

ANTIFONGIQUES



Enseignant : F. Van Bambeke

FARM2129 – année 2008-2009

02/12/2008

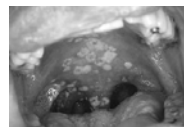
FARM2129 - Antifongiques

1

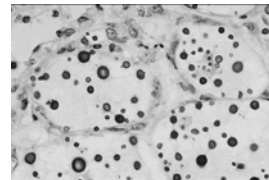
Il y a champignon et champignon.



oncomycose



candidose



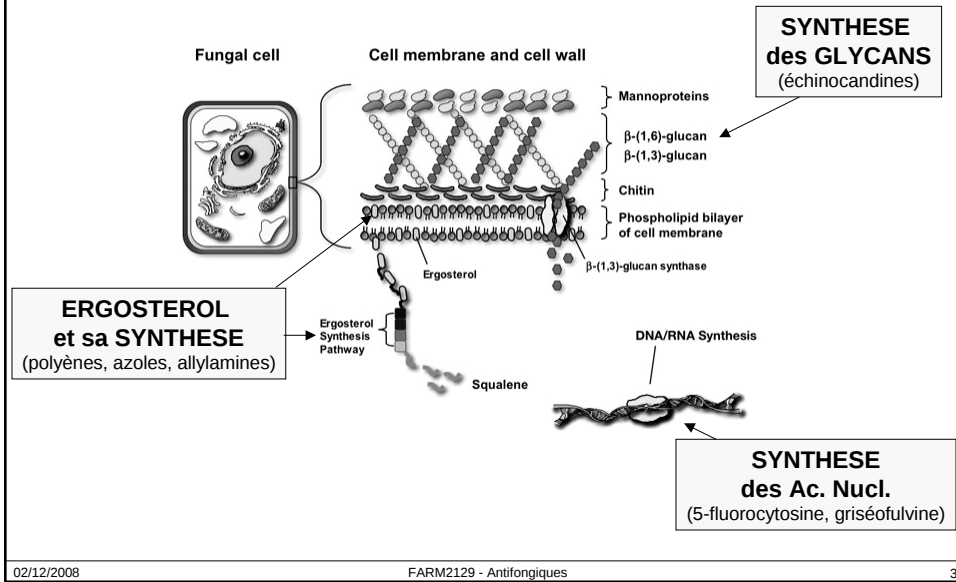
cryptococose pulmonaire

02/12/2008

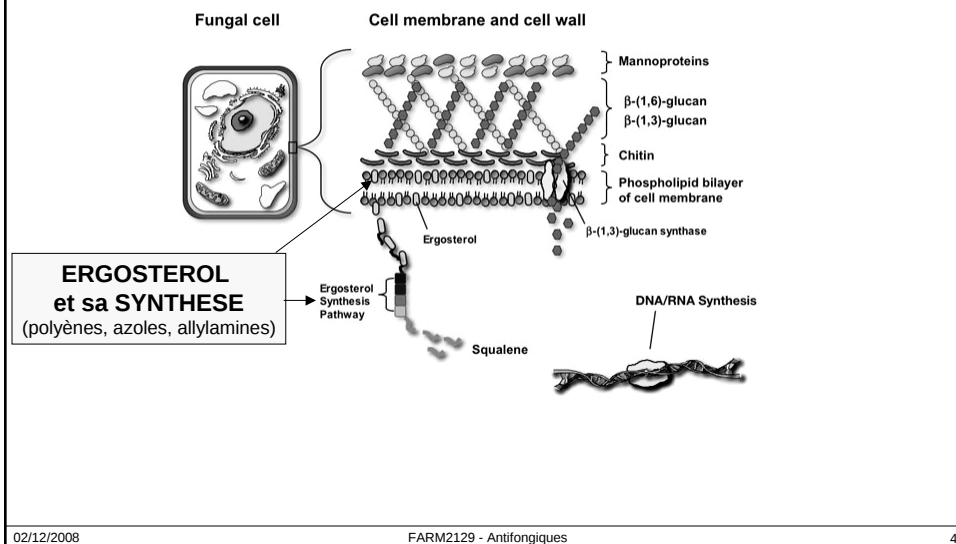
FARM2129 - Antifongiques

2

Cibles des médicaments antifongiques

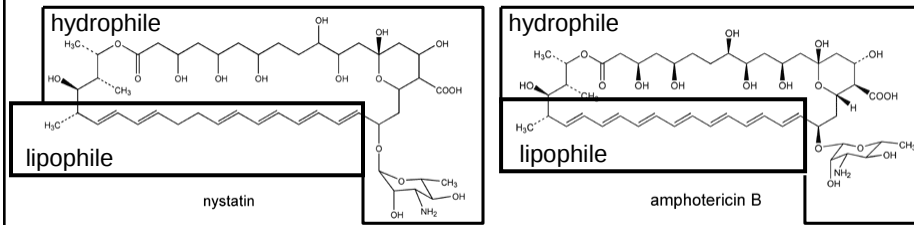


Cibles des médicaments antifongiques



Polyènes antifongiques

Molécules amphiphiles mais volumineuses
→ mal résorbées

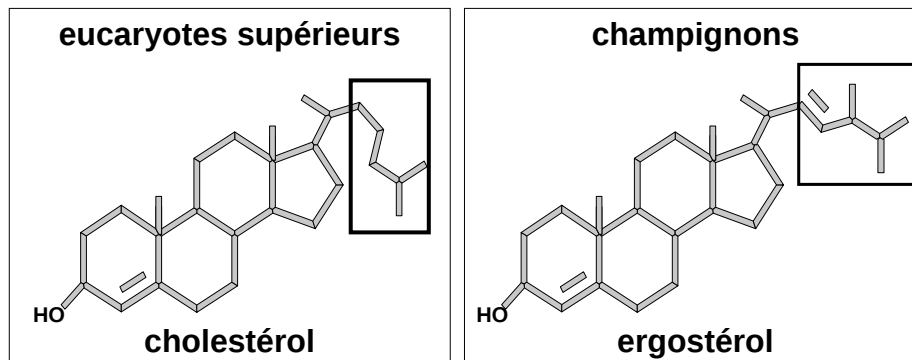


02/12/2008

FARM2129 - Antifongiques

5

Cible pharmacologique: les stérols membranaires



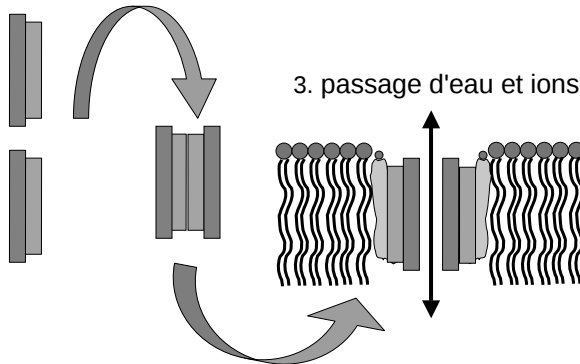
02/12/2008

FARM2129 - Antifongiques

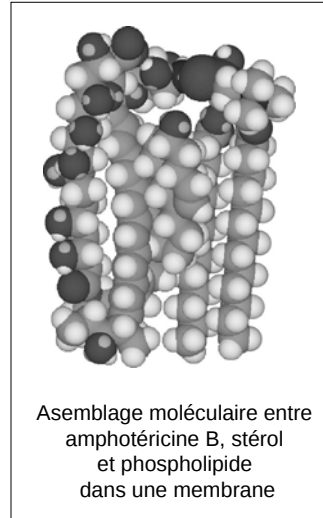
6

Mécanisme d'action des polyènes antifongiques

1. formation de dimères
peu solubles...



2. Insertion dans la membrane
au niveau de l'ergostérol



02/12/2008

FARM2129 - Antifongiques

7

Mécanisme d'action des polyènes antifongiques

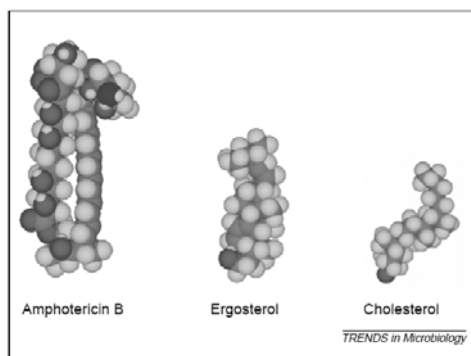


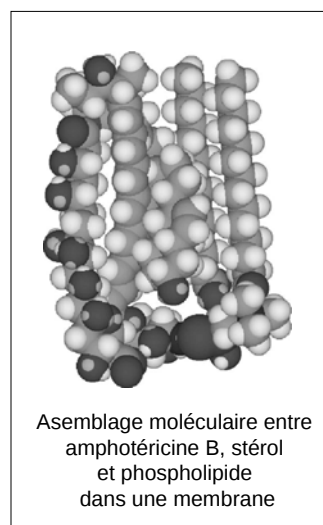
Fig. 3. The polyene antifungal agent, amphotericin B, ergosterol and cholesterol, visualised in three dimensions. Ergosterol, the sterol found in fungal cell membranes, retains a cylindrical shape in all rotations and binds better to the hydrophobic (right-hand) side