

# **ANTIFUNGAL DRUGS.**

**MEDICARE HEALTH PROFESSIONALS  
COLLEGE.**

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# ANTIFUNGAL DRUGS

Drugs used in RX of fungal infections

**They can be classified as follows;**

- ✓ Polyene antifungals
- ✓ Imidazole antifungals
- ✓ Triazole antifungals
- ✓ Allylamine antifungals
- ✓ Other antifungals

# POLYENE ANTIFUNGALS

- They are produced by **streptomyces species**
- They include **Nystatin and Amphotericin B**
- They are not absorbed from the GIT when taken orally and can either be given topically or by injection

## Mode of action

They irreversibly bind to ergosterol in the cell wall of fungi, causing death by promoting leakage of intracellular ions and disruption of membrane active transport mechanisms by formation of a micro-pore.

# NYSTATIN

## Preparations

- Tablets 500,000iu
- Suspension 100000iu/5ml
- Lozenges 100,000iu
- Pessary 100,000iu

**Brands:** Mycostat, Nystash, Mycoren

## Pharmacokinetics

Nystatin is not absorbed from GIT when taken orally, and it is excreted almost entirely in faeces as unchanged drug.

# Indications

- Vaginal candidiasis
- Oesophageal candidiasis/oral candidiasis
- Skin candidiasis
- Intestinal candidiasis

## Contraindications

- Known hypersensitivity to nystatin

## Dose

- Intestinal candidiasis 500,000iu qid for 14 days  
doubled in severe infection (children 100,000qid)
- Vaginal candidiasis: Insert 1 pessary (100,000iu) in  
the vagina at night for 14 days

# Side effects of nystatin

- Nausea Vomiting
- Skin rash Diarrhoea
- Oral irritation

## Key issues to note

- Liquid nystatin should be held in the mouth for several minutes before swallowing
- Nystatin suspension or tablets are effective for minor oral fungal infections
- Shake suspension well before use.

# AMPHOTERICIN-B

**Preparation:** injection 50mg/ml (vial)

**Brands:** Fungizone Amphotret

## Indications

- Cryptococcal meningitis
- Histoplasmosis
- Coccidioidomycosis
- Candidiasis
- Aspergillosis

# Contraindications

- Known hypersensitivity to Amphotericin-B
- Breast feeding, Renal failure
- Patients receiving anticancer drugs

## Dose

- By IV infusion: initial test dose of **0.25mg/kg** infused over 20-30minutes **in D5%** for 2-4 days, then if tolerated increase to **0.7mg-1mg/kg in 500mls of D5%** od for 14days.
- In severe infection: 1.5mg/kg od/alternate days. The daily dose is infused **over 2-4 hours** at a concn of 100mcg/ml in D5%. Slower infusion of up to 6 hrs may be necessary to reduce acute toxic effects



# Mgt of cryptococcal meningitis

## 2. Fungal meningitis( cryptococcal meningitis)

- ✓ Very difficult to RX because of low immunity
- ✓ **IV Amphotericin B** initial test dose 0.25mg/kg over 20-30minutes then 0.7-1mg/kg/day in IV NS/D5 500mls (2-6hours) for 2 weeks
- ✓ **After stabilization**, fluconazole 400mg/day for 8weeks then 200mg/day indefinitely (prevention of relapse of cryptococcal meningitis in AIDS patients after completion of primary therapy)
- ✓ **Alternative RX:** IV fluconazole for initial therapy in patients unable to tolerate amphotericin B

# Side effects of Amphotericin B

- Pain and thrombophlebitis at injection site
- Peripheral neuropathy
- Renal failure
- Liver failure
- Bleeding disorders/thrombocytopenia
- Muscle and joint pains
- Headache, fever
- Nausea and vomiting
- Diarrhoea
- Epigastric pain, anorexia, Malaise

# Drug interactions

- Amphotericin B may increase the toxicity of digoxin
- Corticosteroids may increase loss of  $K^+$  from the body caused by amphotericin B
- Aminoglycosides when given with amphotericin B increase the likelihood of kidney damage/failure
- It may prolong the muscle relaxing effect of neuromuscular blocking agents due to hypokalemia
- Concurrent use with frusemide increases the risk of hypokalemia caused by amphotericin B

# Key issues to note

- Use an antihistamine, Paracetamol or hydrocortisone to prevent or treat infusion reactions
- Monitor renal function tests (RFTs) at least 3 times a week
- Amphotericin B should be protected from light/kept in refrigerator
- It is an antibiotic with antifungal properties.

# IMIDAZOLE ANTIFUNGALS

- Have a broad spectrum of activity against dermatophytes and candida spp.
- Most of the drugs in this class are available in topical form except ketoconazole.

