Antifungal drugs

CLASSIFICATION OF ANTIFUNGAL DRUGS

Drugs for systemic fungal infections

Polyene antibiotics

-Amphotericin B

Pyrimidine antimetabolites

-Flucytosine

Antifungal azoles

-Ketoconazole

-Fluconazole

-Itraconazole

Echinocandins

Caspofungin, micafungin, and anidulafungin

Drugs for superficial fungal infections

Systemic drugs

-Griseofulvin

-Iodide

Topical drugs

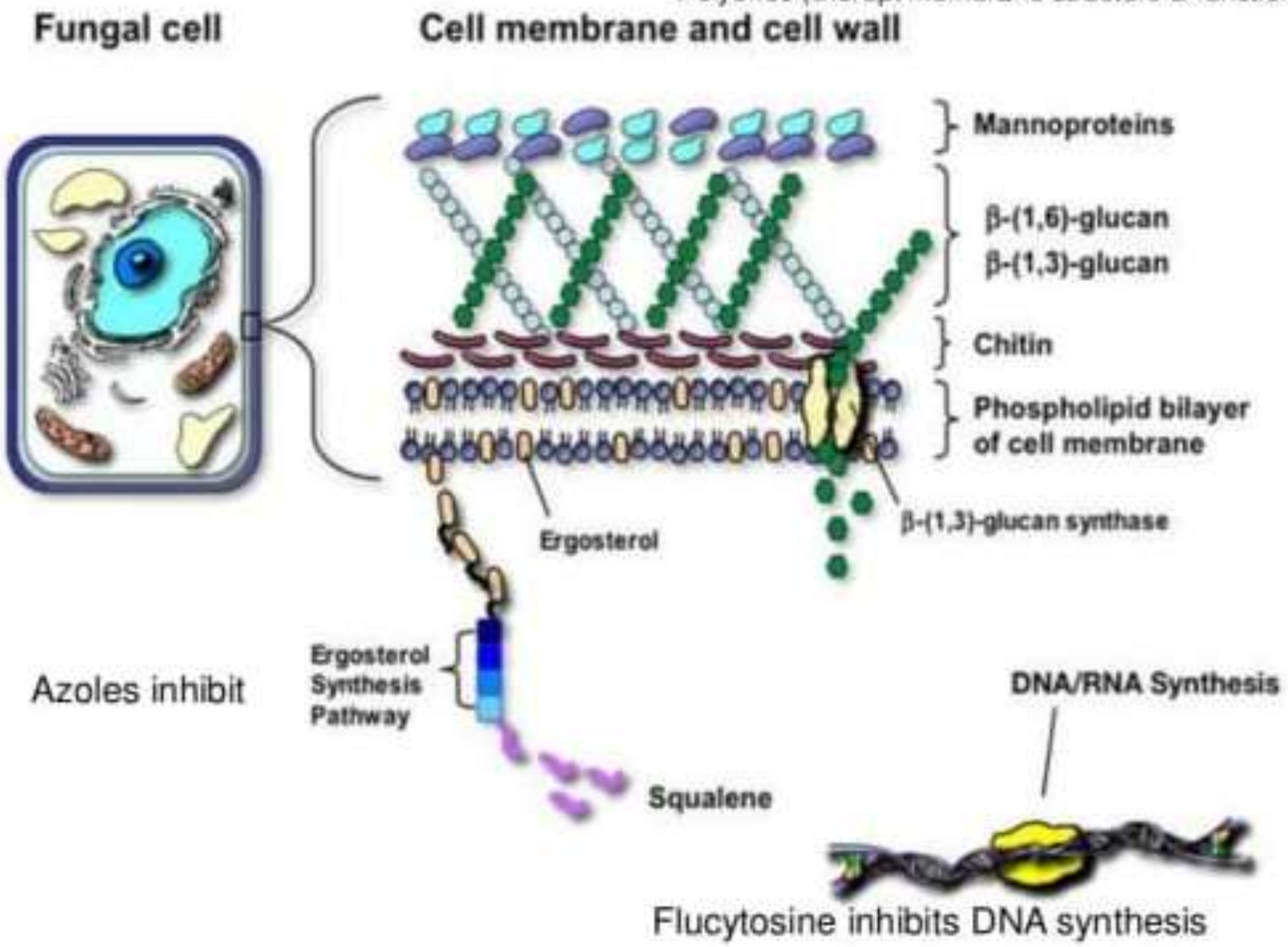
-Nystatin

-Haloprogin

-Tolnaftate

-Azoles (**miconazole**, econazole, clotrimazole, etc.)

Polyenes (Disrupt membrane structure & function)