of the amphotericin B molecule than does cholesterol, with its sigmoid structure. Cholesterol is the membrane sterol found in mammalian cells; the differential binding affinity of amphotericin B for the two sterols is the basis of its selective antifungal action.

Odds, *Trends in Microbiology* (2003) 11:272-279

02/12/2008

FARM2129 - Antifongiques

8



Polyènes antifongiques: propriétés pharmacologiques

+	-
Fongicides Spectre large, peu de résistance	Résorption mauvaise voire nulle (nystatine) Antagonisme avec les azolés Faible spécificité → toxicité: • immédiate: fièvres, frissons, nausées, vomissements, hypotension, arythmies, ... • à court terme: néphrotoxicité • à moyen terme: anémie
nystatine	Amphotéricine B
usage topique • oral: candidoses, dermatophyties • décontamination intestinale	• mycoses systémiques • mycoses oropharyngées et digestives graves

02/12/2008

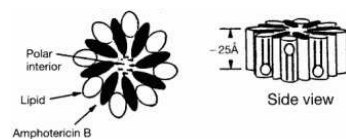
FARM2129 - Antifongiques

9

Formes lipidiques de l'amphotéricine

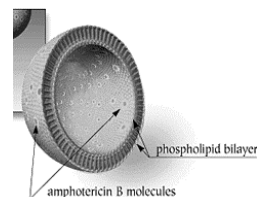
AMBdeoxycholate

ABELCET



AMPHOTEC

AmBisome



The various lipid formulations of AMB have demonstrated antifungal efficacy at least equivalent to the conventional product with significantly reduced nephrotoxicity.

In: THE USE OF LIPID FORMULATIONS OF AMPHOTERICIN B IN CANCER PATIENTS -- Rod Quilitz, PharmD, Department of Pharmacy, H. Lee Moffitt Cancer Center & Research Institute, University of San Francisco, Cal.