## Examples

1. Ketoconazole
2. Miconazole
3. Bifonazole
4. Tioconazole
5. Econazole
6. Isoconazole
7. Clotrimazole (Gel/cream/pessaries 500mg od 6/7)

# Mode of action

Imidazoles suppress cell membrane synthesis of ergosterol leading to their break down, cell leakage and death due to inhibition of synthesis of fungal cytochrome P450 enzyme(lanosterol 14 Demethylase) responsible for ergosterol synthesis.

## KETOCONAZOLE

### Preparations

- Tablets 200mg
- Cream 2%
- Shampoo 2% (liquid form)

**Brands:** Nizoral, Ketozol, Keto, Fungral, Fungicide

# Ketoconazole cont'd

## Pharmacokinetics

When taken orally absorption is variable and increases when the PH in the stomach is acidic. It is metabolised in the liver to inactive metabolites and excreted both as metabolites and unchanged drug in faeces and urine.

## Indications

Oral candidiasis	Athletes foot
Histoplasmosis	Dandruff Seborrheic dermatitis
Vaginal candidiasis	Ring worm
Tinea capitis	Tinea versicolor Prophylaxis in ISS

# Contraindications

- Hepatic impairment
- Breast feeding
- Known hypersensitivity to ketoconazole

## Dose

- **Chronic vaginal candidiasis:** 400mg od for 5 days
- **Other conditions:** 200mg od increased to 400mg if no response
- **Children:** 15-30kg 100mg od
- Over 30kg 200mg od
- 5-12years 100mg od
- 1-4 years 50mg od



# Side effects

- Nausea and vomiting
  - Pruritis
  - Dizziness
  - Paraesthesia/peripheral neuropathy
  - Photophobia
  - Liver damage
  - Gynaecomastia
  - **Tinea versicolor=fungal skin infection causing skin discoloration (darker/lighter patches compared to normal surrounding skin)**
- Abdominal pain
  - Headache
  - Urticaria
  - Thrombocytopenia
  - Skin rash

# Drug interactions

- Antacids, cimetidine, ranitidine and omeprazole may decrease ketoconazole absorption
- Rifampicin, Isoniazid and phenytoin may decrease blood concn of ketoconazole
- Ketoconazole may enhance the anticoagulant effect of warfarin
- Alcohol may increase hepatotoxicity of ketoconazole

# Key issues to note

- Do not use oral ketoconazole to treat superficial fungal infections unless there is no alternative because of the associated toxicities.
- Wait for at least one month before starting ketoconazole after stopping griseofulvin RX
- Acidic environment in the stomach favours absorption of ketoconazole, therefore administer with orange juice or food.

# **TRIAZOLE ANTIFUNGALS**

They are used in RX of systemic fungal infections because of their safety and effectiveness.

## **Examples**

Fluconazole and Itraconazole

## **Mode of action**

They inhibit cytochrome P-450 dependent enzymes resulting in impairment of ergosterol synthesis in fungal cell membranes.

# FLUCONAZOLE

## Preparations

- Tablet 50mg, 150mg, 200mg
- Capsules 100mg, 200mg
- Injection 200mg/100mls

**Brands:** Diflucan, Forcan, Stabilanol

## Pharmacokinetics

Oral absorption of fluconazole is rapid and almost complete, widely distributed with good penetration into CSF. About 80% is excreted unchanged in urine and small amounts of metabolites are excreted in faeces.

# INDICATIONS

- Oral candidiasis
- Cryptococcal meningitis
- Body ring worm
- Vaginal candidiasis
- Coccidioidomycosis
- Tinea versicolor
- Skin candidiasis
- Histoplasmosis
- Tinea pedis (athlete's foot)
- Prevention of fungal infections in ISS patients

# Dose

- **Vaginal and candida balanitis** tab 150mg single dose
- **Oral candidiasis:** 50mg-100mg od for 7-14 days
- **Skin fungal infections:** 50-150mg od for 2-4weeks
- **Children:** 3mg/kg od
- **Cryptococcal meningitis** following amphotericin B:  
oral/IV 800mg od X2/7 then 400mg od for 8/52  
children 6-12mg/kg od
- Prevention of **relapse of Cryptococcal meningitis** in  
AIDs patients after completing primary dose is  
200mg od for life

# Side effects of fluconazole

- ✓ Hypersensitivity reaction
- ✓ Thrombocytopenia (reduced platelets)
- ✓ Hepatic damage
- ✓ Flatulence
- ✓ Abdominal pain
- ✓ Nausea and vomiting
- ✓ Skin rash
- ✓ Diarrhoea
- ✓ Headache
- ✓ Angioedema



# Drug interactions

- The effect of fluconazole may be reduced by rifampicin
- Fluconazole may increase the risk of hypoglycemia with oral sulphonylureas
- Fluconazole may increase the blood levels of phenytoin, atorvastatin, caffeine, diazepam
- Fluconazole may increase the effect of oral anticoagulants.

