Antifungal agents
Lecture 2

Ketoconazole

- The first orally active narrow spectrum azole available for the treatment of systemic mycoses
- Well absorbed orally as acidic environment favors its dissolution
- Only administered orally
- Bioavailability is decreased with H_2 receptor blocking drugs, proton pump inhibitors and antacids and absorption is impaired with food

- Ketoconazole is 84 % bound to plasma proteins
- It does not enter CSF
- Metabolized extensively in liver by cytochrome P450 (CYP3A4) and the inactive metabolites are excreted in bile
- Induction of microsomal enzymes by other drugs like Rifampicin reduces its blood concentration

- Ketoconazole is active against many fungi, including Histoplasma, Blastomyces, Candida, and Coccidioides, but not aspergillus species
- Ketoconazole is available in oral tablet, aerosol , cream and shampoo dosage forms
- The shampoo and aerosols foams containing Ketoconazole are highly effective in treating seborrheic dermatitis

- Ketocoazole inhibits adrenal and gonadal steroidogenesis (cortisol, progesterone, estrogens, and testosterone). This leads to menstrual irregularities in females, loss of libido, impotency and gynaecomastia in males
- Ketoconazole could be used in the management of Cushing's syndrome and Ca of prostate

- **Ketoconazole side effects:**

- Dose dependant nausea, anorexia ,vomiting
- Liver toxicity (main toxicity) is rare but may prove fatal
- Hair loss
- Inhibition of steroid biosynthesis, several endocrinological abnormalities may be evident as menstrual abnormalities, gynecomastia, decreased libido and impotency
- Fluid retention and hypertension
- Ketoconazole (as other azoles) is contraindicated in pregnancy

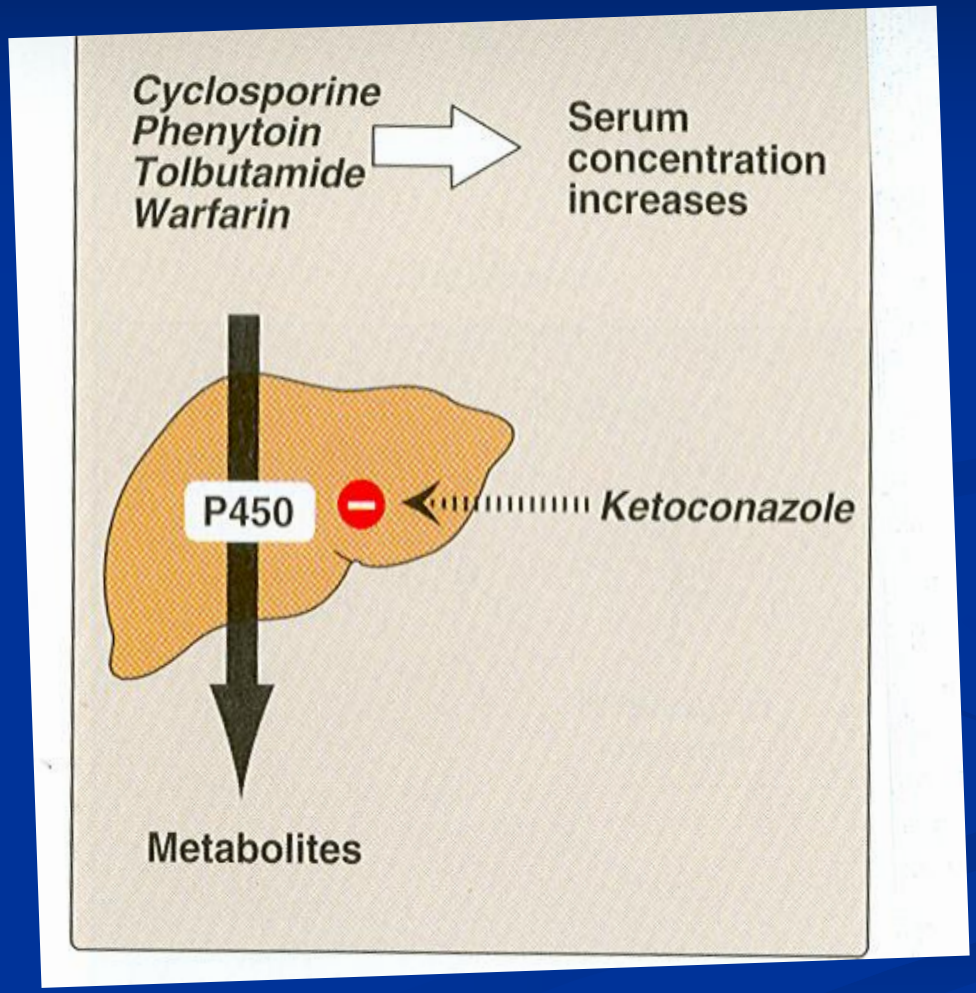
- **Ketoconazole drug-drug interactions:**