<http://www.moffitt.usf.edu/cancjrnl/v5n5/departement3.html>

02/12/2008

FARM2129 - Antifongiques

10

Formes lipidiques: propriétés pharmacologiques

3 Drug profiles of amphotericin B (AMB) formulations

Parameter	AMB deoxycholate	AMB lipid complex	Liposomal AMB
Dosage* (mg/kg per day)	0.5–1.5	5	3–5 (or higher)
Maximum serum concentration†	—	Lower	Higher
Infusion-related toxicity‡	High (50%–60%)	Moderate (20%–40%)	Mild (10%–20%)
Decrease in serum potassium	****	**	**
Anaemia	****	+	+
Nephrotoxicity	**** (up to 80%)	+ (15%–25%)	+ (10%–20%)
Prevention of infusion-related toxicity§	Required	Required	Generally not required

* Commonly prescribed treatment doses; dose varies with pathogen. High-dose liposomal AMB required for zygomycete infection (≥ 5 mg/kg per day). † In comparison with AMB deoxycholate. ‡ Includes fever, chills, headache, joint and muscle pain, and hypotension. Before therapy, a test dose is recommended to identify patients in whom severe infusion-related reactions might occur. § Usually comprises "cocktail" of antipyretic, antiemetic and antihistamine drugs. Value of corticosteroids not proven.

Mais cher et administration intraveineuse obligatoire
→ indications limitées

Chen et al. Med J Aust. (2007) 187:404-9.

02/12/2008

FARM2129 - Antifongiques

11

Formes lipidiques: indications selon la notice

Abelcept	AmBisome
Infections fongiques généralisées: Abelcet est recommandé dans le traitement des infections fongiques graves, chez les patients n'ayant montré aucune amélioration avec l'amphotéricine B conventionnelle, ou chez les patients ayant développé une insuffisance rénale lors du traitement à l'amphotéricine B, même lorsque ce dernier avait été administré en même temps qu'un litre de solution saline physiologique par jour.	AmBisome est destiné au traitement des formes graves de mycoses systémiques et/ou profondes des patients ne répondant pas à l'amphotéricine B conventionnelle ou des patients représentant une contre-indication à l'administration de celle-ci due à l'existence de lésions rénales. Une réponse positive a été obtenue chez 80 % de ces patients traités pour une candidiase systémique, chez 70 % des patients traités pour une aspergilliose et chez 100 % des patients traités pour une cryptococcose....

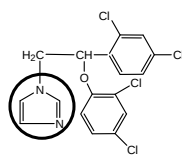
02/12/2008

FARM2129 - Antifongiques

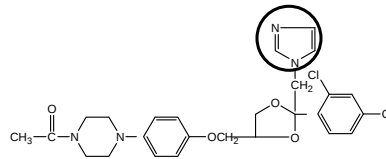
12

Dérivés azolés

imidazoles

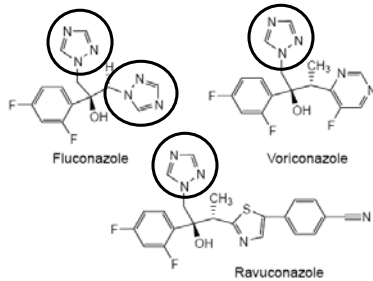


Miconazole



Ketoconazole

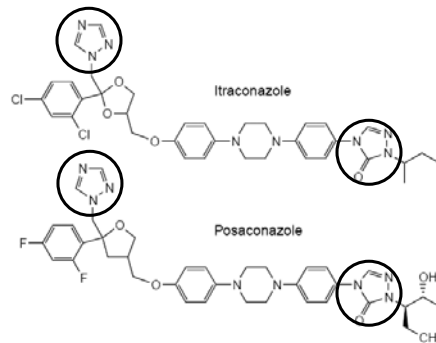
triazoles



Fluconazole

Voriconazole

Ravuconazole



Itraconazole

Posaconazole

02/12/2008

FARM2129 - Antifongiques

13

Biosynthèse de l'ergosterol

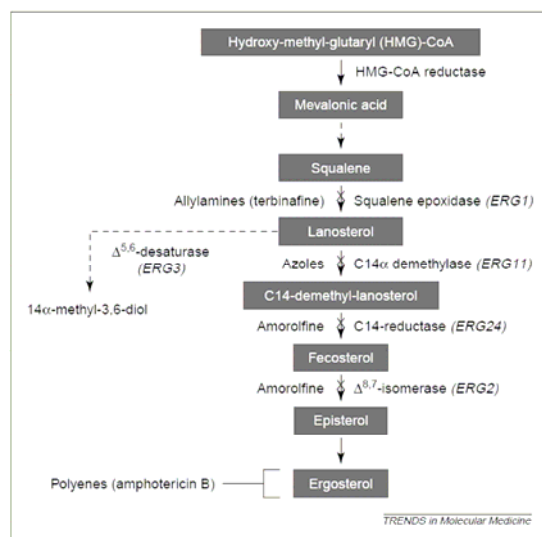


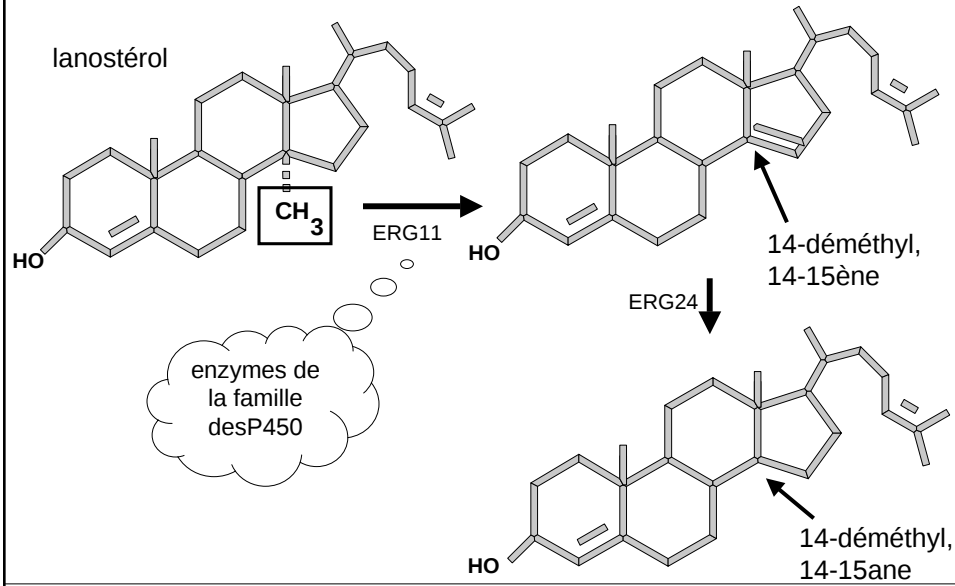
Fig. 2. Mechanism of action of antifungal drugs affecting the ergosterol biosynthetic pathway. The target enzymes are reported on the right with encoding genes in parentheses, whereas the antifungal drugs are reported on the left of the arrows indicating the sequential steps of sterol biosynthesis.

