PC
Pharmacology Concepts
By Rajesh Choudhary

# Antifungals Drugs

Website

Videos

Pharmacology 3

# ANTI FUNGAL DRUGS

These are drugs used to treatment of superf-icial or systemic fungal infections

# Fungal infections are associated with the use of broad spectrum antibiotics, corticosteroids, immuno suppressant drugs, and immunocompromised disease (AIDS), due to breakdown of Host-Defence.

# Amphotericin-B → For Systemic mycosis

# Griseofulvin → dermatophytes (1960s)

# Flucytosine → noted in 1970s

# Imidazoles (mid 1970s), Triazoles (1980s)

## DRUGS: →

### 1. Antibiotics :-

A) Polyenes :- Amphotericin-B, Nystatin

B) Heterocyclic Benzofuran - Griseofulvin

C) Echinocandins - Caspofugin, Micafugin

### 2. Antimetabolite - Flucytosine

### 3. Azoles

A) Imidazole - Systemic - Ketoconazole

Topical → Clotrimazole, Econazole, Miconazole

B) Triazole - Fluconazole, Itraconazole, Voriconazole, Posaconazole

### 4. Allylamine - Terbinafine

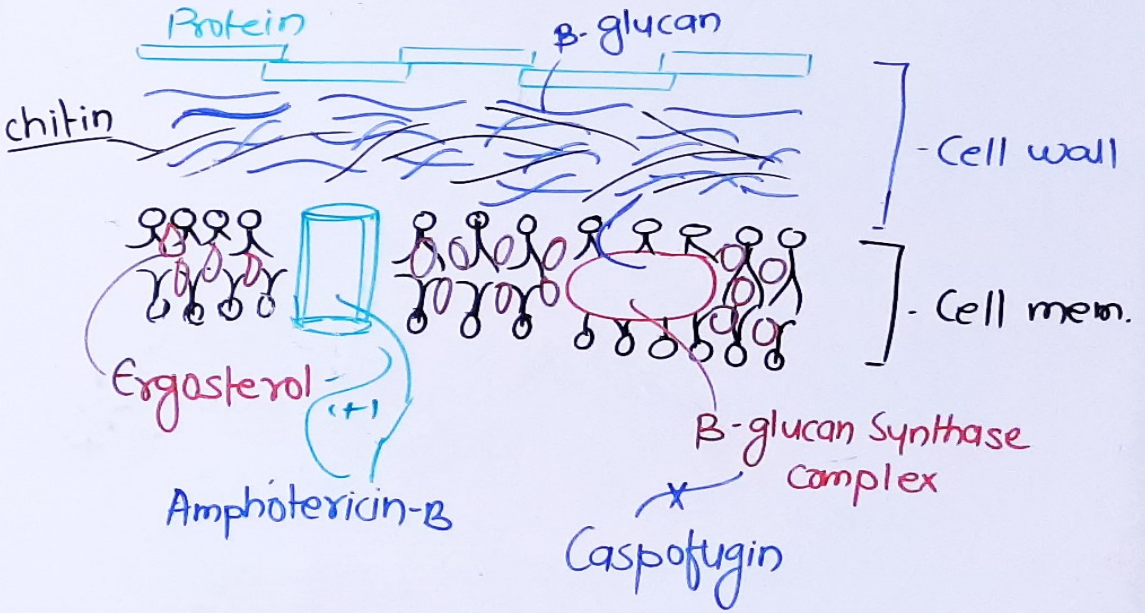
### 5. Topical Agents - Tolnaftate, Benzoic acid Butenafine, Ciclopirox olamine

## Mode of Action

Squalene —S. Epoxidase (Terbinafine)→ S. Epoxide → Lanosterol

Azoles → ✗ Lanosterol 14-dimethylase

"Ergosterol"

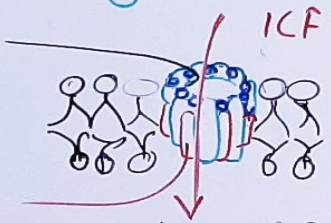


# AMPHOTERICIN-B (AMB) :- Polyene Antibiotics

#Source - "Streptomyces nodusus"

MOA :→ Macrocyclic ring - one side - several conjugated double bond (highly lipophilic), other side → -OH group (hydrophilic). A polar aminosuger (mycosamine) & a carboxylic ā are +nt at one end

Polyenes/AmB — Ergosterol → $(AmB-Ergosterol)_n$




orientation ↓

"Micropore" (Death Ring)

leak out (Amino ā, Ions, hydrophilic mole.)

# These pore stabilized by Van der Waals interaction
# It also causes oxidative damage of fungal cell
# Amphotericin-A has little or no clinical efficacy
# AmB also binds with host cell mem. cholesterol (less affinity) & may shows systemic toxic effects.
# It is also enhances the immunity in animals, this action may aid immunocompromised patient in handling fungal infection

Antifungal Spectrum - Wide range of Yeast & Fungi

low Conc. - Fungistatic
high conc. - Fungicidal

#Candida albicans - Candidasis
# Aspergilus sps - Ringworm of nails
# Blastomyces dermatitidis - Blastomycosis
# Sporothrix - Sporotrichosis
# Also used in Leishmania (protozoal) infectn

Pkinetic - # Not absorbed orally, but use orally for intestinal Candidasis. # use i.v., suspension with doxycholate, # Widly distributed, but poorly in CSF. # Accumulate in body by binding with sterols & LPs. thus $t_{1/2}$ - 15 days. # 60% drug metabolised in liver & excreted through urine & bile both