- Ketoconazole inhibits cytochrome P450 system, so it can potentiate the toxicities of drugs such as Cyclosporine, Phenytoin, Tolbutamide, and Warfarin, among others…

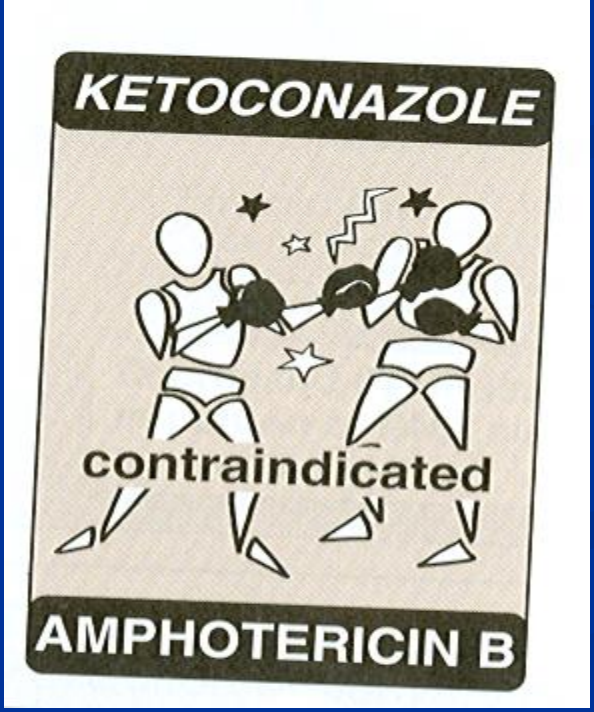
- Cyclosporine and Phenytoin inhibit its metabolism and hence increase Ketoconazole toxicity

- Warfarin and Rifampin increase its metabolism and hence decrease concentration (shorten its DOA)

- H_2 blockers, antacids, proton pump inhibitors and Sucralfate decrease its absorption


Cyclosporine
Phenytoin
Tolbutamide
Warfarin
Serum concentration increases
P450
Ketoconazole
Metabolites

- Ketoconazole decreases ergosterol in the funagal membrane thus, it reduces the fungicidal action of Amphotericin B



Triazoles

- The triazoles (Fluconazole, Itraconazole, Voriconazole) are newer antifungal agents, and are less toxic and more effective
- They damage the fungal cell membrane by inhibiting the enzyme demethylase
- They are selective
- Penetrate to CNS
- Resistant to degradation
- Cause less endocrine disturbances

Fluconazole

- Completely absorbed from GIT
- Excellent bioavailability by oral route including CSF
- Concentration in plasma is same by oral or IV route
- Bioavailability not altered by food or gastric acidity
- It has least effect on hepatic microsomal enzymes
- Drug interactions are less common

- Fluconazole easily penetrates CSF and is considered the drug of choice in cryptococcal meningitis and Coccidioidomycosis
- It can safely be administered prophylactically in patients receiving bone marrow transplants
- Resistance not a problem except in patients with HIV
- Renal excretion

- **Clinical uses to Fluconazole:**

- Candidiasis
- Cryptococcosis
- In AIDS
- **Coccidial meningitis it is drug of choice**
- It has also activity against histoplasmosis, blastomycosis, spirotrichosis and ring worm but Itraconazole is better in the same dose
- Not effective in aspergillosis

- **Side effects to Fluconazole:**

- Nausea, vomiting, headache, skin rash, abdominal pain, diarrhea, reversible alopecia
- No endocrine adverse effects
- Hepatic failure may lead to death
- It is highly teratogenic