02/12/2008

FARM2129 - Antifongiques

14

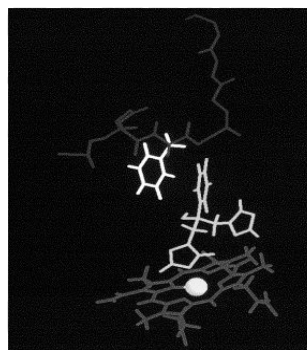
Biosynthèse de l'ergosterol



Dérivés azolés et site actif de Erg11p



Le cytochrome P450 possède un hème essentiel à l'activité oxydo-reductasique



Le cycle imidazole ou triazole se colle à l'hème ...

<http://users.aber.ac.uk/cca/p450/intro.html>

Dérivés azolés et site actif de Erg11p

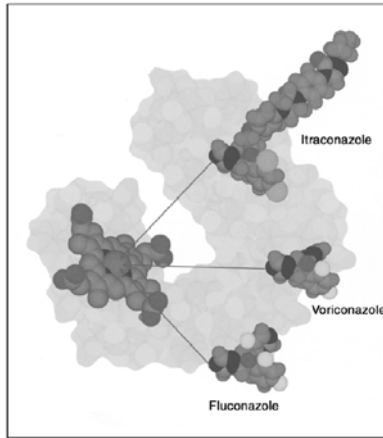


Fig. 4. Cartoon giving an approximate impression of the protoporphyrin moiety located at the active site of Erg11p (Cyp51p), the cytochrome P450 enzyme target for imidazole and triazole antifungals. Three triazole antifungals, itraconazole (top), fluconazole (centre) and voriconazole (bottom) are shown in comparable orientations. Arrows link theazole nitrogen atom to the iron atom where the azoles bind to block the active site of the enzyme. The different side chains attached to the commonazole pharmacophore in the three examples shown will obviously bind differently to the surrounding regions of the whole P450 protein.

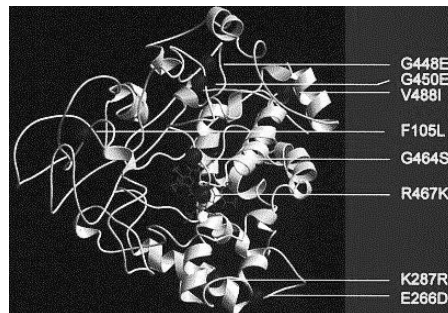
Odds, Trends in Microbiology (2003) 11:272-279

02/12/2008

FARM2129 - Antifongiques

17

Mécanismes de résistance aux dérivés azolés



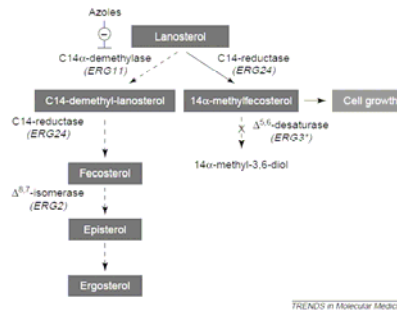
Mechanism	Caused by:	Comments
Alteration in drug target (14 α -demethylase)	Mutations which alter drug binding but not binding of the endogenous substrate	Target is active (i.e., can catalyze demethylation) but has a reduced affinity towards azoles
Alteration in sterol biosynthesis	Lesions in the $\Delta^5(6)$ -desaturase	Results in accumulation of 14 α -methyl fecosterol instead of ergosterol
Reduction in the intercellular concentration of target enzyme	Change in membrane lipid and sterols; overexpression of specific drug efflux pumps (CDR1, PDR5, and BEN ¹)	Poor penetration across the fungal membrane; active drug efflux
Overexpression of antifungal drug target	Increased copy number of the target enzyme	Results in increased ergosterol synthesis; contributes to cross-resistance between fluconazole and itraconazole

02/12/2008

FARM2129 - Antifongiques

18

Mécanismes de résistance aux dérivés azolés



Mechanism	Caused by:	Comments
Alteration in drug target (14α-demethylase)	Mutations which alter drug binding but not binding of the endogenous substrate	Target is active (i.e., can catalyze demethylation) but has a reduced affinity towards azoles
Alteration in sterol biosynthesis	Lesions in the $\Delta^{5(6)}$ -desaturase	Results in accumulation of 14α-methyl fecosterol instead of ergosterol
Reduction in the intercellular concentration of target enzyme	Change in membrane lipid and sterols; overexpression of specific drug efflux pumps (CDR1, PDR5, and BEN)	Poor penetration across the fungal membrane; active drug efflux
Overexpression of antifungal drug target	Increased copy number of the target enzyme	Results in increased ergosterol synthesis; contributes to cross-resistance between fluconazole and itraconazole

