

Antifungals and Drug drug Interactions

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Learning Objectives

- Participants will be able to understand
 - The drug metabolism
 - Basis of drug interactions
 - Help them to identify drug interactions in clinical practice

Why Antifungal drug interactions?

- Antifungal agents (azoles) are more complexly affected by absorption, distribution and metabolism
- Commonly involved with Drug interactions (inhibitors of CYP3A4 and P-gp)

Consequences of drug interactions

Loss of therapeutic effect

Toxicity

Unexpected increase in pharmacological activity



Case History

- 38/F, Live related Post Renal Tx, on stable immunosuppressive (MMF, Tac & Wysolone 5mg) with normal renal function, also receiving OHA for diabetes
- Nephrologist found oral candidiasis during her regular medical follow up
- Started on Tab Fluconazole 200mg PO qd for 14 days

Case continue

- Patient was hospitalized after 12 days with headache, hypertension, insomnia, irritability with hallucinations for last 2 days
- No Fever, No URI symptoms, no urinary complaints
- Physical exam: follow verbal command, irritable, No NR: BP: 170/110mmhg, pulse: 88/min, Temp: N, Chest/CVS/Abd: Normal
- Work up showed S. Creatinine 2.4mg/dl, CBC: 5200, Urine routine: Normal, LFT Normal, electrolytes: Normal

Important Points in her case

- Alright before 12 days, except thrush
- Encephalitis-like symptoms
- Hypertension
- Worsening serum creatinine
- No fever

Causes for clinical
deterioration ???

Drug Interactions between Fluconazole and Tacrolimus

- S. Tacrolimus level : 24, Very High
- Renal Biopsy: Tac toxicity
- Recovered completely by reducing dose of Tacrolimus