Itraconazole

- A new synthetic triazole
- It lacks endocrine side effects of ketoconazole
- It has broad spectrum activity
- Administered orally as well as IV
- Food increases its absorption

- Itraconazole is extensively metabolized in liver by cytochrome P450 (CYP3A4)
- It is highly lipid soluble, it is well distributed to bone , sputum and adipose tissue
- Highly bound to plasma protein
- Does not penetrate CSF adequately as compared to Fluconazole, therefore its concentration is less to treat meningeal fungal infection

- Itraconazole steady state reaches in 4 days, so loading doses are recommended in deep mycosis
- Intravenously reserved only in serious infections

- **Side effects to Itraconazole:**

  Nausea, vomiting, hypertriglyceridemia, hypokalaemia, increased aminotransferase, hepatotoxicty and rash (leads to drug discontinuation)

Voriconazole

- A new drug available in oral and IV dosage forms
- It is similar to Itraconazole but more potent
- High biological availability when given orally
- Hepatic metabolism predominant
- Inhibition of P450 is less
- Reversible visual disturbances

Posaconazole

- Is a new oral, broad-spectrum antifungal agent similar to Itraconazole
- It was approved to prevent Candida and Aspergillus infections in severely immunocompromised patients and for the treatment of oropharyngeal candidiasis
- Due to its spectrum of activity, Posaconazole could possibly be used in the treatment of fungal infections caused by Mucor species and other zygomycetes
- Given orally and well tolerated

- Like Ketoconazole, Posaconazole can cause an elevation of liver function tests and it inhibits cytochrome P450 system

- **Side effects to Posaconazole:**

The most common side effects observed were gastrointestinal symptoms (nausea, vomiting, diarrhea, and abdominal pain) and headaches

Caspofungin

- It is Echinocandin class of antifungal drugs that interfere with the synthesis of fungal cell wall by inhibiting synthesis of β-D-glucan (by inhibiting β-D-glucan synthase)
- Especially useful for aspergillus and candida
- Not active orally given IV
- Highly bound to serum proteins

- Slowly metabolized by hydrolysis and N-acetylation
- Eliminated equally by urinary and fecal route
- Adverse effects include nausea , vomiting, flushing and liver dysfunction
- Very expensive

Antifugal Drugs for Cutaneous Mycotic Infections

- **Topical antifungal preparations**

- Amphotericin B and Nystatin
- Topical Azole derivatives
- Tolnaftate
- Terbinafine…etc

- **Oral anti fungal agents used for topical infections**

- Oral Azoles
- Griseofulvin
- Terbinafine

- **Polyenes (Amphotericine B, Nystatin, Natamycin)**

Amphotericin B, effective in Candida infection and cutaneous leishmaniasis

Available in cream, lotion, ointment and vaginal suppository dosage forms

Nystatin, effective in Candida albicans infection and available in cream, ointment, powder forms, oral suspension and tablets and vaginal tablets

Natamycin, effective in Candida infection and fungal keratitis

Not absorbed when given orally

Available in cream and ophthalmic eye drops

- **Tolnaftate**

Effective in most cutaneous mycosis

Ineffective against Candida

In Tinea pedis cure rate is around 80%

Available in as cream, gel, powder and topical solution

- **Ciclopirox Olamine**: Effective in Tinea versicolor (cream; lotion; solution; shampoo)
- **Naftifine (cream; gel) and Terbinafine (cream; oint.; gel; spray; solution)** : Effective in Tinea pedis (Athlete's foot) , Tinea cruris, and Tinea corporis

- **Topical Azoles**

- Miconazole, Clotrimazole, Butoconazole and Terconazole are topically active drugs that are only rarely administered parenterally because of their severe toxicity

- Their mechanism of action and antifungal spectrum are the same as those of Ketoconazole

- Topical use of azoles is associated with contact dermatitis, vulvar irritation, and edema. Miconazole is a potent inhibitor of Warfarin metabolism and has produced bleeding in Warfarin-treated patients even when it is applied topically. No significant difference in clinical outcomes is associated with any azole or Nystatin in the treatment of vulvar candidiasis