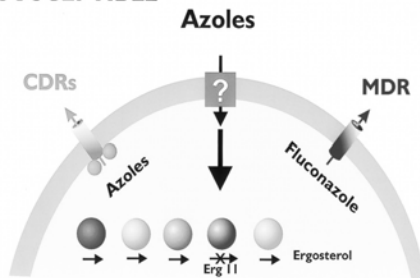
02/12/2008

FARM2129 - Antifongiques

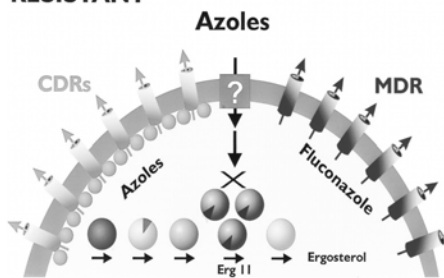
19

Mécanismes de résistance aux dérivés azolés

SUSCEPTIBLE



RESISTANT



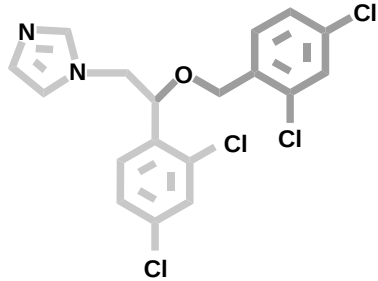
Mechanism	Caused by:	Comments
Alteration in drug target (14α-demethylase)	Mutations which alter drug binding but not binding of the endogenous substrate	Target is active (i.e., can catalyze demethylation) but has a reduced affinity towards azoles
Alteration in sterol biosynthesis	Lesions in the $\Delta^{5(6)}$ -desaturase	Results in accumulation of 14α-methyl fecosterol instead of ergosterol
Reduction in the intercellular concentration of target enzyme	Change in membrane lipid and sterols; overexpression of specific drug efflux pumps (CDR1, PDR5, and BEN)	Poor penetration across the fungal membrane; active drug efflux
Overexpression of antifungal drug target	Increased copy number of the target enzyme	Results in increased ergosterol synthesis; contributes to cross-resistance between fluconazole and itraconazole

02/12/2008

FARM2129 - Antifongiques

20

Miconazole



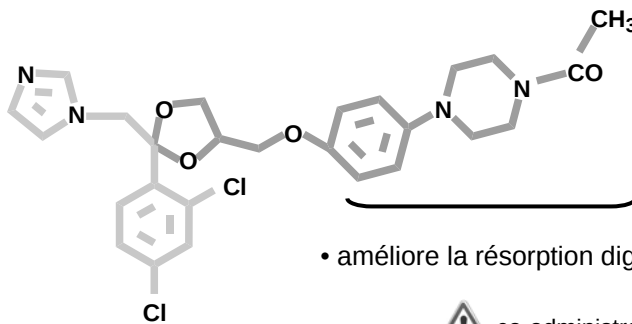
- premier antifongique azolé
- mauvaise résorption digestive
- usage essentiellement topique (candidoses)

02/12/2008

FARM2129 - Antifongiques

21

Kétoconazole



- améliore la résorption digestive en milieu acide



co-administration d'anti-acides

indications (peu utilisé aujourd'hui):

- candidoses (histoplasmose, coccidioïdomycose)
- prophylaxie des colonisations par levures chez les neutropéniques

02/12/2008

FARM2129 - Antifongiques

22

Fluconazole

The diagram shows the chemical structure of Fluconazole, which consists of a central benzene ring with two fluorine (F) atoms at the 4 and 5 positions. Attached to the 1 and 3 positions of the benzene ring are two 1,2,4-triazole rings. The 2-position of the benzene ring has a hydroxyl (OH) group. Annotations with arrows point to specific features: '1er triazole' points to the left triazole ring; 'augmente la spécificité et diminue la dégradabilité' points to the 1,2,4-triazole system; 'augmente l'activité' points to the right triazole ring; '2ème triazole' points to the right triazole ring; and 'Résorption digestive même à pH neutre' points to the fluorine atoms on the benzene ring.

1er triazole

augmente l'activité

2ème triazole

Résorption digestive même à pH neutre

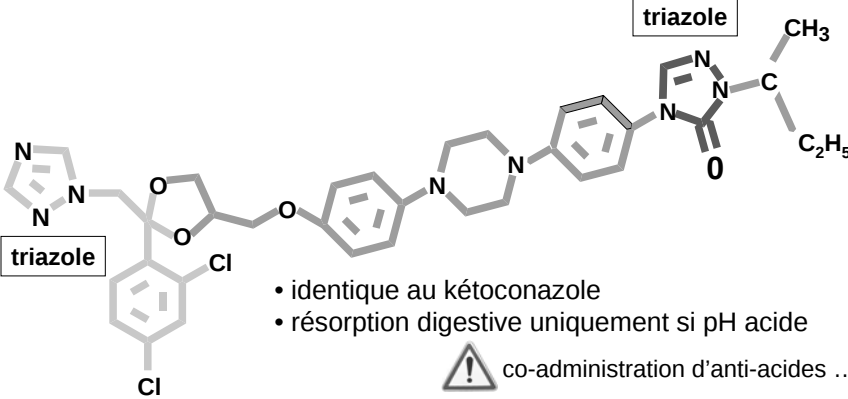
augmente la spécificité et diminue la dégradabilité

Indications :

- méningites cryptococciques (pénétration dans LCR)
- candidoses.

02/12/2008 FARM2129 - Antifongiques 23

Itraconazole



The chemical structure of Itraconazole is shown. It features a central 1,4-dioxane ring substituted with a 2-chlorophenyl group, a 4-chlorophenyl group, and a 4-(4-(2-ethoxy-2H-1,2,4-triazol-5-yl)phenyl)piperazine group. A 1,2,4-triazole ring is also present, substituted with a methyl group and an ethyl group. The structure is labeled with 'triazole' in two boxes and 'CH₃' and 'C₂H₅' for the methyl and ethyl groups respectively.

