

PROBLEMS IN ANTIFUNGAL THERAPY

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PROBLEMS IN ANTIFUNGAL THERAPY

A close look

- **Poor absorption**
- **Drug interactions**
- **Resistance development – right dosing**
- **Risk for sudden death**

Problems in absorption of older azoles

- Ketoconazole, itraconazole poorly absorbed
- Elevated gastric pH may decrease absorption of ketoconazole by 90 %
- Fluconazole well absorbed
 - bioavailability around 90 %
- Voriconazole well absorbed
 - high inter-individual variability
 - saturable metabolism
 - with increased dose bioavailability increased i.e. proportion of dose absorbed increased

Absorption of itraconazole

- **High inter-individual variability**
 - Bioavailability in an average 55 %
 - In some patients bioavailability only some %
- **Probably also high intra-individual variability**
 - some doses less absorbed / not absorbed
 - failure in pulse therapy?
 - resistance development?
- **Oral solution with improved bioavailability**
 - more reliable
 - bioavailability increased by 30-40 %

Absorption of itraconazole

Practical points

- **Needs acidic stomach**
 - Antacids, H₂-blockers and proton pump inhibitors reduce absorption by 20 %
 - Food improves bioavailability
- **Acidic drinks improve bioavailability**
- **Active metabolite hydroxy-itraconazole accumulates twice more than itraconazole**
 - counteracts problems in topical infections

Drug interactions

- Absorption
- Distribution
 - binding to plasma proteins
 - drug concentrations in tissues
- Excretion
 - into urine
 - into bile
- Drug metabolism
- Effect on same organ / body system

DRUG INTERACTIONS IN METABOLISM

1. Enzyme induction

- a drug increases production of drug metabolizing enzymes
- autoinduction – own metabolism facilitated
- heteroinduction – metabolism of other drugs facilitated
- leads to **decreased drug concentrations**
 - elimination half life shortened
 - first pass metabolism diminished
- needs at least a few days to occur

2. Enzyme inhibition

- inhibits metabolism of other drugs
- leads to **increased concentration of the other drug**
- usually competitive
- starts immediately

Cytochromal enzymes - CYP

- Expressed throughout the phylogenetic spectrum
- Catalyse biotransformation of several endogenous substances and xenobiotics
- Concentrated in liver – main pathway for drug metabolism
- many isoforms
 - human CYP's
 - 3 families: 1-3
 - 12 main subfamilies: 1A1 - 3A7
- drugs metabolised by same CYP have a possibility for interaction
- enzyme induction – usually many (all) isoforms)
- enzyme inhibition – may be isoform selective

Antifungals and CYP

- Azoles inhibit a CYP-family enzyme in fungal membrane – 14- α -demethylase
- All azoles are CYP inhibitors
 - potency variable
 - target isoenzymes different
 - possibility to cause interaction
- Many azoles eliminated through CYP mediated metabolism
 - keto-, itra-, vori-, posaconazole
 - potential targets for interaction
- Fluconazole eliminated through excretion into urine
- Terbinafine is a potent CYP 2D6 inhibitor
- Terbinafine metabolised by non-CYP enzymes
- Amfotericin B and caspofungin no effect on CYP

Enzyme inducers and antifungals

- **Azole concentrations decreased**
 - also first pass metabolism enhanced
- **Azoles increase concentrations of many inducers, e.x. carbamazepine and phenytoin**
-> risk for toxicity
- **Concentrations of caspofungin may be decreased**
 - dose increased to 70 mg x 1
- **Probably no effect on terbinafine**

Common Enzyme Inducers

- Barbiturates
- Phenobarbital
- **Fenytoin**
- **Carbamazepin, (oxcarbazepin)**
- **Rifampicin, Rifabutin**
- **Spiroinolactone**
- **Griseofulvine**
- Ethanol

CYP inhibition by antifungals

3A4

- ketoconazole most powerful
- miconazole
- itraconazole, powerful
- voriconazole, powerful
- posaconazole, powerful
- fluconazole, high doses > 200 – 400 mg/day