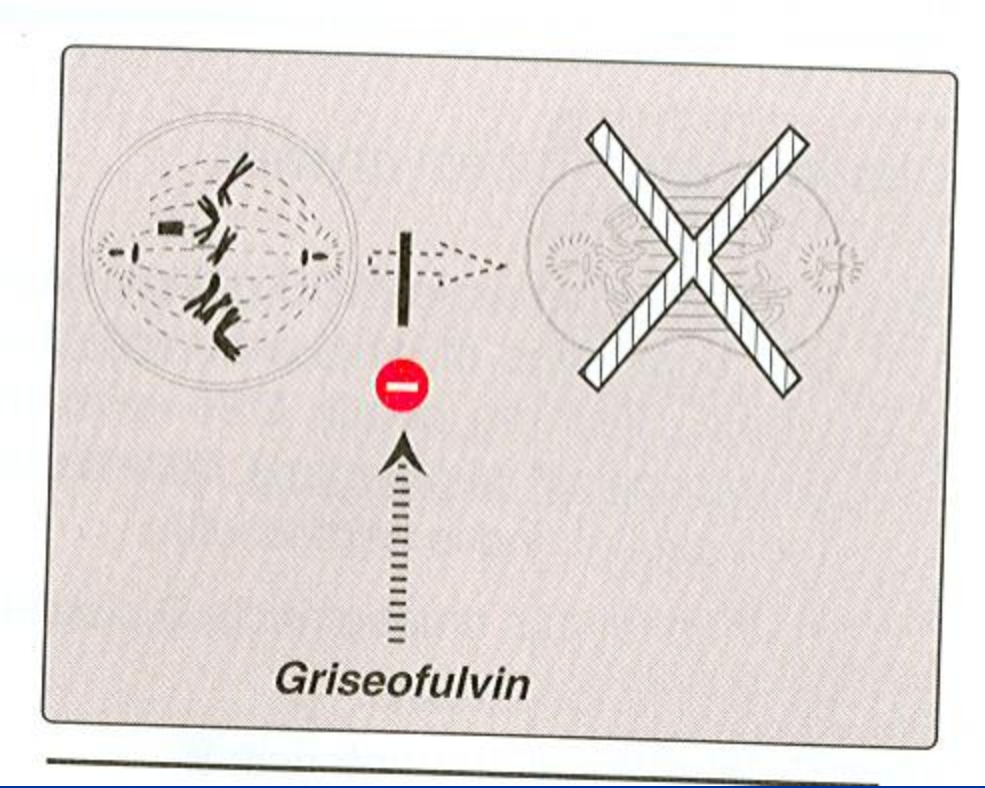
- **Oral Antifungal Agents used for topical infections**

- Oral Azole Derivatives:

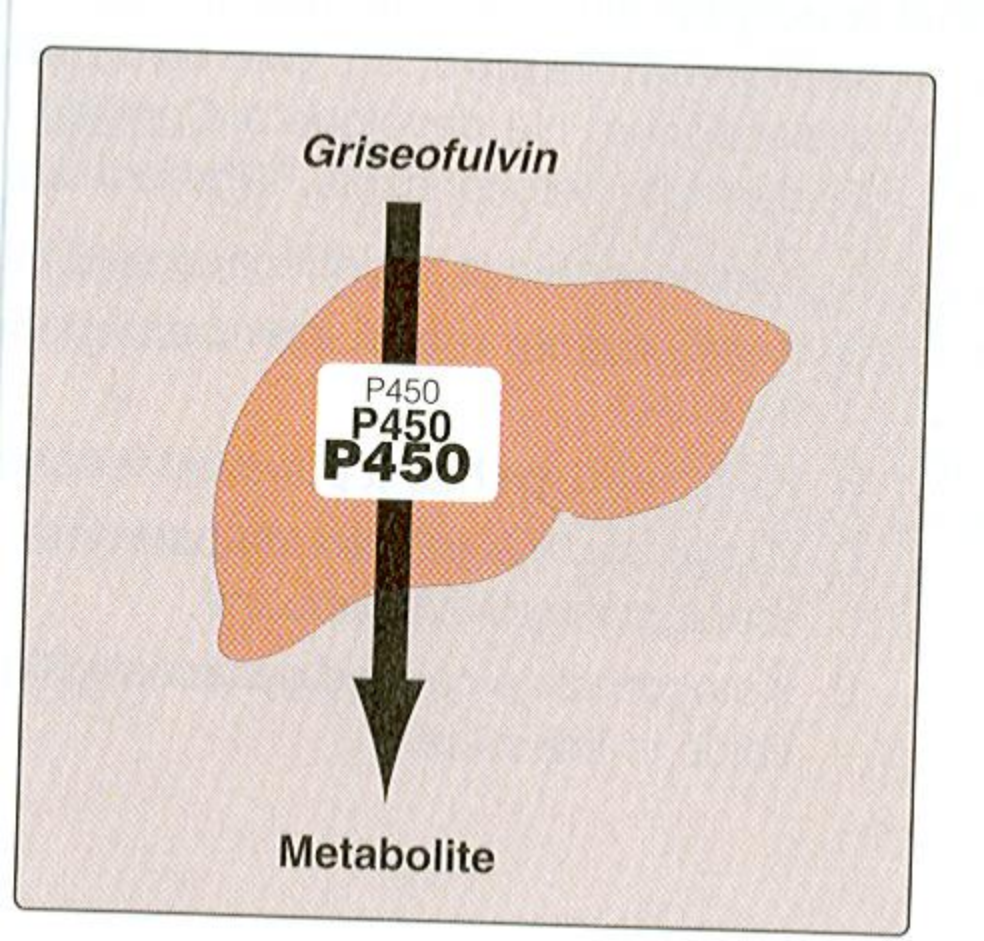
Fluconazole, Itraconazole, Ketoconazole…

- Affect the permeability of fungal cell membrane through alteration of sterol synthesis
- Effective in systemic mycosis, mucocutaneous candidiasis, and other cutaneous infections
- Might lead to systemic side effects: hepatitis; liver enzyme elevations, and drug interactions

- **Griseofulvin**
- It has largely been replaced by Terbinafine for treatment of dermatophytic infections of the nails because of toxicity
- Very insoluble in water
- It is useful for dermatophytes
- It is fungistatic for species of dermatophytes, and has narrow spectrum
- It interacts with microtubules function and hence interferes with mitosis