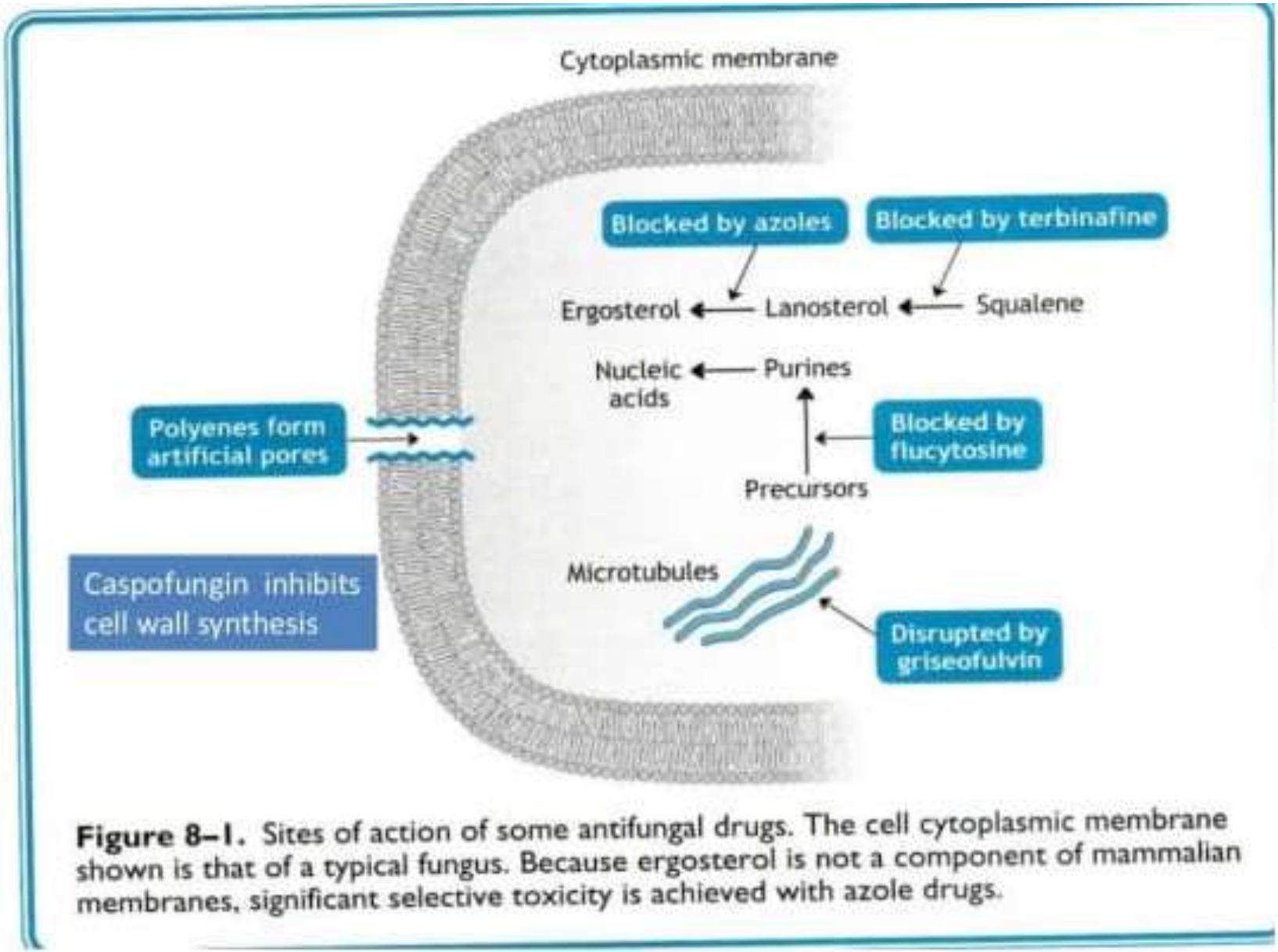
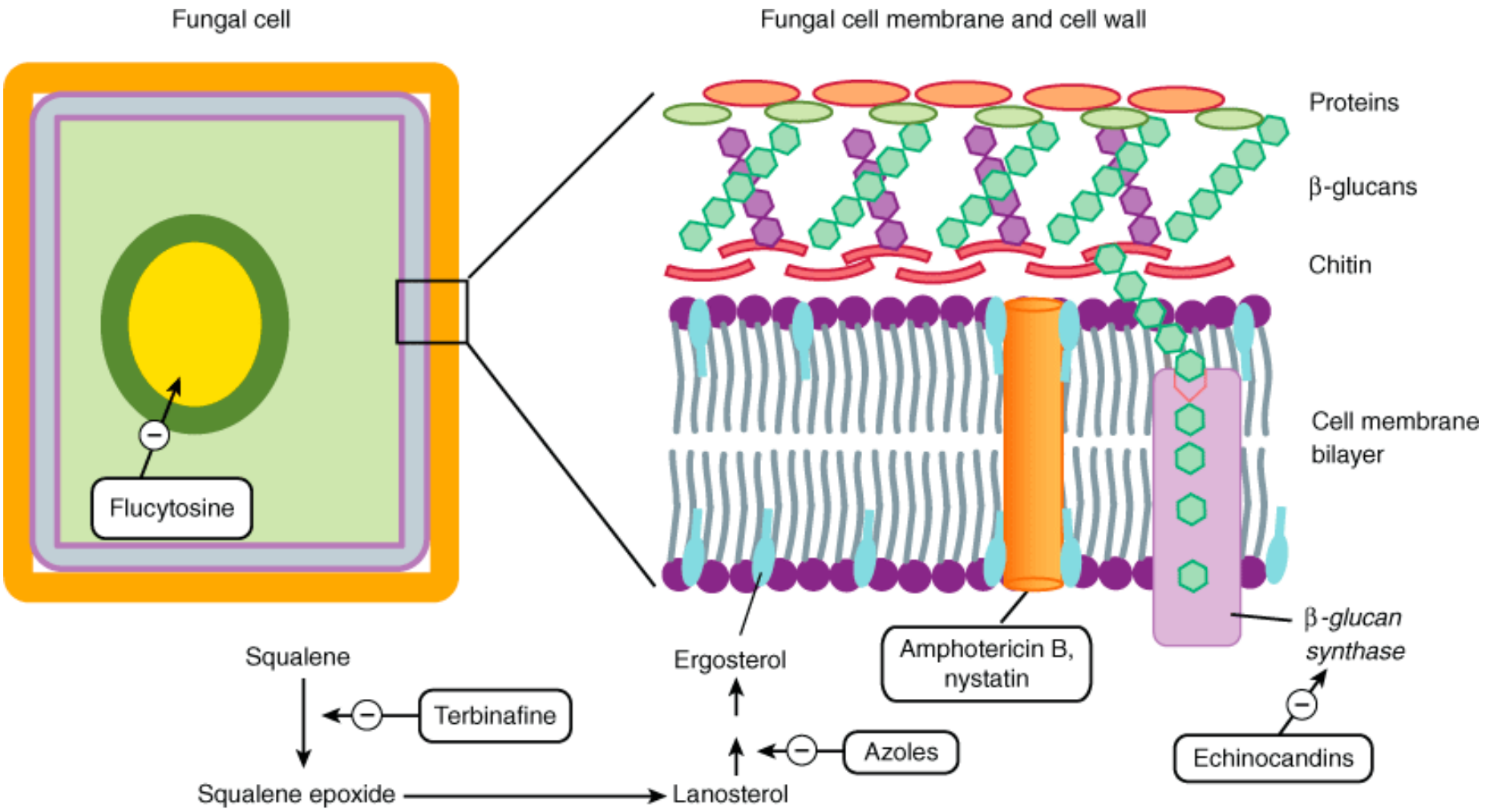


Figure 8–1. Sites of action of some antifungal drugs. The cell cytoplasmic membrane shown is that of a typical fungus. Because ergosterol is not a component of mammalian membranes, significant selective toxicity is achieved with azole drugs.