2C9 + 2C19

- fluconazole and miconazole, powerful
- voriconazole

2D6

- terbinafine

CYP 3A4 Substrates

- Alfentanil
- Alprazolame
- Amiodarone
- Atorvastatin
- Buspirone
- Diazepam
- Dihydroergotamine
- Diltiazem
- Disopyramide
- Donepezil
- Ebastine
- Ergotamiini
- Ethinyliestradiol
- Feksofenadine
- Finasteride
- Granisetron
- Chinidine
- Chinine
- HIV-protease inhibitors
- Imatinibe
- Carbamazepine
- Ketiapine
- Cortisol
- Loratadin
- Methadone
- Methylprednisolone
- Midazolame
- Mizolazine
- Montelukast
- Nefazodone
- Nifedipine
- Nisoldipine
- Pioglitazone
- Prednisone
- Repaglinide
- Risperidone
- Sertindole
- Sibutramine
- Cyclosporine
- Sildenafil
- Simvastatin
- Sirolimus
- Cyclofosfamide
- Tacrolimus
- Terfenadine
- Tiagabine
- Tratsodone
- Triazolame
- Tsaleplone
- Venlafaksin
- Verapamil

CYP 3A4 inhibition

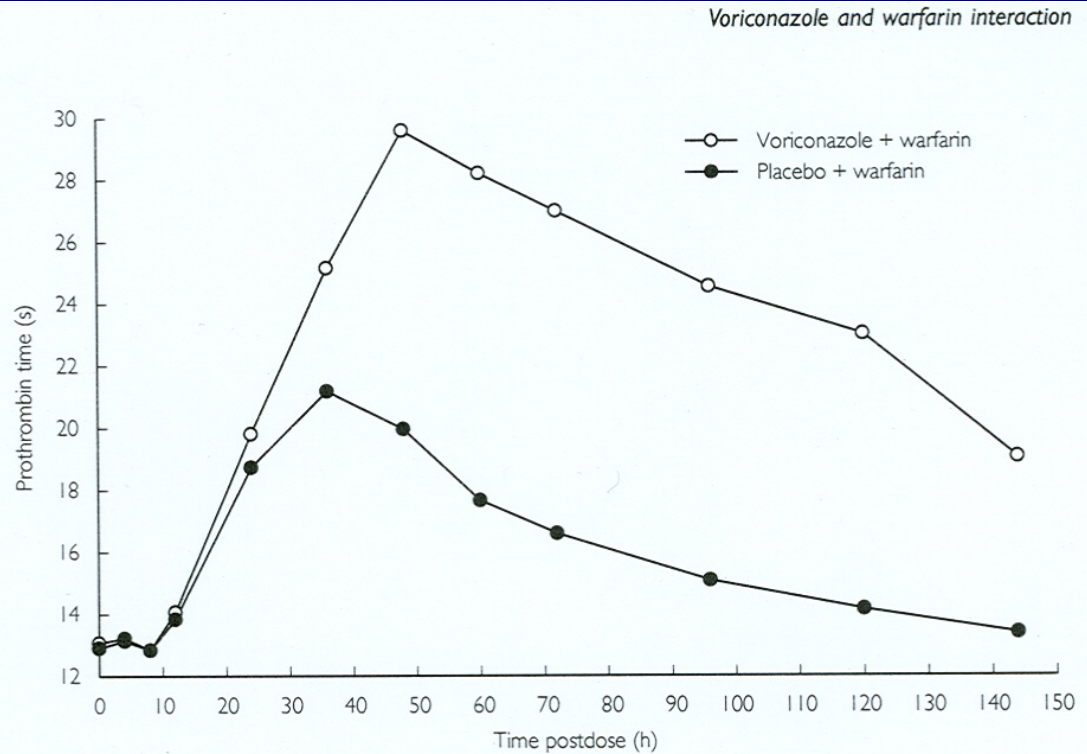
Itraconazole, voriconazole, high dose fluconazole

INCREASED CONCENTRATIONS OF OTHER DRUG

- Anticonvulsants
 - phenytoin, carbamazepine
 - azole concentrations decreased
- Benzodiazepines
 - in particular midazolam, triazolam, alprazolam
- Buspirone
- Calcium channel blockers
- Digoxin
- Statins
 - not pravastatin, rosuvastatin
- Antiarrhythmic drugs
 - amiodarone, chinidine, lidocaine
- Warfarin

Effect of voriconazole on warfarin concentrations

Figure 1 Mean prothrombin time profiles of warfarin for voriconazole and placebo treatment periods.