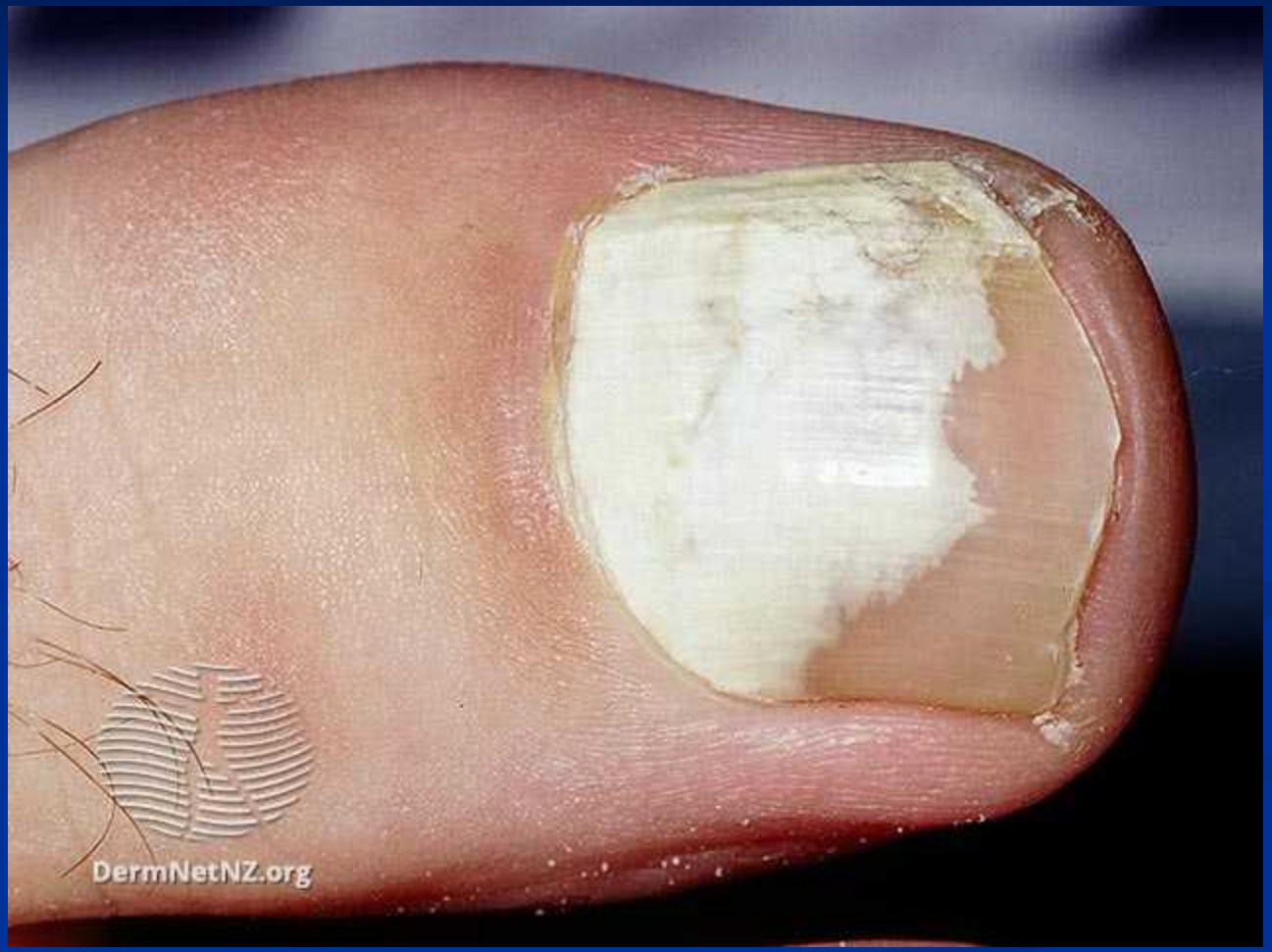

Griseofulvin

- Griseofulvin absorption increases with fatty meal
- Barbiturates decrease the absorption from GIT
- It is ineffective topically it has to be given orally for Rx of hair and nail dermatophyte infections
- The drug has to deposit first in keratin of growing skin, nail and hair to get rid of disease
- Extensively metabolized in liver and induces CYP450


Griseofulvin
P450
P450
P450
Metabolite

- **Clinical uses of Griseofulvin:**

- Mycotic diseases of skin, hair (particularly for scalp) and nail
- It is also highly effective in athlete's foot
- Treatment required is 1 month for scalp and hair ringworm, 6-9 months for finger nails, and at least 1 year for toe nails
- Not effective in subcutaneous or deep mycoses


DermNetNZ.org

- **Griseofulvin side effects:**

- Headache

- Peripheral neuritis, lethargy, mental confusion, impairment in performance of routine task

- Fatigue, vertigo, syncope, blurred vision

- **Terbinafine**
- It is synthetic allylamine
- It is the drug of choice for treating dermatophytes
- As compared to Griseofulvin it is better tolerated and requires shorter duration of therapy
- It inhibits fungal squalene epoxidase decreasing synthesis of ergosterol
- It is fungicidal but activity is limited to Candida albicans and dermatophytes

- Effective for the treatment of onychomycosis (fungal infections of nails). 250 mg daily for 6weeks for finger nail infection and for 12 weeks in toe nail infection
- Well absorbed orally, bioavailability decreases due to first pass metabolism in liver
- Protein binding more than 99% in plasma and metabolized by P450 system
- The drug accumulates in skin, nails and fat
- Severely hepatotoxic (liver failure may lead to death)

- Initial half life of Terbinafine is 12 hrs but terminal half life extends to 200-400 hrs which reflects its slow release from the tissues
- Can be found in plasma for 4-8 weeks after prolong therapy
- Terbinafine accumulates in breast milk and, therefore, should not be given to nursing mothers
- Metabolites excreted in urine and its clearance is reduced in moderate renal and hepatic impairment
- Not recommended in azotemia or hepatic failure

- **Side effects to Terbinafine:**

- GIT disturbances
- Taste and visual disturbance
- Severe allergic reactions
- Transient rise in serum liver enzymes

** Rifampicin decreases and Cimetidine increases its blood concentrations