- identique au kétoconazole
- résorption digestive uniquement si pH acide

⚠ co-administration d'anti-acides

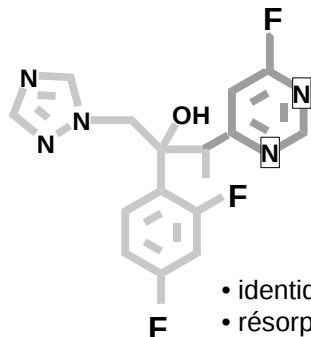
- 2 triazoles; meilleure activité

Indications :

- candidoses
- aspergilloses

02/12/2008 FARM2129 - Antifongiques

Voriconazole



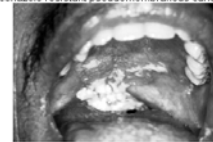
- spectre large; puissante activité
- pas de résistance croisée avec les autres azolés

- identique au fluconazole
- résorption digestive même à pH neutre

• indications :

- aspergilloses invasives
- infections invasives graves à **Candida résistant au fluconazole**.
- Traitement des infections fongiques graves à *Scedosporium* spp. ou *Fusarium* spp.
- en première intention aux patients immunodéprimés, atteints d'infections évolutives, pouvant menacer le pronostic vital.

Fluconazole résistant pseudomembranous candidiasis



02/12/2008

FARM2129 - Antifongiques

25

Dérivés azolés et interactions avec CYP (CYP2C19, CYP2C9 et CYP3A4)



2 Major drug interactions encountered with triazole agents

	Degree of interaction				Effect	Clinically significant
	FLU	ITC	VOR	POS		
Substrates of CYP3A4 and CYP2C9*	++	+++	+++	++	Increased plasma concentrations of other drug substrates	Yes (some contraindicated)
Inducers of CYP3A4 and CYP2C9†	++	+++	+++	++	Decreased plasma concentrations of triazoles	Yes (some contraindicated)
Warfarin	++	+++	+++	++	Increased prothrombin time	Yes
Phenytoin	+++	+++	+++	+++	Increased phenytoin levels, decreased triazole levels	Yes
Rifampicin	+++	+++	+++	+++	Decreased triazole levels	Yes (contraindicated with ITC, VOR, POS)
Proton-pump inhibitors	++	++	+++	++	Increased proton-pump inhibitor levels, decreased triazole absorption	Yes
Cyclosporine	++	++	+++	++	Toxicity, renal failure	Yes
Tacrolimus	++	++	+++	++	Toxicity, renal failure	Yes
Sirolimus	++	++	+++	++	Toxicity, renal failure	Yes (contraindicated with VOR)
Statins	++	+++	+++	++	Increased statin levels	Yes

FLU = fluconazole; ITC = itraconazole; POS = posaconazole; VOR = voriconazole; ++ = mild, +++ = moderate, ++++ = high, +++++ = very high. * Includes but not restricted to cisapride (contraindicated with FLU, ITC, VOR, POS), terfenadine, astemizole, pimozide, quinine, ergot alkaloids (contraindicated with ITC, VOR), sirolimus (contraindicated with VOR), tacrolimus, cyclosporin, statins, warfarin, omeprazole, phenytoin, benzodiazepines, HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and sulfonylurea oral hypoglycaemics. † Includes rifampicin (contraindicated with ITC, VOR, POS), rifabutin (contraindicated with ITC, VOR), long-acting barbiturates (contraindicated with VOR), phenytoin, HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors.

- contre-indiqués: terféndine, astémizole, cisapride, quinidine, alcaloïdes de l'ergot
- surveillance étroite: ciclosporine, tacrolimus, anticoagulants oraux, sulfonylurées
- adaptation de posologie: statines, benzodiazépines

Chen et al. Med J Aust. (2007) 187:404-9.

02/12/2008

FARM2129 - Antifongiques

26

Dérivés azolés : propriétés pharmacologiques



Pharmacocinétique

- absorption variable; parfois dépendante du pH.
- distribution variable; LCR : fluconazole
voie orale: itraconazole, fluconazole, voriconazole
- demi vie longue (> 24 heures) sauf kétoconazole (8 h) et voriconazole (6 h)

Effets secondaires

- toxicité hépatique (surtout kétoconazole)
- troubles digestifs (miconazole)
- intolérance cutanée par voie locale

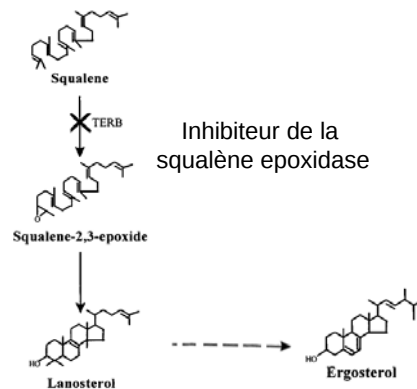
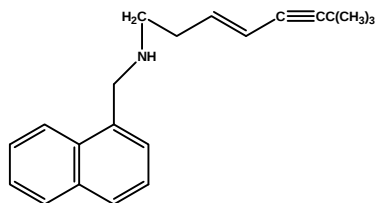
02/12/2008

FARM2129 - Antifongiques

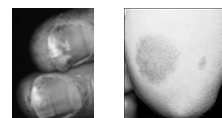
27

Allylamines

terbinafine



- actif uniquement sur les dermatophytes
- bien résorbée mais effet de premier passage important
- interaction avec inhibiteurs et inducteurs des cytochromes