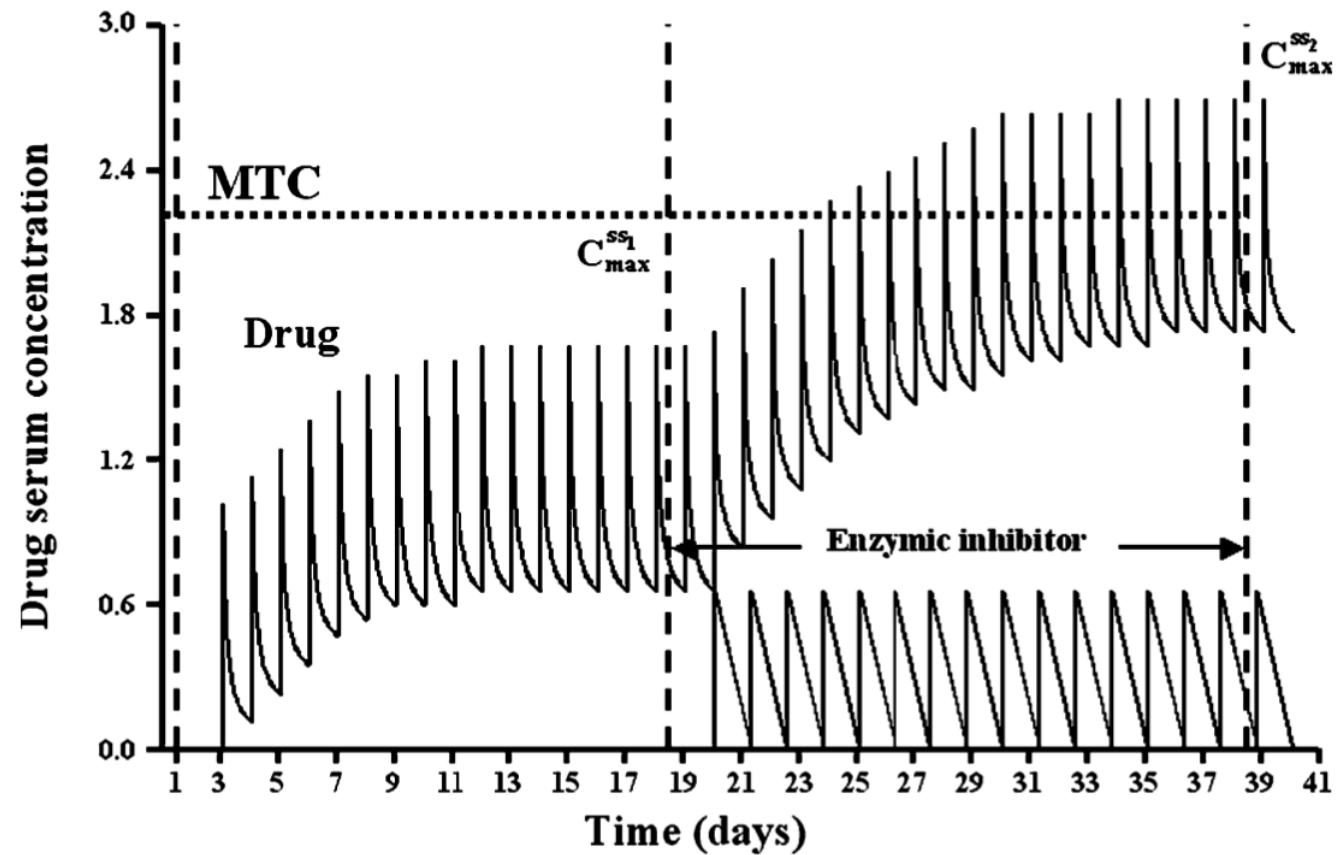
Fluconazole and Tacrolimus

Fluconazole: CYP 3A4
and P-gp inhibitor

Tacrolimus: substrate
for 3A4 and P-gp

Fluconazole increased
exposure of tacrolimus

Drug Interactions



PK & PD Drug Interactions

Pharmacokinetic

- **Absorption**
 - Mg and Al antacids/PPI impair ITR absorption
 - Food increases absorption ITR/POS
 - Food decreases absorption of VORI
- **Distribution**
 - TMP/SMX displaces warfarin from protein binding
- **Metabolism**
 - Rifampin induces CYP450 metabolism of Azoles
 - RTV inhibits CYP 3A4
- **Excretion**

Pharmacodynamic

- Extension of the pharmacologic effect of the drug resulting in enhanced toxicity or in antagonism of two agents
 - **Additive**
 -
 - **Synergistic**
 - Amphotericin + 5 FC
 - **Antagonistic**
 - Amphotericin B & Azoles

PK-PD parameter overview

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Pharmacodynamic

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 - **Additive**
 - Ampho + Colistin/ Aminoglycosides
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Nomenclature