CYP 3A4 inhibition

Itraconazole, voriconazole, high dose fluconazole

INCREASED CONCENTRATIONS OF OTHER DRUG

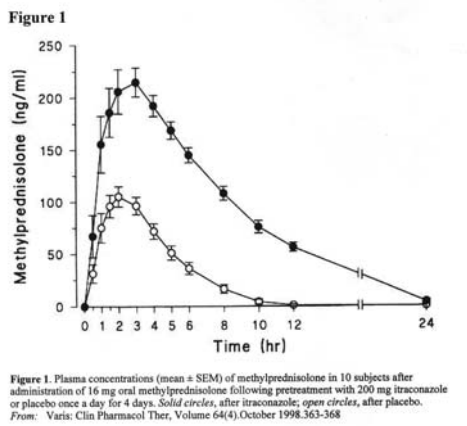
- Cyclosporine, tacrolimus
- HIV protease inhibitors
 - ritonavir boosting increases azole concentrations
- Oral diabetes agents
 - sulphonylurea, glitazones
- Impotence drugs
 - sildenafil, tadalafil
- Some antipsychotics
 - haloperidol
- Opiates
 - fentanyl, sufentanyl, alfentanil, methadone
- Corticosteroids variably

CYP 3A4 inhibition and corticosteroids

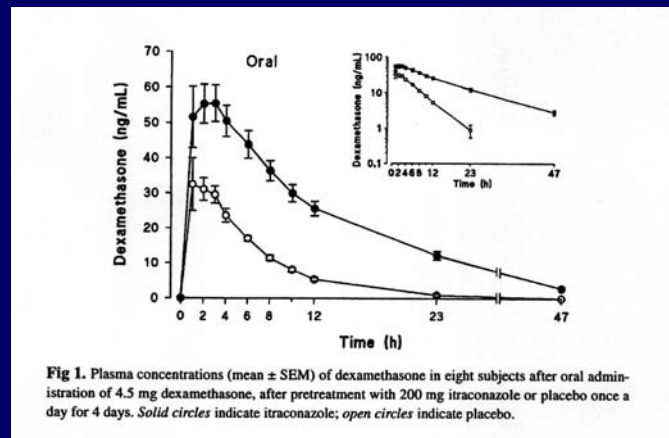
Itraconazole, voriconazole, high dose fluconazole

- Elevated dexamethasone and methylprednisolone concentrations
- Smaller / No effect on prednisone

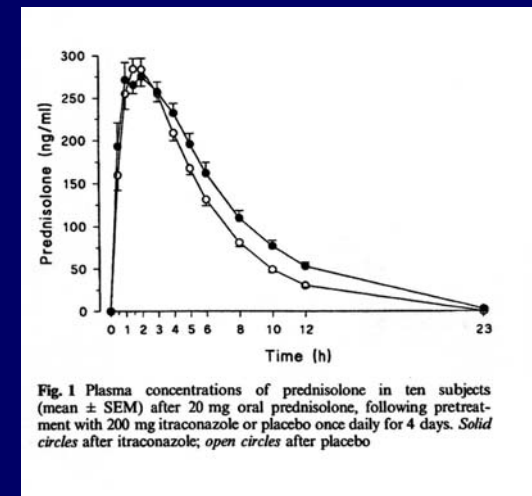
methylprednisolone



dexamethasone



prednisone



Varis T ym, Clin Pharmacol Ther 1998;64:363, Eur J Clin Pharmacol 2000;56:57, Clin Pharmacol Ther 2000;68:487,

CYP 2C9 ja 2C19 inhibition

fluconazole, voriconazole, (ketoconazole)

INCREASED CONCENTRATIONS OF OTHER DRUG

- **Tricyclic antidepressants**
- **Cyclosporine, tacrolimus**
- **Warfarine**
- **Oral diabetes drugs**
 - **sulphonylurea-derivatives**
- **Anticonvulsants**
 - **Phenytoin**
- **Theophylline ?**

Interactions even in local administration

Miconazole oral cream

- **No data on how much absorbed**
 - **”all drug from mouth to liver”**
- **Interactions reported with systemic use of miconazole**
- **CYP 3A4 and 2C9 inhibition**
- **Significant effect on warfarin reported**
- **Consider interaction possibility = itraconazole**