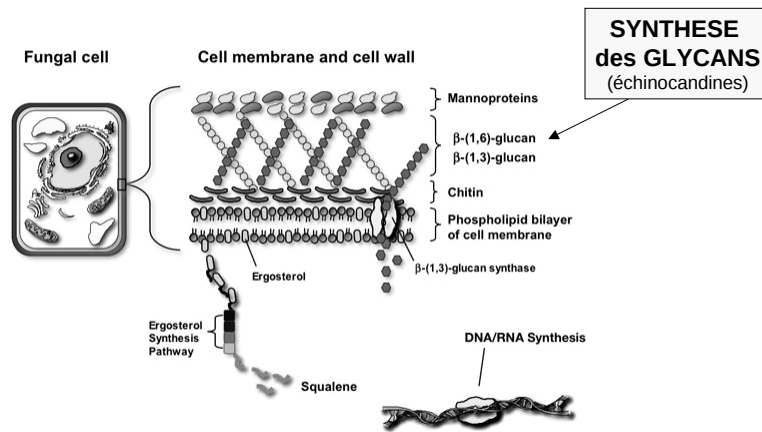


02/12/2008

FARM2129 - Antifongiques

28

Cibles des médicaments antifongiques



02/12/2008

FARM2129 - Antifongiques

29

Echinocandines : caspofungine

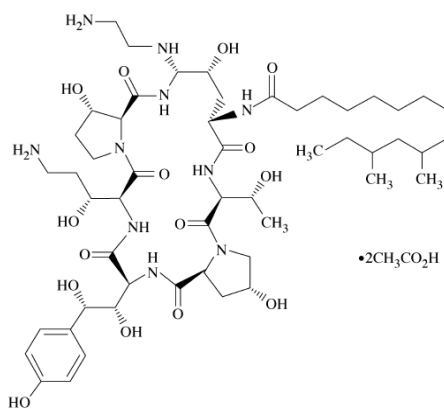


Figure 1. Structure of caspofungin.

02/12/2008

FARM2129 - Antifongiques

30

Echinocandines

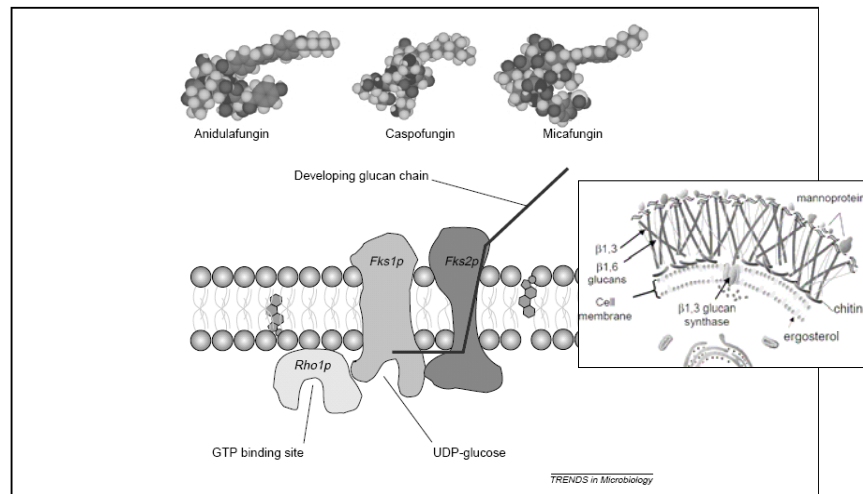


Fig. 6. Cartoon depicting the transmembrane complex of two proteins, Fks1p and Fks2p, involved in synthesis of β -1,3 glucan in the cell walls of *Saccharomyces cerevisiae*. Activity of the complex is regulated by the GTP-binding peptide, Rho1p. Fks1p is the target of the echinocandins, with the structures of the three agents now entering clinical use illustrated above. Evidence for *Candida albicans* suggests that the Fks2p homologue in this species might not be expressed in growing cells. Much remains unknown about the glucan synthase protein complex and the manner of interaction of echinocandins with the complex.

Odds, *Trends in Microbiology* (2003) 11:272-279

02/12/2008

FARM2129 - Antifongiques

31



Caspofungine: propriétés pharmacologiques

Indications:

- candidoses (oropharyngées, oesophagiennes)
- aspergilloses invasives chez les patients qui ne répondent pas ou sont intolérants aux autres traitements

Pharmacocinétique:

- Mauvaise résorption orale
- Accumulation dans l'organisme lors d'un traitement prolongé (25-50 % d'augmentation de l'AUC après 2 à 3 semaines de traitement).
- Métabolisation par le foie; demi-vie, environ 10 h.

Effets secondaires

- phlébite au site d'injection
- fièvre, nausées et vomissements.

Interactions médicamenteuses

- $\nearrow$ AUC de la caspofungine par cyclosporine
- $\searrow$ AUC par inducteurs des cytochromes P450 (rifampicine, inhib. protéases du HIV, phénytoïne, carbamazépine, dexaméthasone).

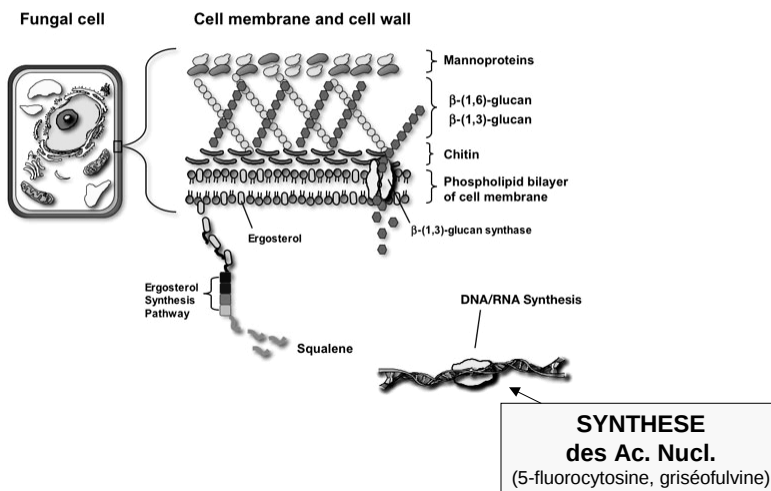
Patients à risque
d'infection fongique!