Substrate

- Undergo metabolism or transport

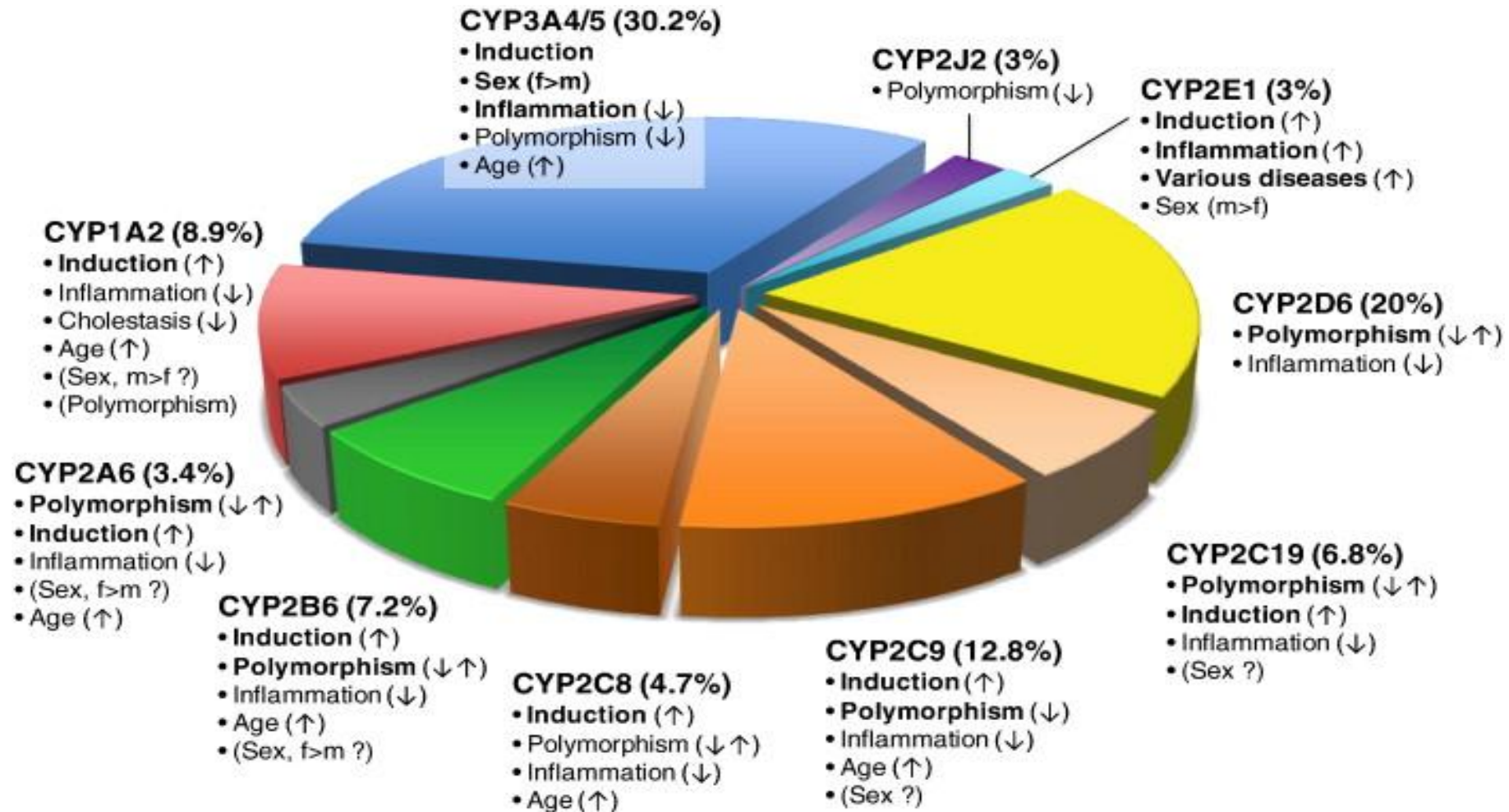
Inhibitors

- Decrease the ability of isoenzyme(s) to metabolize substrate
- May also be substrate

