ANTI-FUNGAL AGENTS

Prepared By

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CLASSIFICATION

- Antibiotics:
  - ✓ Polyenes - Amphotericin B, Nystatin, Hamycin
  - ✓ Heterocyclic benzofuran - Griseofulvin
- Antimetabolite - 5-Flucytosine
- Allylamine - Terbinafine
- Azoles:
- **A. IMIDAZOLES**
  - I. TOPICAL - Clotrimazole, Econazole, Miconazole
  - II. SYSTEMIC - Ketoconazole
- **B. TRIAZOLES**
  - I. SYSTEMIC - Fluconazole, Itraconazole
- Others: Undecylenic acid, benzoic acid, tolnaftate

GRISEOFULVIN

- Extracted from "*Penicillium griseofulvum*".
- Active against dermatophytes.

  Eg: epidermophyton, trichophyton, microsporum
- Not active against Candida.
- Dermatophytes actively concentrate it-selective toxicity.
- It doesn't has any anti-bacterial activity.
- It is FUNGISTATIC but not fungicidal.

MECHANISM OF ACTION

- Interferes with MITOSIS.
- Causes abnormal metaphase configurations.
- The daughter nuclei fail to move apart or move only a short distance.
- As a result, multi-nucleated and stunted fungal hyphae occurs.
- Disorients the microtubules (pulls chromosomes apart).

PHARMACOKINETICS

- Absorption: Irregular due to low water solubility.
- It can be improved by taking it with fats and by microfining the drug particles.
- Deposited in keratin forming cells of skin, hair and nails.
- Newly formed keratin is not invaded by fungus, but the fungus which persists in already infected keratin, till it sheds off.
- It persists for weeks in skin and keratin.

ADVERSE EFFECTS & USES

- Very low.
- Headache is the commonest complaint.
- G.I.T disturbances are observed.
- Discontinuation – if Rashes, Photoallergy was observed.
- **USES**:
- Used systemically only for dermatophytosis.

DOSES & INTERACTIONS

- 125 – 250 mg QID with meals.
- Duration of Treatment depends upon Site of infection, Thickness of infected keratin and Turnover rate.
- Body skin – 3 weeks
- Palm, soles - 4 – 6 weeks
- Finger nails - 4 – 6 months
- Toe nails - 8 – 12 months
- INTERACTIONS:
- Induces warfarin metabolism.
- Reduces efficacy of oral contraceptives.
- Failure of therapy with phenobarbitone.
- Causes intolerance to alcohol.

AMPHOTERICIN-B

- Extracted from "Streptomyces nodosus".
- **Chemistry:**
- contains macrocyclic ring- one side has several conjugated double bonds (highly lipophilic) and other side with many OH groups (hydrophilic).
- Selectivity of AMB is low.
- also effects cholesterol in human cell membrane due to structural resemblence with ergosterol.
- Active against wide range of yeast and fungi.
- DOSE: 50-100 mg QID

MECHANISM OF ACTION

- AMB has high affinity with ergosterol in fungal cell wall.
- combines with it, gets inserted into membrane and several AMB molecules orient together to form a **micropore**.
- hydrophilic side forms interior through which water, ions, aminoacids move out.
- micropore is stabilized by sterols of AMB.
- This leads to increased cell permeability.
- AMB enhaces immunity in animals

PHARMACOKINETICS

- Absorption: Not absorbed. Can be given orally for intestinal candidiasis without systemic toxicity.
- IV suspension is taken made with deoxycholate-widely distributed.
- Poor CSF penetration.
- Binds to sterols in body tissues and stays for longer periods.
- Half life-15 days. metabolized in liver.
- Excretes slowly through urine and bile.

ADVERSE EFFECTS & USES

- Acute reaction: chills, aches, fever, Nausea,vomiting, dyspnea.
- Thrombophlebitis.
- nephrotoxicity-long term
- Reduced GFR, acidosis, hypokalemia
- Anaemia, CNS toxicity
- USES: for oral, vaginal and cutaneous candidiasis, leishmaniasis.