02/12/2008

FARM2129 - Antifongiques

32

Cibles des médicaments antifongiques



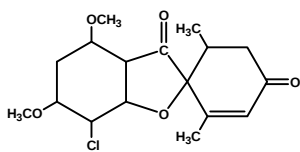
02/12/2008

FARM2129 - Antifongiques

33

Inhibiteurs de synthèse des acides nucléiques

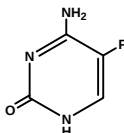
griséofulvine



- infections à dermatophytes (cuir chevelu, peau, ongles)
- adm. orale, résorption $\nearrow$ par aliments riches en graisse
- réactions allergiques, maux de tête, troubles digestifs



5-fluorocytosine



- inhibition de la thymidilate synthase; résistance fréquente $\rightarrow$ utiliser en association avec l'ampho B pour les candidoses et les cryptococcoses
- concentration dans l'urine $\rightarrow$ infection urinaire
- leuco- et thrombopénie



02/12/2008

FARM2129 - Antifongiques

34

PHARMACOTHERAPIE DES INFECTIONS FONGIQUES



02/12/2008

FARM2129 - Antifongiques

35

Spectre des anti-fongiques

Levures, *Candida*, *Crypto*

	AMB	5FC	FCZ	ITZ	VRZ	PSZ	CAS
<i>Candida albicans</i>							
<i>Candida tropicalis</i>							
<i>Candida parapsilosis</i>							
<i>Candida krusei</i>							
<i>Candida glabrata</i>							
<i>Candida lusitanae</i>							
<i>Crypto neoformans</i>							

Champignons filamenteux *Aspergillus*, *Fusarium*

<i>Aspergillus fumigatus</i>							
<i>Aspergillus terreus</i>							
<i>Fusarium spp.</i>							

E. Dannaoui

02/12/2008

FARM2129 - Antifongiques

36

Infections superficielles

4 Guidelines for antifungal therapy of superficial fungal infections

Condition	Causative pathogens	Treatment recommendations
Tinea pedis/cruris	Dermatophytes	Topical azoles*
Tinea corporis	Dermatophytes	Usually requires oral azole (itraconazole preferred) or terbinafine (E2)
Onychomycosis	Dermatophytes, yeasts	Terbinafine (preferred) (E1) or oral azole (itraconazole) (E2)
Cutaneous candidiasis	<i>Candida</i> spp.	Topical azoles* (E3 ₁) Topical nystatin (E3 ₁)
Vulvovaginal candidiasis†	<i>Candida</i> spp.	Topical azoles* or topical nystatin (E3 ₁); single dose oral fluconazole; 7-day course of oral fluconazole ¹⁶ (E2)
Oral candidiasis†	<i>Candida</i> spp.	Topical nystatin or amphotericin B; systemic fluconazole in immunocompromised patients (E2)
Oesophageal candidiasis	<i>Candida</i> spp.	Systemic fluconazole (E2); echinocandin (E2) or newer triazoles (E2) if indicated

* Clotrimazole, miconazole, econazole most commonly used. All formulations (creams, powders, troches) available without prescription. † Refers to treatment of uncomplicated, non-recurrent disease.

Chen et al. Med J Aust. (2007) 187:404-9.

02/12/2008

FARM2129 - Antifongiques

37

Infections profondes

6 Guidelines for antifungal therapy of invasive fungal infections

Infection	Antifungal agent	Treatment duration
Yeast infections		
Candidaemia and other forms of invasive candidiasis	AMB, FLU, CAS and VOR equally effective (E2). Lipid AMB formulations can also be considered if neutropenic (E3 ₁). Tailor choice of agent to species of <i>Candida</i> and susceptibility result.	Candidaemia: 14 days after last positive culture or after resolution of all symptoms and signs if neutropenic (expert opinion). Other invasive candidiasis: varies with site of infection ³¹
Cryptococcosis	Initial therapy: AMB with or without flucytosine (for central nervous system disease and if not neutropenic) (E2). Maintenance therapy: FLU (E2), or other triazole (E4).	Induction therapy: 2–6 weeks. Maintenance therapy: 3 months to 1–2 years; varies with host status and disease extent (E2).
Mould infections		
Invasive aspergillosis	Initial therapy: VOR is treatment of choice (E2). If patient is intolerant to VOR, lipid AMB is preferred over conventional AMB (E2). Maintenance therapy: VOR (E2), POS (E4). Salvage therapy: CAS (E4).	Until complete response evident, along with recovery of immune deficit. Indefinite treatment if persistent immunosuppression (expert opinion).
Zygomycosis	Initial therapy: high-dose lipid AMB formulation (> 5 mg/kg per day) (E4). Maintenance therapy: POS (expert opinion).	Until complete response evident, along with recovery of immune deficit. Indefinite treatment if persistent immunosuppression (expert opinion).
Scedosporium infections	Initial therapy: VOR with or without terbinafine (E4). Maintenance therapy: VOR (E4).	Until complete response evident, along with recovery of immune deficit. Indefinite treatment if persistent immunosuppression (expert opinion).
Infections caused by dimorphic fungi	Initial therapy: AMB formulation (E2). Maintenance therapy: ITC (E2); FLU (E4), VOR (E4), POS (E4) second line.	Until complete response evident, along with recovery of immune deficit. Indefinite treatment if persistent immunosuppression (expert opinion).

AMB = amphotericin B; CAS = caspofungin; FLU = fluconazole; ITC = itraconazole; POS = posaconazole; VOR = voriconazole.

Chen et al. Med J Aust. (2007) 187:404-9.

02/12/2008

FARM2129 - Antifongiques

38