Inducers

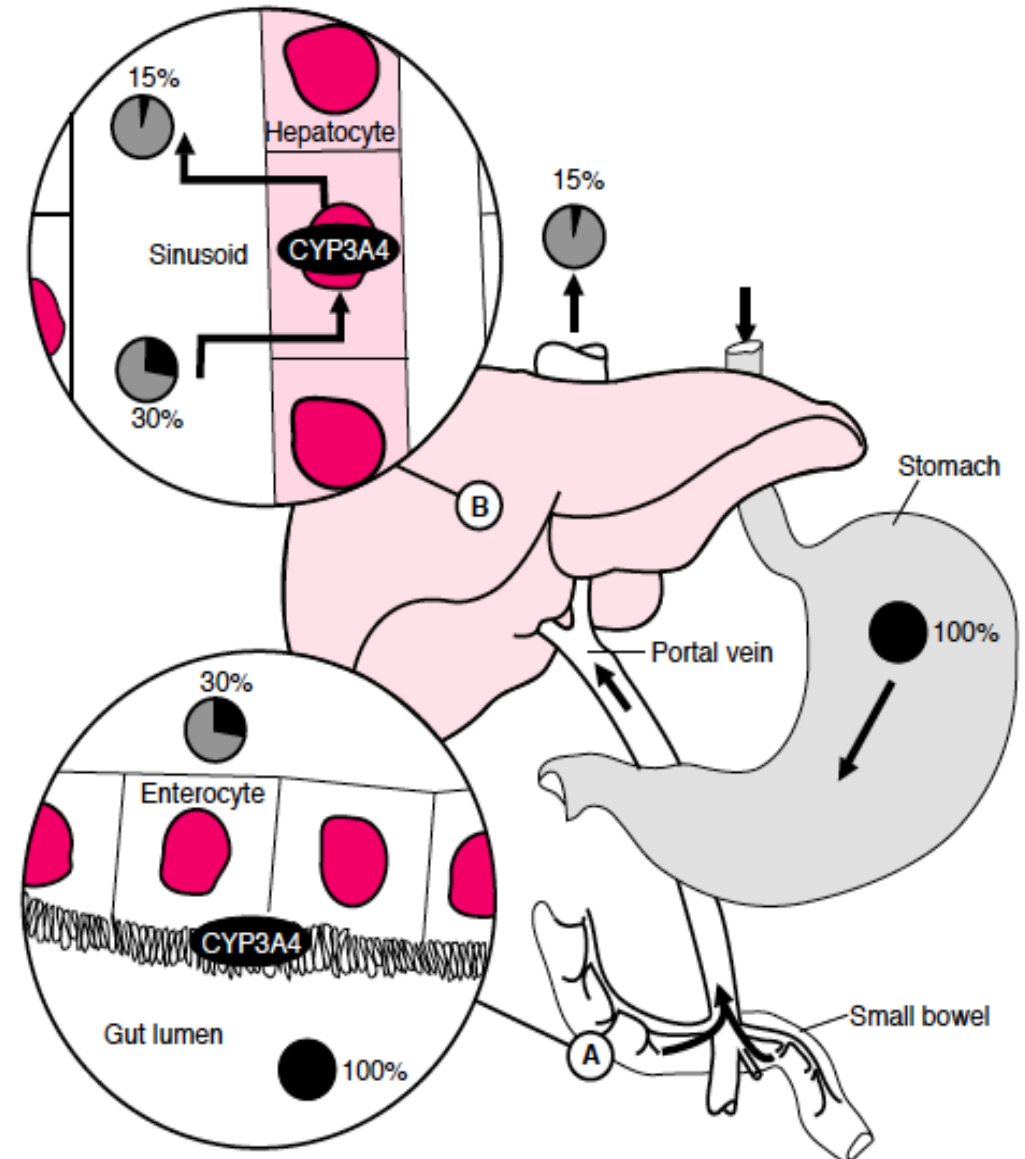
- Increase the amount/ability of the isoenzyme(s) to metabolize substrate
- May also be substrate

METABOLISM



CYP 3A4

- Oxidative biotransformation of 60% of all drugs
- The location of CYP3A4
 - Liver
 - Small bowel
- Works in concert with P-glycoprotein to eliminate drugs