ANTIMETABOLITES

- **5-FLUCYTOSINE:**
- Pyrimidine antimetabolite, inactive as such.

5-FC

↓ taken up by fungal cells & converted to

5-Fluorouracil

↓ Converted to

5- Fluorodeoxyuridylic acid

(INHIBITS thymidilate synthesis)

↓

No DNA formation in fungal cell

5 - FLUCYTOSINE

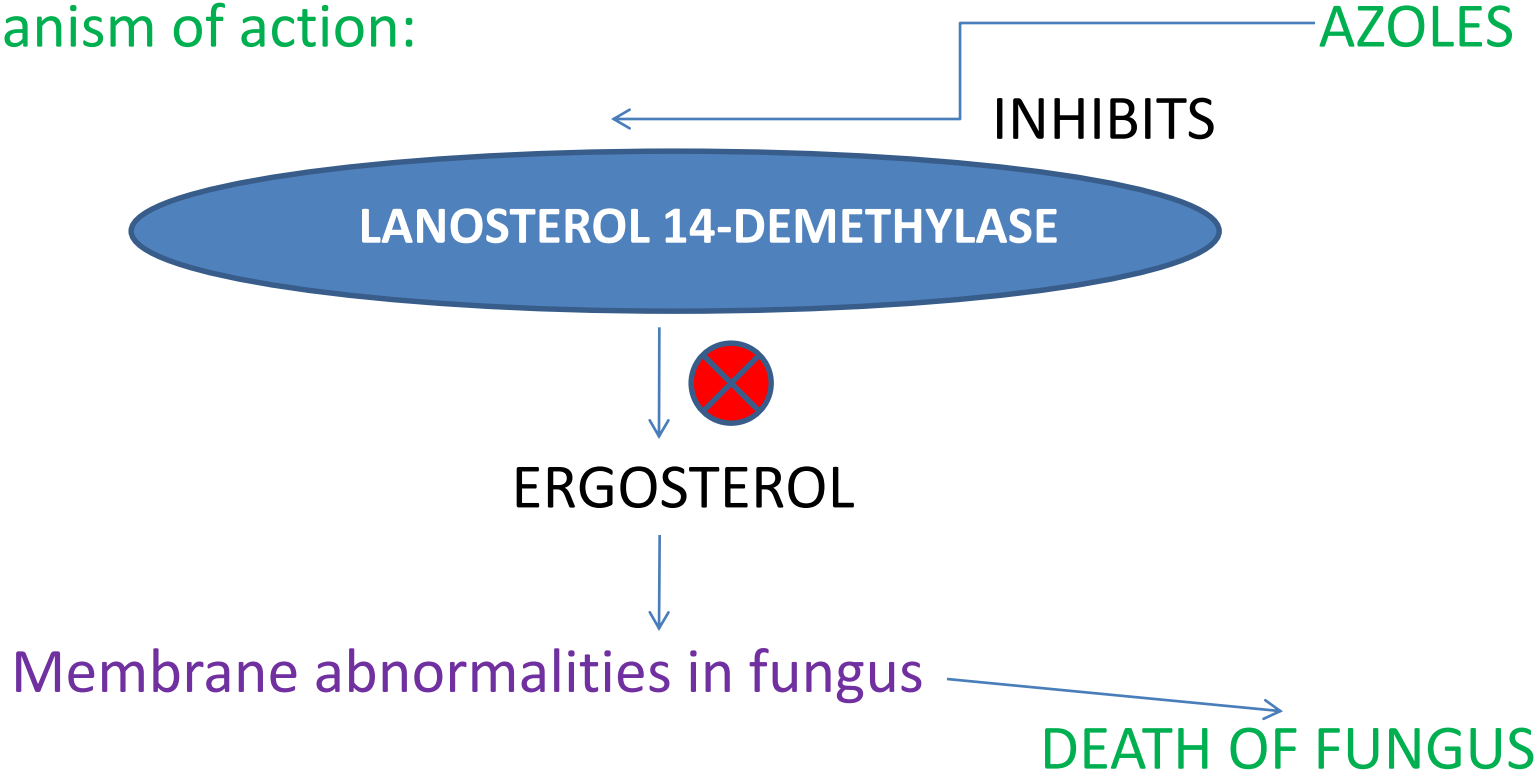
- Mammalian cells have low capacity to convert 5-FC to 5-FU. So fungal selectivity action occurs.
- Active against *Cryptococcus, Torula* and few strains of *Candida.*
- ADVERSE EFFECTS:

  1. Leucopenia
  2. thrombocytopenia
  3. bone marrow depression
  4. G.I disturbaces
  5. Diarrhoea in some cases
  6. Mild liver dysfunction – reversible.

- USES: Not used as a SOLE therapy.
- Used in cryptococciasis with Amphotericin-B.

AZOLE ANTIFUNGALS

- Currently most extensively used antifungals.
- They have broad spectrum activity. Effective against dermatophytes, *Candida, Nocardia, Staph. aureus, Strept. faecalis, Bac. fragilis* and *Leishmania.*
- Mechanism of action:



CLOTRIMAZOLE

- Effective in topical treatment of tinea infections – 60 to 100% cure rates with 2 – 4 weeks application on a twice daily schedule.
- Effective for athletes foot,

  otomycosis,

  oral, cutaneous, vaginal candidias.
- Mostly for vaginitis due to long lasting residual effect after one application.(7 day course)
- For oropharyngeal candidias, 10mg in mouth 3-4 times a day
- Well tolerated
- Local irritation with burning sensation occurs sometime

ECONAZOLE & MICONAZOLE

- **ECONAZOLE:**
- Similar to clotrimazole. Effectively penetrates through skin.
- Highly effective in dermatophytosis, otomycosis, oral thrush, but somewhat inferior to clotrimazole in vaginitis.
- NO adverse effects. Local irritation in a few was reported.
- 1% ointment & 150 mg vaginal tab.
- **MICONAZOLE:**
- Highly efficacious drug (>90% cure rate) for tinea, cutaneous and vaginal candidias, otomycosis.
- Has very good penetrating power. Even single application on skin acts for few days.
- A higher evidence of vaginal irritation was reported.
- 2% gel & 2% powder solution.

KETOCONAZOLE (KTZ)

- First ORALLY effective broad spectrum antifungal drug.
- Oral absorption is facilitated by gastric acidity, as it is soluble at lower pH.
- Larger binding to albumin, extensive hepatic metabolism, excretion in urine and faeces.
- A short $t_{1/2}$ - $1_{1/2}$ to 6 hours.
- DOSE: 200 mg OD or BD.
- ADVERSE EFFECTS:
- Nausea, vomiting – reduced by taking with meals.
- Loss of appetite, headache, rashes and hair loss.
- Decreases androgen production (testosterone) in men. It results in gynaecomastia, loss of hair and libido.
- Menstrual irregularities in women due to suppression of estradiol synthesis.
- Contraindicated in pregnants and nursing women.

KETOCONAZOLE

- **DRUG INTERACTIONS:**

- Antacids – Decreases oral absorption.
- Rifampicin, phenobarbitone, Phenytoin – Induces metabolism
- Warfarin, diazepam, sulfonyl ureas – Increased concentration.

  (due to inhibition of CytP450 by Ketoconazole)

- Terfenadine, cisapride – Induces Ventricular tachycardia, fatal ventricular fibrillation.

- **USES:**

- In dermatophytosis – concentrated in stratum corneum.
- High doses are used in Cushing's syndrome.
- Fluconazole and itraconazole have replaced the KTZ largely due to their lesser side effects, toxicity (lower affinity for mammalian CytP450) and higher efficacy.

FLUCONAZOLE

- Newer water soluble triazole having wide range of activity than KTZ.
- Mostly used in crpytococcal meningitis, systemic and mucosal candidiasis. PREFERRED drug fro Fungal Meningitis.
- Doesn't inhibit the steroid synthesis –NO Antiandrogenic effect.
- **PHARMACOKINETICS:**
- 94% absorbed- Oral BA is not affected by food or gastric pH.
- Excreted unchanged in urine. T1/2 is 25-30 hrs.
- Fungicidal concentrations are achieved in Nails, vagina and saliva.
- Penetration into Brain and CSF is good.
- Dose reduction is needed in renal impairment.
- **ADVERSE EFFECTS:**
- Nausea, vomiting, abdominal pain, rash, headache.
- NOT recommended in pregnant women and lactating mothers.