Targets of antifungal drugs



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

Classification based on mechanism of action

1. Fungal cell wall synthesis inhibition: Caspofungin.
2. Bind to fungal cell membrane ergosterol: Amphotercin–B, Nystatin.
3. Inhibition of ergosterol + lanosterol synthesis: Terbinafine, Naftifine, Butenafine.
4. Inhibition of ergosterol synthesis: Azoles
5. Inhibition of nucleic acid synthesis: 5–Flucytosine.
6. Disruption of mitotic spindle and inhibition of fungal mitosis: Griseofulvin.
7. Miscellaneous:
   - Ciclopirox, Tolnaftate, Haloprogin, Undecylenic acid, Topical azoles.

PHARMACOLOGY OF AMPHOTERICIN B

Chemistry

-**Amphotericin B** is a polyene antibiotic (polyene: containing many double bonds)

Mechanism of action

-Binding to ergosterol present in the membranes of fungal cells

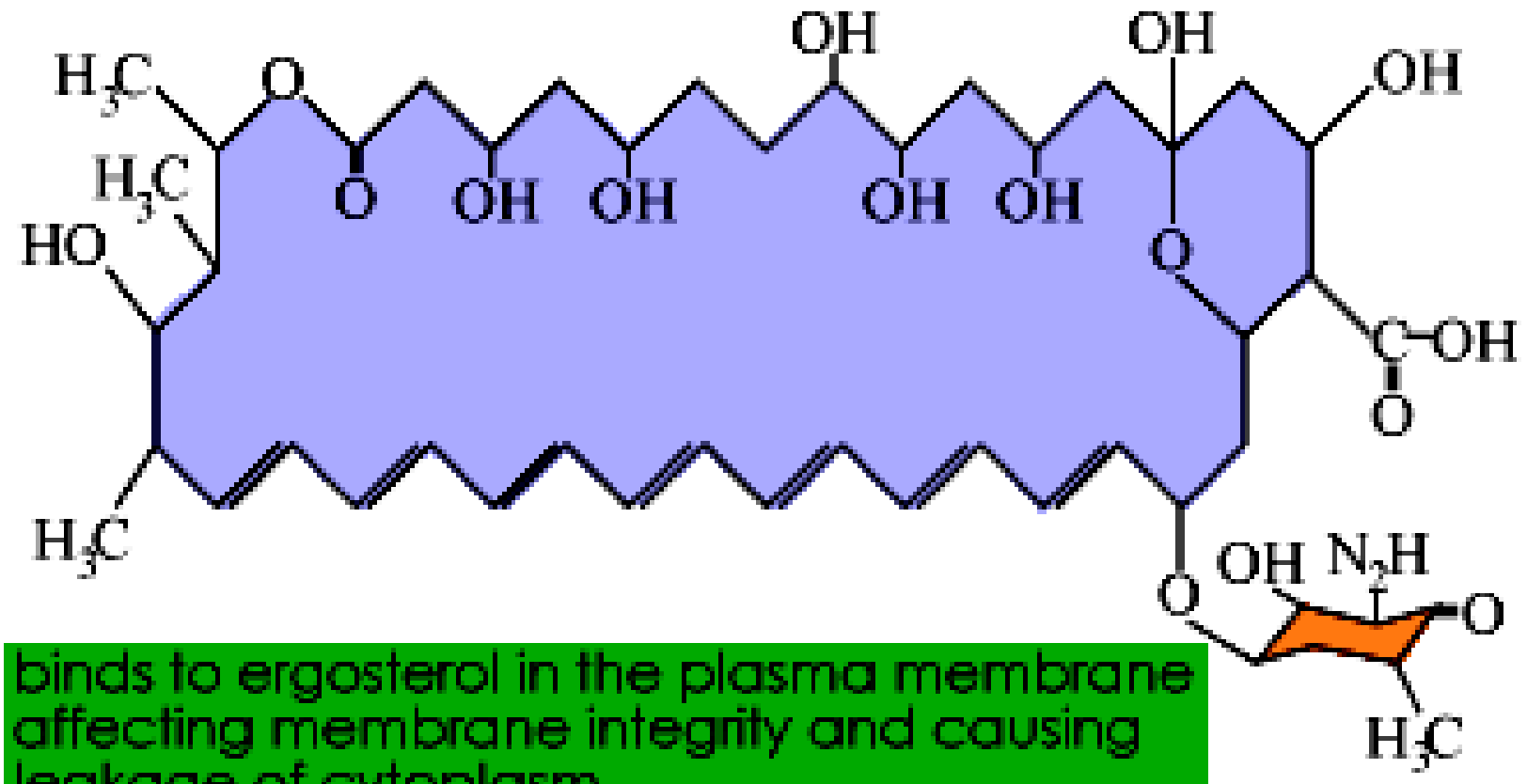
↓

Formation of "pores" in the membrane

↓

Leaking of small molecules (mainly K+) from the cells

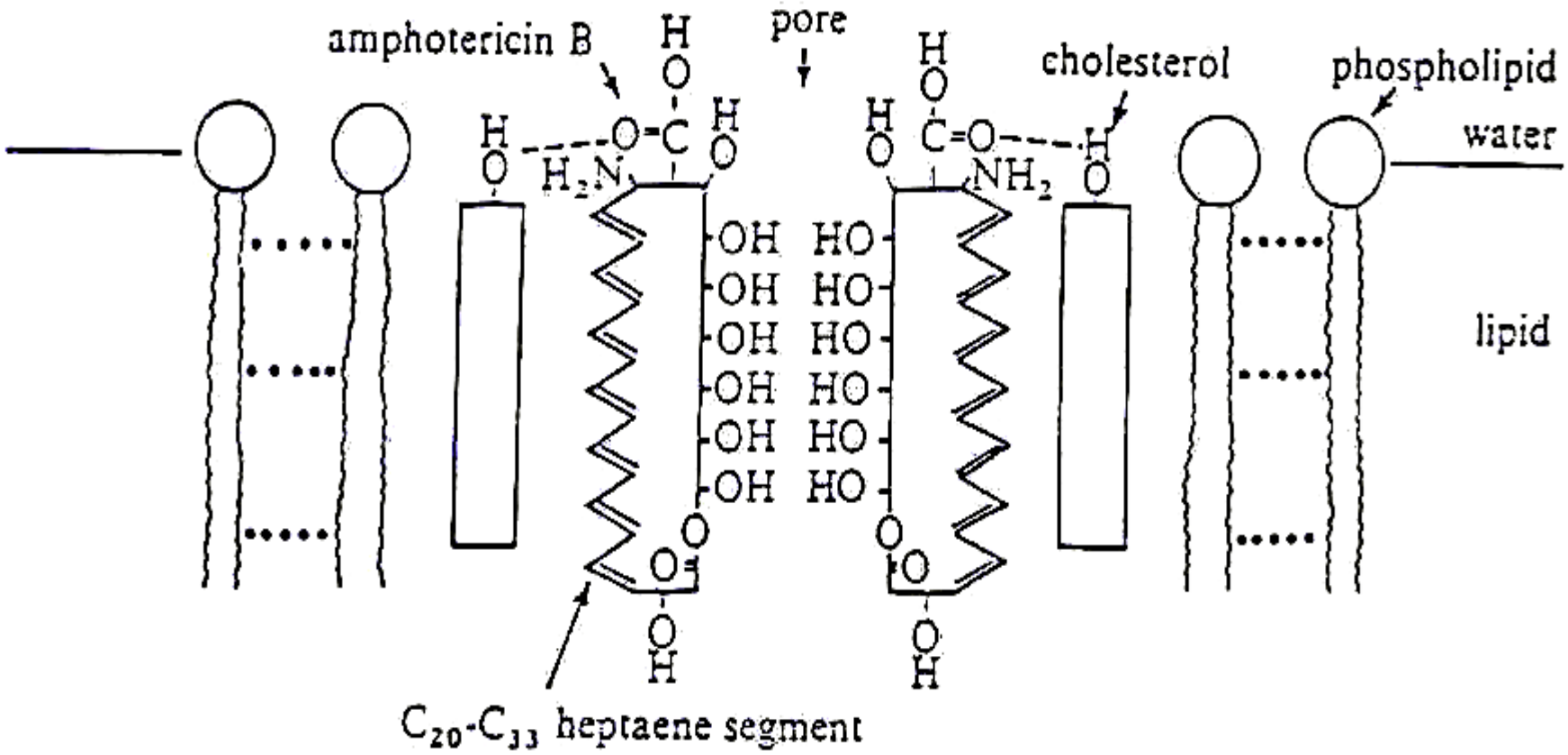
-The ultimate effect may be ***fungicidal*** or ***fungistatic*** depending on the organism and on drug concentration.



binds to ergosterol in the plasma membrane affecting membrane integrity and causing leakage of cytoplasm

Amphotericin B

Model for Amphotericin B induced Pore in Cell Membrane



Antifungal spectrum and resistance

-Antifungal spectrum includes:

- *Histoplasma capsulatus*
- *Coccidioides immitis*
- *Paracoccidioidoides braziliensis*