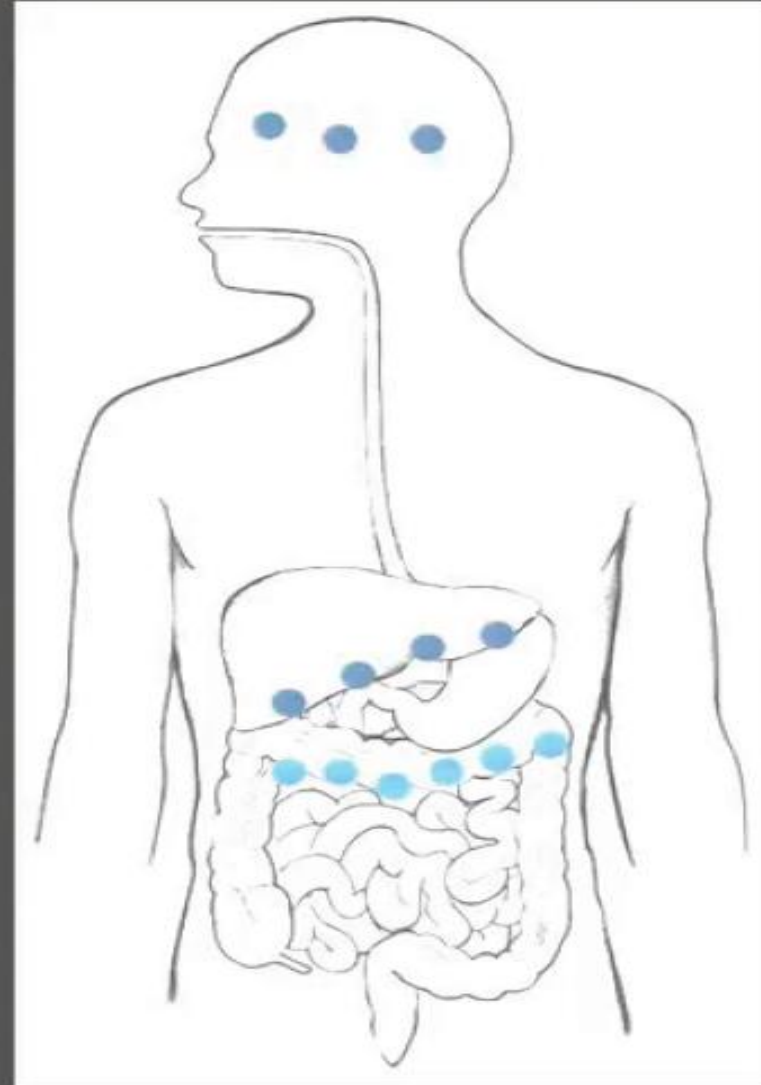
P-glycoprotein

Efflux transporter

- Actively transporting compounds out of cells into intestinal lumen

Location:

- apical membranes of intestines
- hepatic epithelial cells
- renal proximal tubules cells
- endothelial cells lining the blood brain barrier
- lymphocytes



P-glycoprotein

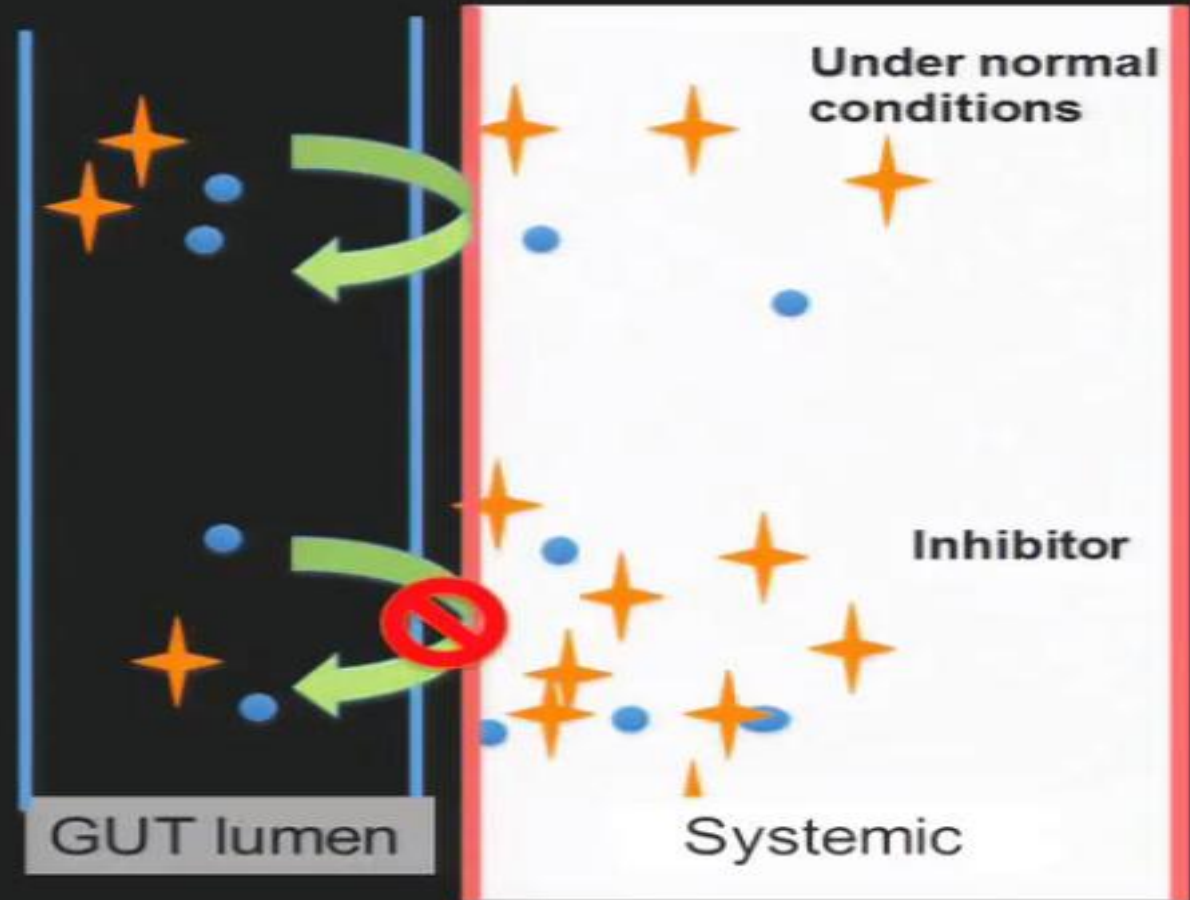
Function: decrease absorption and increase excretion of its substrates