FLUCONAZOLE

- **DRUG INTERACTIONS:**
- Increases plasma levels of phenytoin, cisapride, warfarin, zidovudine, etc.
- With cisapride – produces ventricular tachycardia.
- **USES:**
- In vaginal candidiasis – 150 mg p.o
- Tinea and cutaneous infections – 150 mg weekly for 4 weeks
- Cryptococcal meningitis – 200-400 mg/day for 4-12 weeks
- Fungal keratitis – eye drops (0.3%).
- It is Longer acting,

  Safer and

  More efficacious than KTZ.

ITRACONAZOLE

- Has Broad spectrum activity than KTZ or Fluconazole.
- It is fungistatic.
- NO steroidal hormone inhibition or hepatotoxicity.
- **PHARMACOKINETICS:**
- Oral absorption is enhanced by food and gastric acid.
- High protein bound.
- Accumulates in vaginal mucosa, skin and nails. Poor CSF entry.
- High metabolism. Excreted in faeces.
- **ADVERSE EFFECTS:**
- Dizziness, pruritis, headache and hypokalemia.
- Unsteadiness and impotence are infrequent.

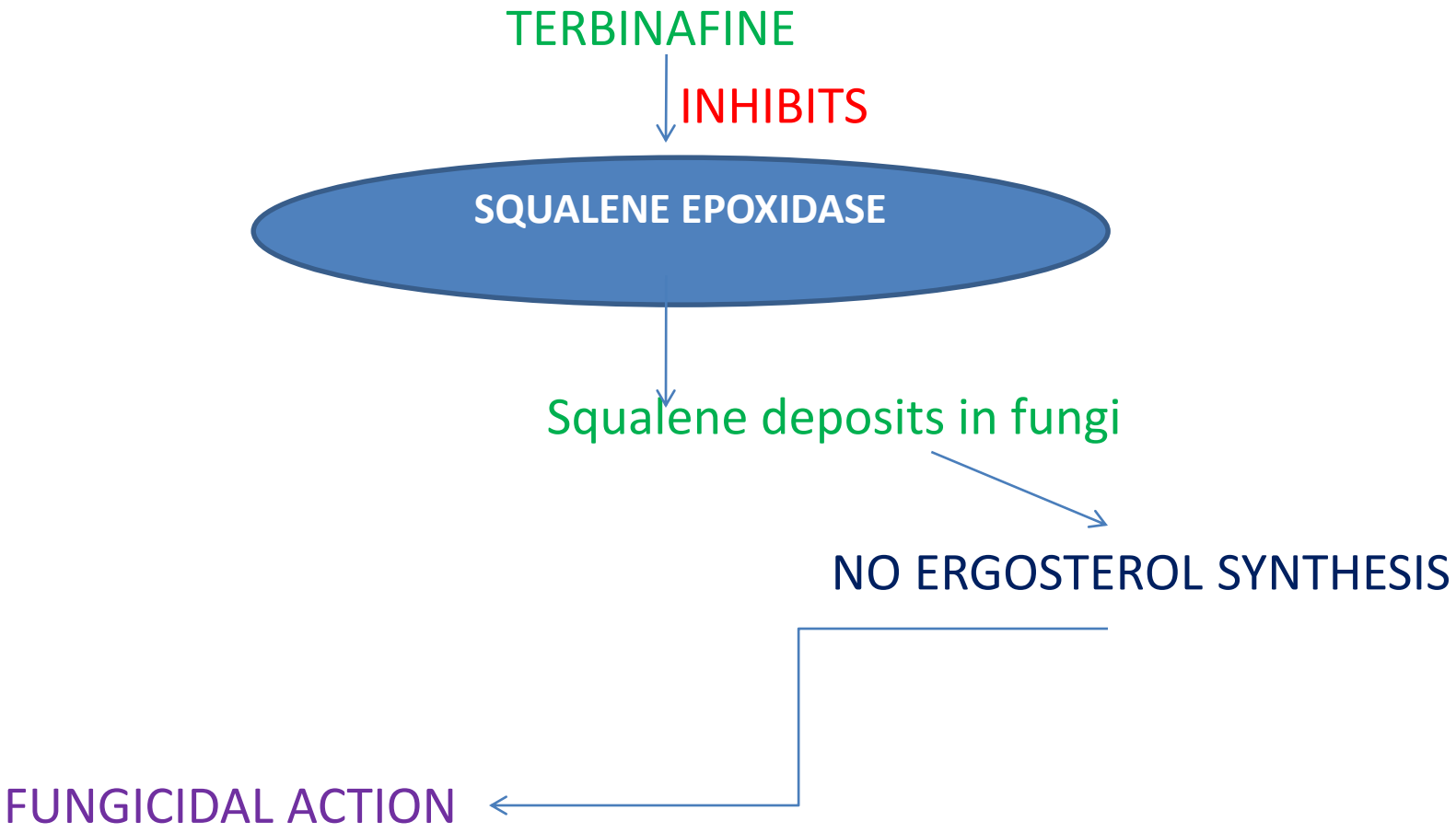
ITRACONAZOLE

- **DRUG INTERACTIONS:**
- Antacids – Reduces oral absorption.
- Phenytoin, rifampicin, Phenobarbitone – Induces metabolism
- Warfarin, digoxin – concentration in plasma increases.
- Cisapride – induces Ventricular arrhythmias.
- **USES:**
- Drug of choice for chromomycosis and paracoccidiomycosis.
- In aspergillosis – 200mg OD/BD with meals for 3 months.
- Vaginal candidiasis – 200 mg OD for 3 days.
- Dermatophytosis - 100 – 200 mg OD for 7 – 15 days.

➢ Onchomycosis - 200 mg/day for 3 months.

TERBINAFINE

- An allylamine – orally and topically active against candida and dermatophytes (1st line drug).
- It is fungicidal. More efficacious than griseofulvin, itraconazole.



