* **Nystatine:**
* Polyene antibiotic, similar to amphotercin mechanism.
* Not absorbed orally.
* Used for oral and intestinal candidiasis.
* Used topically for candida only.
* **Miconazole:**
* Very toxic systematically, so used topically for vaginal and skin candidiasis.

**Notes:**

* Patient allergic to penicillin should not take griseofulvin.
* **Immunosuppressant antibiotics:**

1. Erythromycin, roxithromycin, rifampicin.
2. Gentamycine, ampicillin.

* **Immunostimulant antibiotics:**

1. Imipenem.
2. Cefotizime.
3. Clindamycin.