Substrate:

- ✓ Tacrolimus
- ✓ Cyclosporine
- ✓ Sirolimus

Inhibitor:

- ✓ Protease Inhibitors

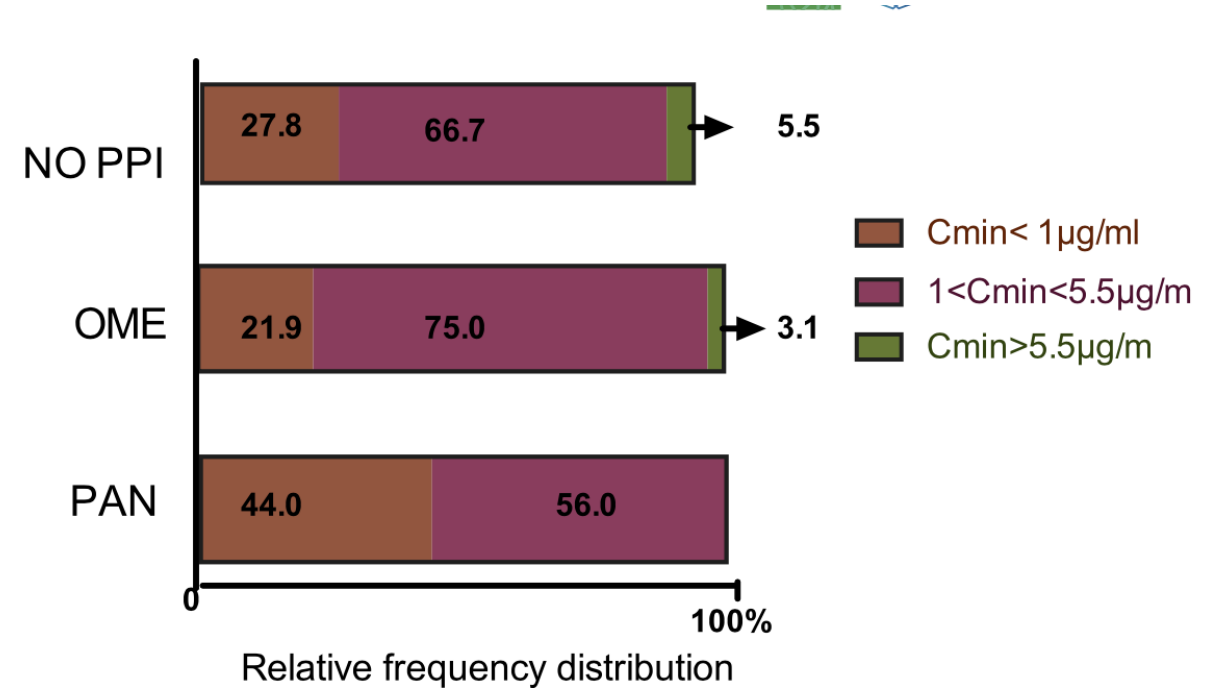
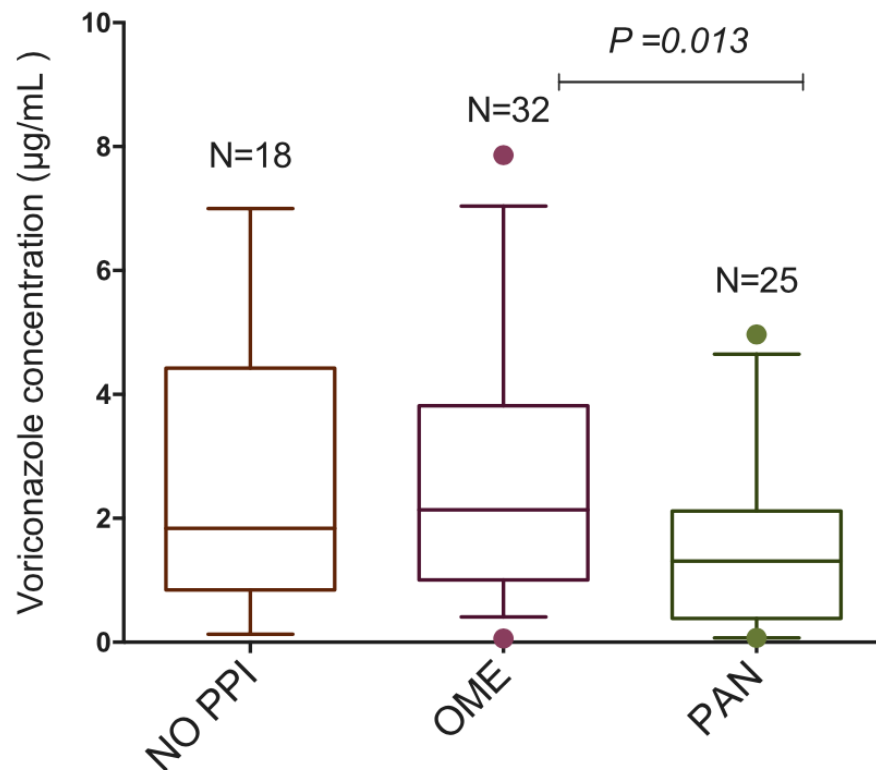