- *Aspergillus fumigatus*
- *Blastomyces dermatitidis*
- *Cryptococcus neoformans*
- *Candida albicans*
- *Sporothrix schenckii*
- *Mucor and Rhizopus spp*
- Resistance may occur but is very rare

Pharmacokinetics

-F(oral): < 1% (too irritant to be given IM)

-Distribution in all body tissues, except CNS and eye

(concentrations in CSF are <10% than in plasma; however therapeutic concentrations in CNS can usually be achieved with parenteral administration)

-Biotransformation: > 95%

-Renal excretion: < 5%

-Half life: » 14 days

Drug formulations and administration

-Formulations:

a) complex with deoxycholate

b) liposomal complex (adverse effects seem diminished)

-Administration:

IV infusion, intrathecal, topical, oral (to treat intestinal mycoses)

Adverse effects

(the therapeutic index of the drug is very narrow)

-Headache, arthralgias, nausea and vomiting fever and chills, hyperpnea, shock-like fall in blood pressure (they may appear during IV infusion and may be reduced by concomitant administration of antipyretics or meperidine)

-Malaise, weight loss

-Nephrotoxicity (azotemia , decreased GFR, renal tubular acidosis, renal wasting of K+ and Mg++,). It is common (up to 80% of patients) and may be severe

-Normocytic anemia, likely due to decreased production of erythropoietin (frequent)

-Thrombophlebitis

-Delirium, seizures (after intrathecal injection)

Therapeutic uses

Amphotericin is the drug of choice for:

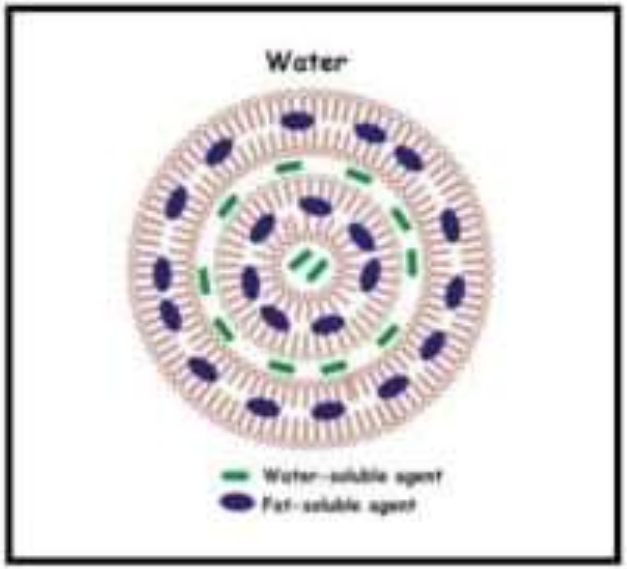
-Disseminated histoplasmosis
-Disseminated and meningeal coccidioidomycosis
-Disseminated and meningeal cryptococcosis
-Invasive aspergillosis
-Deep candidiasis
-Mucormycosis

Amphotericin is an alternative drug for:

-Blastomycosis
-Paracoccidioidomycosis
-Extracutaneous sporotrichosis

[Amphotericin is preferred when these mycoses are rapidly progressive, occur in immunocompromised host or involve the CNS]

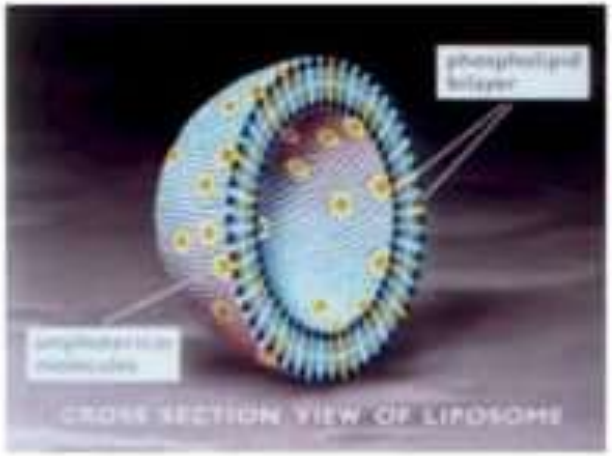
The 'LIPOSOME'..



•Liposomal AMB (Small unilamellar vesicles) :

10% AMB incorporated in SUV made up of lecithin

Lipid formulations: 20-50 times more expensive than AmB-deoxycholate



PHARMACOLOGY OF FLUCYTOSINE

Chemistry

-Flucytosine is a fluorinated pyrimidine

Mechanism of action

-The drug is accumulated in fungal cells by the action of a ***membrane permease*** and is converted by a ***cytosine deaminase*** to 5-fluorouracil (selectivity occurs because mammalian cells do not accumulate and do not deaminate flucytosine)

↓

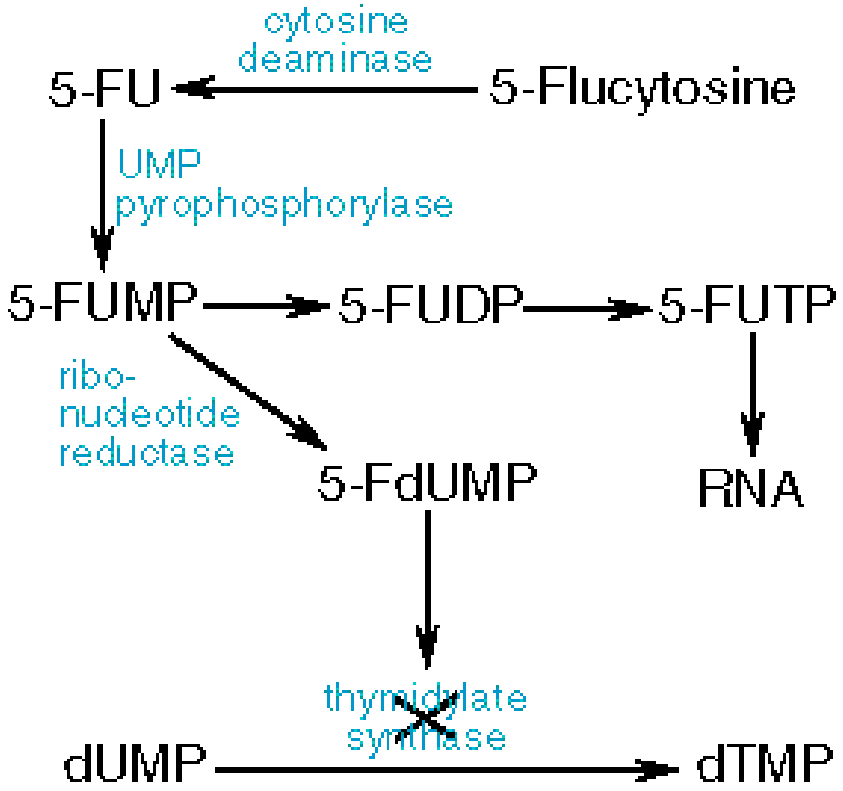
5-fluorouracil is metabolized to 5-fluorouridylic acid

which can be

a) incorporated into the RNA (this leads to a ***misreading of the fungal genetic code***)

b) further metabolized to 5-deoxyfluorouridylic acid, a potent inhibitor of thymidylate synthase (this leads to a ***blockade of fungal DNA synthesis***)

-The ultimate effect may be ***fungicidal*** or ***fungistatic*** depending on the organism and on drug concentration.



Action of flucytosine in fungi.

5-Flucytosine is transported into the fungal cell, where it is deaminated to 5-fluorouracil (5-FU). The 5-FU is then converted to 5-fluorouracil-ribose monophosphate (5-FUMP) and then is either converted to 5-FUTP and incorporated into RNA or converted by ribonucleotide reductase to 5-FdUMP, which is a potent inhibitor of thymidylate synthase.

Antifungal spectrum and resistance

-Antifungal spectrum includes *Cryptococcus neoformans, Candida albicans, Aspergillus fumigatus, and several soil fungi which cause chromomycosis.*

-Resistance may arise rapidly during therapy and is an important cause of therapeutic failure when the drug is used alone.

