

ANTIFUNGAL DRUGS

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- Fungi causing mycosis live as commensals or are present in the environment.
- Earlier superficial infections were uncommon and systemic rather rare.
- Recently there is increase in local as well as systemic fungal infections.
- Reason for this is **opportunistic infections**

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Opportunistic infections

- Immuno-suppression due to
 - Cancer chemotherapy
 - AIDS
 - Corticosteroid overuse
- Indiscriminate use of broad spectrum antibiotics

Fungal infections

Superficial

Skin
Hair
Nails
Mucous
membrane

Deep

Tissues
Organs

Causative fungi

Superficial infections by

Dermatophytes

Candida

Deep infections are

Candidiasis

Aspergillosis

Coccidiomycosis

Histoplasmosis etc

Antifungal drugs

1. Antifungal antibiotics
2. Antimetabolite
3. Azoles
4. Allylamine
5. Topical agents

Antifungal antibiotics

Polyenes

1. Amphotericin B
2. Nystatin
3. Hamycin
4. Natamycin

Heterocyclic benzofurans

Griseofulvin

Antimetabolite

Flucytosine

Azoles

Imidazoles

- Clotrimazole
- Econazole
- Miconazole
- Ketoconazole

Triazoles

- Fluconazole
- Itraconazole

Allylamine

Terbinafine

Topical agents

1. Tolnaftate
2. Undecylenic acid
3. Benzoic acid
4. Quinodochlor (antibacterial as well)
5. Ciclopirox olamine

Amphotericin B

- Derived from *Streptomyces nodosus*
- High affinity for ergosterol present in fungal cell membrane
- Closely resemble cholesterol of host cell membrane but affinity is less
- Most toxic antifungal
- Bacteria lack sterols so insensitive to polyenes

Antifungal spectrum

- Fungicide at high and static at low conc.

- Effective against

Candida albicans

Histoplasma capsulatum

Cryptococcus

Pharmacokinetics

- Insoluble in water
- Unstable at 37degree
- Poorly absorbed from GIT
- Cannot cross BBB
- Highly bound to plasma proteins
- Takes 2 months for complete clearance of drug

- Given as I/V infusion
- For fungal meningitis given intrathecally
- Has immuno-stimulant action also
- Given in immuno-compromised patients for fungal infections

Resistance

- Due to reduction in membrane ergosterol
- Alteration in amphotericin binding site

Uses

- Broad spectrum antifungal
- Useful for
 1. Candida that causes
 - oral
 - vaginal
 - cutaneous candidiasis
 - 2 Cryptococcus
 - 3 Histoplasma
 - 4 Aspergillosis
 - 5 Also effective for Leishmaniasis
(Reserve drug for resistant cases of Kala Azar)

Adverse Drug Reactions

- Acute reactions- occurs with each infusion
 1. Chills
 2. Fever
 3. Aches
 4. Pain
 5. Nausea
 6. Vomiting
 7. Dyspnoea

So corticosteroids are administered along with the drug

- Thrombophlebitis
- Bone marrow depression
Reversible anemia

- On intrathecal injection

Headache

Vomiting

Nerve paralysis

- Renal toxicity leading to

1. Azotemia

2. Decreased GFR

3. Acidosis

4. Hypokalemia

5. Inability to conc. urine

Newer Amphotericin B

They are developed to overcome

1. Side effects
2. To improve tolerability
3. To get the drug at site of action
4. To reduce the toxicity i.e.. less nephrotoxic and minimal anemia

Newer formulations are

1. Amphotericin B lipid complex
2. Amphotericin B colloidal dispersion
3. Liposomal Amphotericin B

(Only drawback of these formulations
is less efficacy)

Interactions

1. With Flucytocin-synergistic action
2. Rifampicin
3. Minocyclin
(Both potentiate Amphotericin B)
- 4 Vancomycin
- 5 Aminoglycoside
(Both inc. risk of nephrotoxicity)

Nystatin

- More toxic than Amphotericin B
- Used only for superficial candidiasis of
 1. Skin
 2. Mouth
 3. Vagina
 4. Intestine
- As ointment ,oral tablets & suppositories

Hamycin

- Water soluble
- Absorption from GIT not reliable
- Not used for systemic fungal infections
- Used topically for
 1. Aspergillus
 2. Candida
 3. Monilial
 4. Trichomonas vaginalis infections

Natamycin

- Broad spectrum
- Used topically for
 1. Keratitis
 2. Monilial infections
 3. Trichomonas vaginalis

Griseofulvin

- Used for superficial fungal infections by dermatophytes
- Derived from *Penicillium griseofulvum*
- No direct effect on fungi
- Taken up by newly formed keratin
- Drug containing keratin is resistant to fungi
by interfering with its nucleic acid synthesis & its cytoplasmic functions

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- Given orally
- Absorption depends on the particle size
- Duration of treatment depends upon tissue turn over
 1. 3-6 wks for skin & hair
 2. 3-6 months for nailsTreatment should continue till whole infected tissue is shed off.

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ADR

- Safe with mild side effects
 1. GIT upsets
 2. CNS symptoms
 3. Hepatotoxicity
 4. Leucopenia
 5. Photosensitivity
 6. Allergy etc.

- Microsomal enzyme inducer
- Causes decrease in activity of anticoagulants
- Cause intolerance to alcohol
- Phenobarbitone reduces its oral absorption so failure of therapy

Flucytosine

- Orally absorbed
- Widely distributed even in CSF.
- Exc. in urine.
- Converted in fungal cell to 5-FU which is antimetabolite.
- Mammalian cells remain unaffected except few bone marrow cells.

Uses

- Never used alone.
- Narrow spectrum.
- Resistance develop rapidly.
- With Amphotericin B for systemic infection
- Useful for cryptococcal meningitis as it can penetrate CSF.

ADR

1. Mild BM depression
2. Loss of hair
3. Dose should be decreased in the presence of renal impairment.

Azoles

- Synthetic antifungal agents
- Broad antifungal spectrum
- Act by blocking ergosterol synthesis and by increasing cell permeability
- Amphotericin B & Azoles have antagonistic actions
- Ketokonazole acts by causing accumulation of lethal hydrogen peroxide.

	Ketokonazole	Fluconazole	Itraconazole
1	Broad spectrum	Still wider range	Fungi static
2	Dermatophyte & deep mycosis	Cryptococcal & coccidial meningitis	For immunocompromised patients
3	Absorbed at low pH	Good oral absorption	Varies with food & pH
4	Highly bound to PP	Not much	Highly bound

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4	More S/E, headache, androgen inhibition	Less S/E, headache & rash	Hypokalemia, pruritis & dizziness
5	Causes hepatic impairment	Mild	Not hepatotoxic
6	Inhibit cytochrome P450	Inhibit only fungal P450	No effect
7	Used for Monilial vaginitis. Cushing's syn	Candidiasis, Keratitis, Cryptococcal meningitis	Mycosis, meningitis Chromo & paracocci.

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Local azoles

- Clotrimazole
- Econazole
- Miconazole

(For Tinea, Athlete's foot, otomycosis, oral, cutaneous & vaginal candidiasis)

S/E of miconazole is vaginal irritation & pelvic cramp.

Terbinafine

- Given both orally & locally
- Lipophilic so widely distributed
- Fungicidal
- Inhibit ergosterol synthesis
- Used for dermatophytes & candida
- Dose is 250mg OD for 2-6 wks
- Locally 1% ointment.

Side effects

With oral

1. GIT upset
2. Rash
3. Taste disturbance

On local application

1. Dryness
2. Rash
3. Itching
4. Erythema