TERBINAFINE

- ## PHARMACOKINETICS:

- 75% is absorbed. FIRST PASS metabolism reduces Oral BA.
- Lipophilic, widely distributed in body.
- Concentrated in sebum, stratum corneum and nail plates.
- Mostly excreted in urine. Less through faeces.
- **SIDE EFFECTS:**
- Gastric upset, rashes, taste disturbance.
- Topical route causes erythema, itching, dryness, irritation and rashes.
- Enzyme inducers lower and enzyme inhibitors raise the steady state plasma levels of terbinafine.
- **USES:**
- Topically 1% cream or Orally 250 mg OD in case of Tinea infections. 2 to 6 weeks treatment depending upon site.
- Onchomycosis – 3 to 12 months oral therapy.

OTHER ANTIFUNGALS

- **TOLNAFTATE:**
- Effective drug for *Tinea cruris* and *T. corporis*.(1-3 weeks)
- Poor penetrability – Less effective in *T. capitis* (scalp) *T. unguium* (nails). Relapses are common. Not effective in candidiasis.
- Salicylic acid is used along for keratolytic action.
- Causes little irritation. Inferior in action to imidazoles.
- **UNDECYLENIC ACID:**
- Fungistatic. Used topically in combination with Zinc salt.
- Lower cure rates even after prolonged treatment.
- Still used for T. pedis, nappy rashes and T. cruris.
- **BENZOIC ACID: (RING CUTTER ointment)**
- Fungistatic. Needs prolonged application till keratin sheds off
- In Hyperkeratotic lesions, used with salicylic acid as WHITFIELDS OINTMENT (Benzoic acid-5% and Salicylic acid- 3%).
- Salicylic acid helps to remove the infected tissue and promotes penetration of benzoic acid into the lesion.
- Irritation and burning sensation occurs