Pharmacokinetics and administration

-F(oral): > 80%

-Distribution in all body tissues, including CNS and the eye.

-Volume of distribution: » 42 L

-Renal excretion: » 99%

-Half-life: » 4 hours (in renal failure, half-life may be as long as 200 hours)

-Administration: oral, IV

Adverse effects

(toxicity is generally not pronounced)

-Anorexia, nausea and vomiting, diarrhea

-Severe ulcerative enterocolitis (rare)

-Skin rashes

-Headache, dizziness, confusion

-Reversible bone marrow depression (8-13%)(leukopenia, thrombocytopenia)

-Liver dysfunction (5-10%)

-Alopecia, peripheral neuritis (rare)

[toxicity may be due to the conversion of flucytosine to 5-fluorouracil by the intestinal flora of the host]

Therapeutic uses

-Deep candida infections, cryptococcal meningitidis (always in combination with amphotericin B)

-Chromomycosis (effectiveness is limited)

Contraindications

-Pregnancy (5-fluorouracil is teratogenic)

PHARMACOLOGY OF ANTIFUNGAL AZOLES

Chemistry

-Imidazole derivatives: **ketoconazole**, miconazole, econazole, clotrimazole

-Triazole derivatives: **itraconazole, fluconazole**.

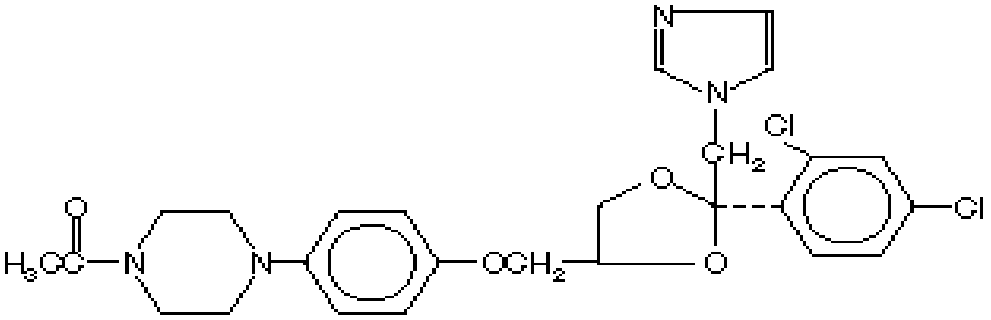
Mechanism of action

-Inhibition of sterol 14-alpha-demethylase, a cytochrome P450-dependent enzyme (relative selectivity occurs because the affinity for mammalian P450 isozymes is less than that for the fungal isozyme)

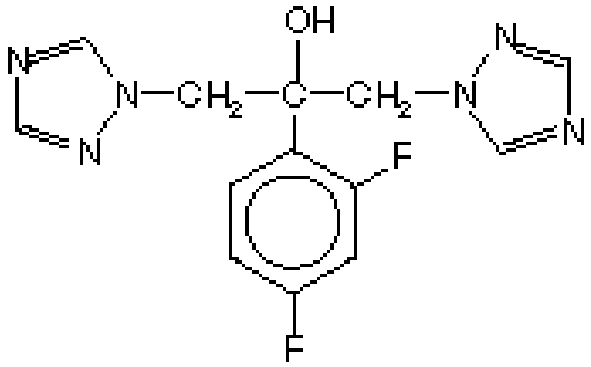
↓

blockade of the synthesis of ergosterol in fungal cell membranes

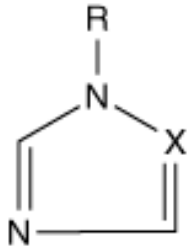
-The ultimate effect may be ***fungicidal*** or ***fungistatic*** depending on the organism and on drug concentration.



KETOCONAZOLE

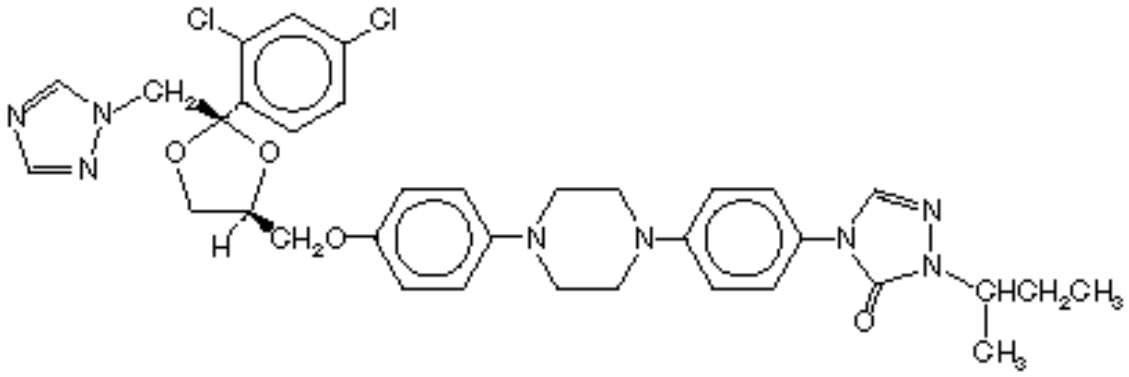


FLUCONAZOLE



Azole nucleus

X = C, imidazole
X = N, triazole



ITRACONAZOLE

Antifungal spectrum and resistance

-Antifungal spectrum includes:

Histoplasma capsulatus, *Coccidioides immitis*

Paracoccidioidoides braziliensis , *Aspergillus fumigatus*

Blastomyces dermatitidis, *Cryptococcus neoformans*

Candida albicans , *Sporothrix schenckii*

Dermatophytes (Microsporum, Epidermophyton, Trichophyton, Malassezia furfur)

-Resistance can occur but is rare.

-Cross-resistance between azoles is a common finding.

Other effects

-Azoles may inhibit certain mammalian cytochrome P450 isozymes and therefore they may

1) inhibit the synthesis of androgens and of corticosteroids

2) potentiate the effects of several drugs including cyclosporine, phenytoin, terfenadine, astemizole, tolbutamide and warfarin.