ADR :→ The toxicity of AmB is high

# Acute Reactn - Chills, fever, pain, naysea, & dyspnoea due to release of Cks (IL-1 & TNFα)
# Long term - Nephrotoxicity, Anaemia (BMS)
CNS toxicity (only in intrathecal injectn)

Use - Fungal infections, Leishmania

# topically for oral, veginal, cutaneous candidasis, Fungal corneal & otomycosis
# Febrile Neutropenia - ↓ Fever

Interactn - AmB + Flucytosine(5FC) - Supraadditive
AmB + Aminoglycoside → Nephrotoxicity

## ECHINOCANDIN - CASPOFUNGIN

# Semisynthetic antifungal antibiotics having complex cyclic lipopeptide.
# Potent & low toxicity than Amphotericin-B

MOA:- It inhibits the complex of β-glucan Synthase enzyme & further inhibits the β-glucan synthesis,
# β-1,3-glucan → Component of cell wall that cross link with chitin & gives toughness of cell wall.
# ↓ β-glucan → ↓ Cell wall integrity → ↑ Osmotic drive

Spectrum - Candida & Aspergillus
# Azole Resistant Candida strains are susceptible

PKinetic → # I.V. route (aqueous solutn); # Distributed into tissue but not in CSF; Metabolites are Exc. through urine & Faeces. t1/2 = 10h

Uses:- # Preferred for deep & invasive candidasis.
# Esophageal candidasis & salvage therapy of nonresponsive invasive Aspergillosis
# Neutropenic immunocompromised patients to reduce fever

ADR:- # Acute Febrile reaction, # Phlebitis of Inj. vein, # Rash # Vomitting, # Dyspnoea, # Join Pain.
# Hypokalemia

## GRISEOFULVIN - HET. BENZOFURAN

# Source - P. griseofulvum
# used in dermatophytosis in 1960s
MOA - It interferes with the Mitosis (Cell division)
GR → binds with tubulin → ↓ Polymerizatn of Microtubules → ↓ Mitosis (Metaphase) ← ↓ Cell Division

Spectrum - Fungistatics for dermatophytes - Epidermophyton, Trichophyton, Microsporum etc.

PKinetic → # Oral absorptio is poor (enhance by Fat.)
# It is a keratophylic - deposited in keratin forming cells of skin, hair & nails.
# Metabolized by methylation (in Liver) and excreted through urine.

ADR - Headache, GI disturbance, CNS symptoms, Peripher Neuritis, (Rash, Photoallergy)
Interactn → Cyp450 Enz. inducer → ↓ Therapeutic loss of warfarin & oral contraceptives

Uses - Orally only for dermatophytes
Scalp - 4 weeks
Palms, soles - 6-8 weeks
Finger, nails - 6-8 months
Toe nails - 10-12 months

# ANTIFUNGAL DRUGS – AZOLES

IMIDAZOLE – Systemic & Topical – Ketoconazole
Topicals → Cotrimazole, Econazole, Miconazole
TRIAZOLES → Itraconazole, Fluconazole, – Better
Voriconazole, Posaconazole = New

Spectrum :– "Broad Spectrum Fungistatic"
↳ # Dermatophytes, # Candida # Deep mycosis agent,
# Nocardia # Leishmania

MOA – "Ergosterol Synthesis Inhibitors

Lanosterol ⟶ Ergosterol
Lanosterol 14-demethylase
(Fungal Cyp450 Enzyme)

"Azoles" ⟶ ✕

# Triazoles have higher selectivity, Thus lower toxicity

## "KETOCONAZOLE PHARMACOLOGY"

# First oral active broad spectrum antifungal drug

P'kinetic – # oral abs is facilitated by Gastric acidity.
# Metabolites (Liver) are excreted through Urine & Faeces
$t_{1/2}$ = 4-8h.

ADR – # Common – Nausea, Vomiting, Appetite loss, paresthesia, rash, hair loss.
# Gynaecomastia (↓ Adrogen production)
# Displace the testosterone From its protein binding site
# Oligozoospermia # Irregular menstrual cycle

Drug Interaction :→
# Azoles are Metabolic Enz. inhibitor, thus it may enhance plasma conc. of other drugs – Phenytoin, Digitoxin, warfarin, Sulfonyl urea, Protease Inhibitors, DHPs, etc
# $H_2$ blockers, Antacids – ↓ oral abs. of ketoconazole
# Enz Inducers (Rifampin, Barbitone) – ↓ Pc of KTZ

uses – Antidandruff Shampoo, Topical Creams

## ITRACONAZOLE PHARMACOLOGY

# Better broad spectrum than Fluconazole & KTZ
# Fungistatic, Effective in immunocompromised Pat.
# Steroid hormone Syn. Inhibition is absent & Rare hepatotoxicity.

P'kinetics – Oral absorptn variable, enhanced by Foods & gastric acid. High protein binding & distribution (Vd ≃ 10L/kg), but poor in CSF. active metabolites excreted through Faeces mainly.

ADR – Dizziness, pruritis, headach, Hypokalemia, long term may impared in left ventricle function

Use: – # Systemic mycosis, # Veginal Candidasis
# Dermatophytosis # Onychomycosis
# Pityriasis versicolor

Interactn – Similar as Ketoconazde