**Key issues:** Monitor Liver function tests while on RX

- It is not the 1<sup>st</sup> line for dermatophytes, use topical antifungals 1<sup>st</sup> & reserve it for resistant cases.

# GRISEOFULVIN

- It is an Abc derivative from penicillium griseofulvin
- It is effective against a wide range of dermatophytes but not effective against candida.
- It is used in RX of extensive dermatophyte infections which are not responding to topical RX and those affecting the nail and scalp.

**Preparations:** Tablets 500mg

**Brands:** Griso, Fulcin, Creafulvine

**MOA:** Inhibits cell mitosis at metaphase by disrupting the cell's microtubule fxn, it binds to human keratin making it resistant to anti fungal invasion

# Pharmacokinetics

- It is fairly absorbed from GIT but fatty meal improves its absorption.
- It is metabolized in the liver and excreted in urine.

## Indications

- Tinea cruris (fungal infection of groin common in men, eczema maginatum, joke's itch)
- Onychomycosis (nail infections)
- Tinea pedis (Athelete's foot)
- Tinea corporis (ring worms)
- Other skin fungal infections
- Tinea capitis (head)

# Contraindications

- Severe liver disease
- Pregnancy
- Breast feeding
- Porphyria
- Hypersensitivity to griseofulvin

## Dose

- Tablets 500mg-1000mg for 4-8weeks
- Nail infections: 1000mg od for 4-6months or longer
- Children: 10mg/kg od or in 2 divide dose 4-8weeks

# Side effects

- Dry mouth
- Angular stomatitis
- Insomnia
- Headache
- Altered taste
- Urticaria
- Diarrhoea
- Dizziness
- Nausea and vomiting
- Skin rash   Fatigue

## Drug interactions

- It may decrease the effect of oral contraceptives and warfarin
- Phenobarbitone may decrease its GIT absorption
- It may increase the effect of alcohol

# Key issues to note

- It should be taken with a fatty meal to increase its absorption
- Advise the patient not to take alcohol during RX
- Inform the patient with nail infections that RX is long term since the infected nail has to grow out
- Advise women to use additional non hormonal contraceptives e.g condoms since effectiveness of oral contraceptives is reduced
- Advise men to not to father a child during RX and 6 months after RX since sperm it affects sperm quality

# ALLYLAMINE DERIVATIVES

- Allylamine antifungals are the newest and have a broad spectrum activity against dermatophytes.
- They are fungicide in action

**Examples:** Terbinafine and Butenafine

## **Mode of action**

They act by inhibiting fungal sterol biosynthesis, causing accumulation of squalene within the fungal cell and cell death.

# TERBINAFINE

## Preparations

- Tablets 125mg, 250mg
- Cream 1%

**Brands:** Exifine, Lamisil, Fungisafe

## Pharmacokinetics

- It is well absorbed from GIT, distributed into the stratum corneum of the skin, nail plate and hair.
- It is metabolized in the liver to inactive metabolites which are excreted mainly in urine.



# Indications

- Athlete's foot (tinea pedis)
- Body ring worm
- Tinea cruris
- Onychomycosis
- Tinea versicolor

## Contraindications

- Known hypersensitivity to terbinafine
- Severe hepatic disease

# Dose

- **Adult:** 250mg od for 2-6 weeks (**most infections**)
- **Onychomycosis:** 250mg od 6 weeks to 3 months
- **Children:** 6-11 years 125 mg od for 2 weeks
- 1-5 years 62.5mg od for 2 weeks

## Side effects

- |                     |            |                    |
|---------------------|------------|--------------------|
| ➤ Skin rash         | Myalgia    | Dyspepsia          |
| ➤ Urticaria         | Arthralgia | Flatulence         |
| ➤ Headache          | Diarrhoea  | Malaise            |
| ➤ Taste disturbance |            | Photosensitivity   |
| ➤ Dizziness         | Anorexia   | Visual disturbance |

# Drug interactions

- Sudden PV bleeding may occur when take with oral contraceptives
- Cimetidine may increase blood levels of terbinafine
- Rifampicin may reduce the blood levels and therapeutic effect of terbinafine

## Key issues to note

- Advise the patient to complete Rx even if symptoms have resolved
- Terbinafine may used for other forms of tinea where griseofulvin is ineffective and RX is for 4-6/52
- Tablets may be given without regard to meals.