Pharmacologic properties of five systemic azole drugs

	Water Solubility	**Absorption**	**CSF: Serum Concentration Ratio**	***t*** $_{1/2}$ **(Hours)**	**Elimination**	**Formulations**
Ketoconazole	Low	Variable	< 0.1	7–10	Hepatic	Oral
Itraconazole	Low	Variable	< 0.01	24–42	Hepatic	Oral, IV
Fluconazole	High	High	> 0.7	22–31	Renal	Oral, IV
Voriconazole	High	High	. . .	6	Hepatic	Oral, IV
Posaconazole	Low	High	. . .	25	Hepatic	Oral

Pharmacokinetics and administration

-F(oral): itraconazole » 55%, fluconazole >90%.
(acidity favors oral absorption of ketoconazole)
-Distribution in all body tissues. Penetration into CNS is generally negligible, ***but good for fluconazole***.
-Renal excretion: fluconazole » 75%, others < 1%
-Half-lives (hrs): ketoconazole » 8, itraconazole » 35
-Administration: oral, IV, topical

Adverse effects

-Anorexia, nausea and vomiting (they are dose-dependent and patients receiving high doses may require antiemetics)
-Gynecomastia, decreased libido, impotence, menstrual irregularities (with ketoconazole, due to blockade of adrenal steroid synthesis)
-Hepatitis (is rare, but can be fatal)
-Hypokalemia, hypertension (itraconazole)
-Azoles are potent teratogenic drugs in animals

Therapeutic uses

Azoles are first choice drugs for:

-Blastomycosis (ketoconazole)
-Paracoccidioidomycosis (ketoconazole)
-Chronic pulmonary histoplasmosis
-Meningeal coccidioidomycosis (fluconazole)
-Meningeal cryptococcosis (fluconazole)
-Cutaneous and deep candidiasis

Azoles are alternative drug for:

-Invasive aspergillosis
-Sporotrichosis

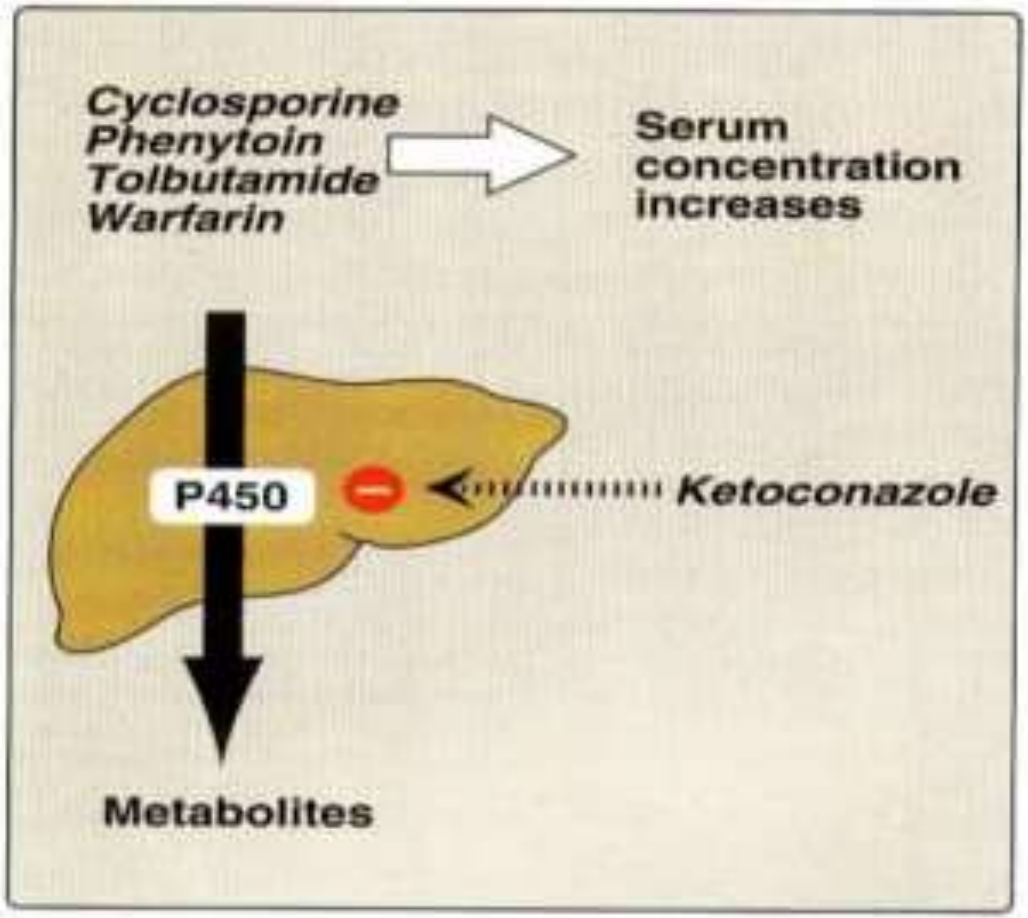
Topical azoles are used for:

-Dermatophytoses (not of hair and nails)
-Tinea versicolor
-Mucocutaneous candidiasis

Contraindications

-Systemic azoles are contraindicated in pregnancy (potential teratogenic effects and endocrine toxicity for the fetus)

Drug Interactions



PHARMACOLOGY OF GRISEOFULVIN

Chemistry

-Griseofulvin is a benzofuran derivative

-The drug is practically insoluble in water

Mechanism of action

-An active transport accumulates the drug in sensitive fungal cells where

↓

griseofulvin causes disruption of the mitotic spindle by interacting with polymerized mycrotubules

-The ultimate effect is ***fungistatic***

Antifungal spectrum and resistance

-Antifungal spectrum includes only *Dermatophytes (Microsporum, Epidermophyton, Trichophyton)*

-The drug is ineffective against other fungi producing superficial lesions (like *Candida* and *Malassezia furfur*) and those producing deep mycoses.