Inhibition In Vivo Cytochrome P450

Molécule	CYP3A4		CYP2C8/9		CYP2C19	
	Inhibitor	Substrate	Inhibitor	Substrate	Inhibitor	Substrate
Posaconazole	✓					
Fluconazole	✓		✓			
Itraconazole	✓	✓	✓			
Ketoconazole	✓	✓	✓			
Voriconazole	✓	✓		✓		✓
Isavuconazole	✓	✓				

Wexler D et al. *Eur J Pharm Sci.* 2004;21:645-653., Cupp MJ et al. *Am Fam Phys.* 1998;57:107-116.
Drug interactions. *Med Letter.* 2003;45(W1158B):46-48.
Hyland R et al. *Drug Metab Dispos.* 2003;31:540-547.

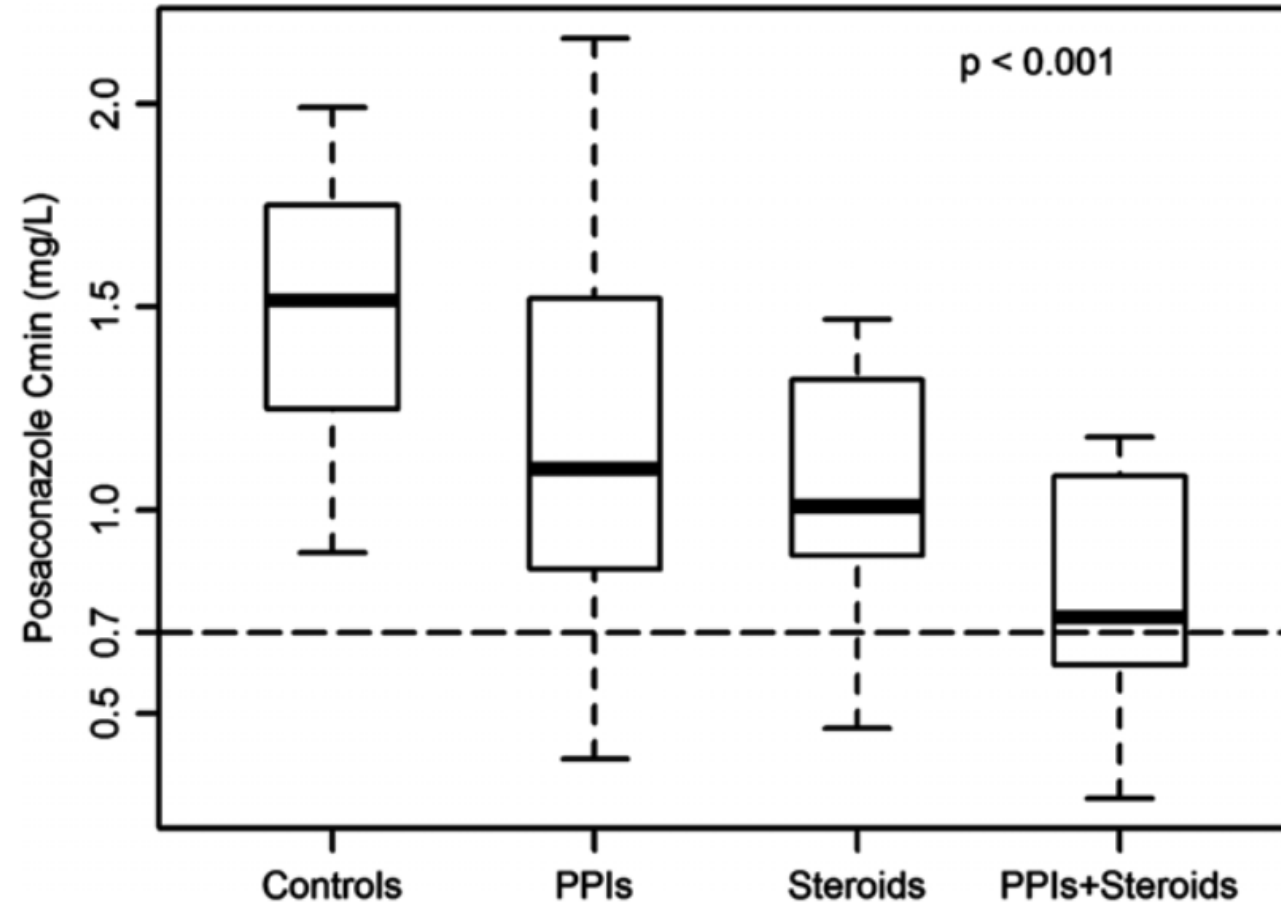
Impact of PPI on Voriconazole concentration: Multicenter study from Spain



Posaconazole

- Metabolized by UGT and it's a substrate of P-gp
 - P-gp inhibitors: Verapamil, ciclosporin, quinidine, clarithromycin, erythromycin, ritonavir increases level
 - P-gp induces: Rifampicin, anticonvulsants decrease the level
- Posaconazole is inhibitor of CYP 3A4

Effect of PPI/ Steroids on Posaconazole DR concentration



Isavuconazole: Key Interactions

Isavuconazole is a substrate of CYP3A4

Isavuconazole is a moderate inhibitor of CYP3A4

- Increase exposure
 - Calcineurin and mTOR inhibitors
 - Corticosteroids
 - Cyclophosphamide
 - Vincristine and vinca alkaloids
 - Methotrexate
- Rifampicin reduces the level of Isavuconazole
- Avoid or higher dose TDM guided

Life threatening drug interactions in ICU



Amiodarone, Digoxin AND Enzyme inhibitors (Clarithro, Ritonavir, Fluconazole, Voriconazole etc)



Warferin and Fluconazole/Voriconazole

Post Transplant patients

- Tacrolimus level increase
- **Enzyme inhibitors**
 - Fluconazole
 - Voriconazole
 - Itraconazole
 - Protease Inhibitors
 - Clarithro, Erythro
- Tacrolimus level decrease
- **Enzyme inducers**
 - Rifampicin
 - Carbamezapine
 - Phenytoin
 - Phenobarbital
 - St John's wart

Echinocandins and drug interactions

Caspofungin, has more extensive hepatic metabolism compared to micafungin and anidulafungin

Micafungin and anidulafungin have fewer significant drug interactions

- Caspofungin can reduce the tacrolimus AUC by 20%
- Cyclosporine increases the AUC of caspofungin by approximately 35%
- Caspofungin has no effect on cyclosporine levels
- Enzyme Inducers: Efavirenz, nelfinavir, nevirapine, phenytoin, rifampin, dexamethasone, and carbamazepine reduce caspofungin exposure
- Increase caspofungin dose with co-administered with rifampicin

Conclusions



Drug interactions represent a challenge to clinicians



Successful management requires familiarity with a variety of references and vigilant surveillance



Ref book/software help in management of clinically significant interaction