-Resistance is uncommon. It seems to be due to a decrease of the energy-dependent transport mechanism.

Echinocandins

- Newest class of antifungal agents
- Intravenous
- inhibiting the synthesis of (1–3)-glucan
- Well tolerated
- **Caspofungin**
- **Micafungin**
- **Anidulafungin**

Pharmacokinetics and administration

-F(oral): » 50% (micronization of the drug and a high-fat food favor oral absorption)
-Distribution is ***mainly in keratinized tissues where the drug is tightly bound*** and where it can be detected 4-8 hours after oral administration. Concentration in other tissues and body fluids is negligible.
-Elimination: mainly in the feces.
-Half-life (hrs): » 24 hours
-Administration: oral

Adverse effects

(*incidence is quite low)*
-Xerostomia, nausea and vomiting, diarrhea
-Headache (up to 15%), fatigue, blurred vision, vertigo, increased effects of alcohol
-Hepatotoxicity (rare)
-Leukopenia, neutropenia
-Allergic reactions (urticaria, skin rashes, serum sickness, angioedema)
-Teratogenic effects in several animal species

Therapeutic uses

-Mycotic disease of the skin, hair and nails (long treatments are needed)

TOPICAL ANTIFUNGAL DRUGS

Nystatin

-A polyene antibiotic useful only for local candidiasis.

-Administration: cutaneous, vaginal, oral.

Haloprogin

-The drug is fungicidal to various species of dermatophytes and candida.

-Principal use: in tinea pedis (cure rate » 80%)

Tolnaftate

-The drug is effective against most dermatophytes and *Malassezia furfur* but not against *Candida*

-In tinea pedis the cure rate is » 80%

Antifungal azoles

-Azoles are reported to cure dermatophyte infections in 60-100% of cases

-The cure rate of mucocutaneous candidiasis is > 80% and that of tinea versicolor > 90%.

-Administration: cutaneous, vaginal.

-Cutaneous application rarely causes erythema, edema, vescication, desquamation and urticaria

-Vaginal application may cause mild burning sensation and abdominal pain.

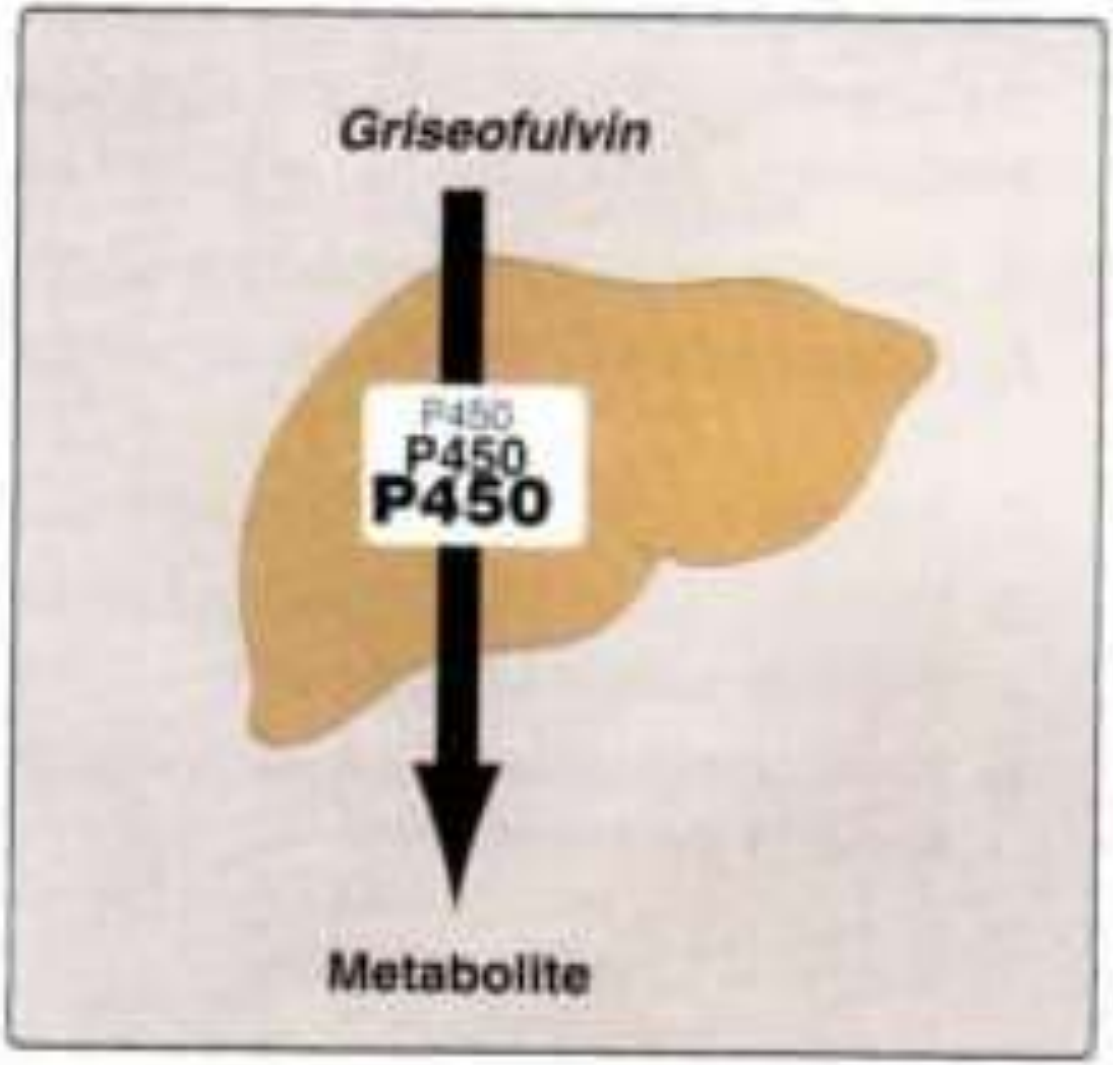


Figure 35.16
Induction of hepatic cytochrome