Pemberton et aö, Brit Dent J 2004

Terbinafine CYP 2D6 inhibition

INCREASED CONCENTRATIONS OF OTHER DRUG

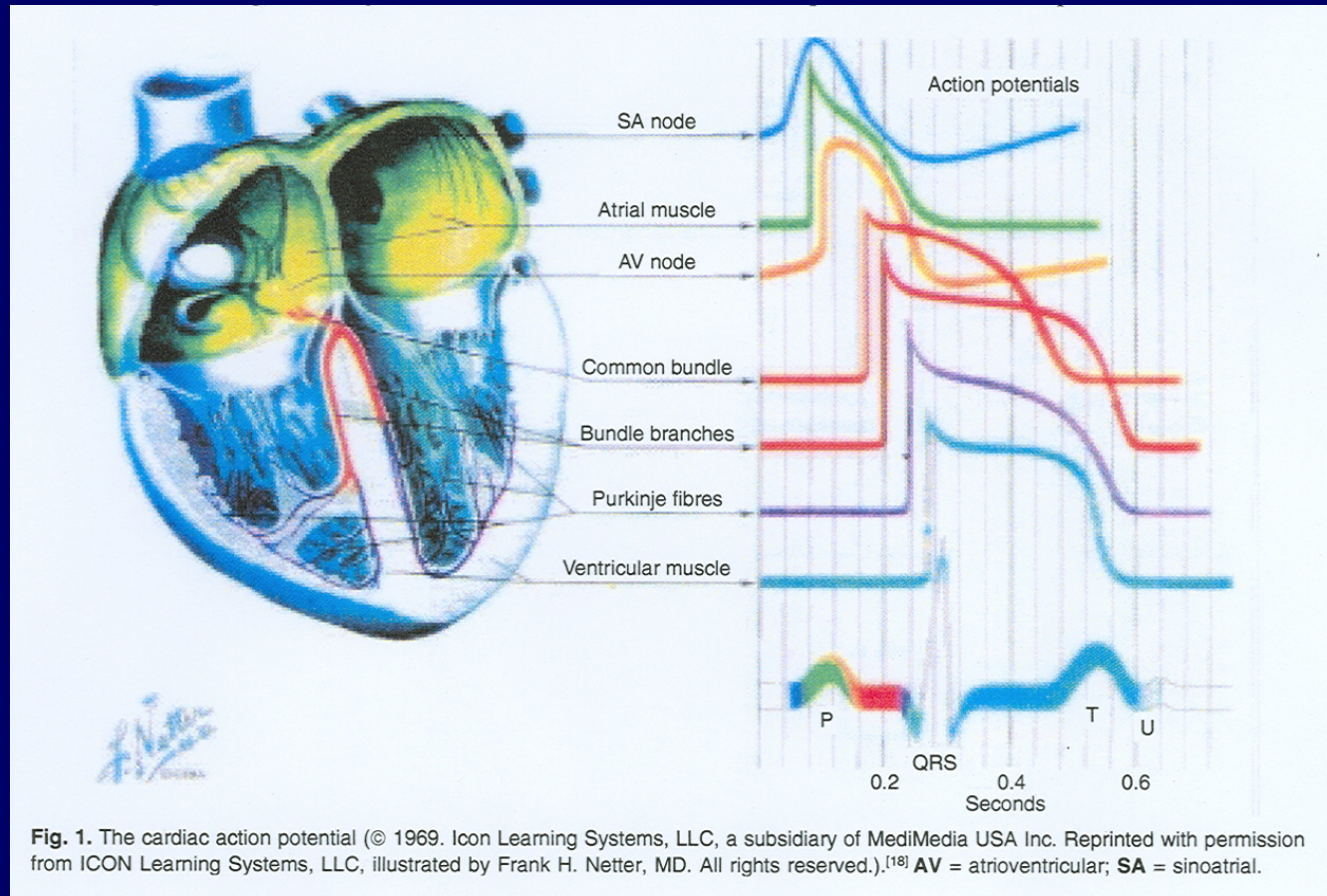
- **Tricyclic antidepressants**
- **Some antipsychotics**
 - perfenazine, risperidone, tioridazine, haloperidol
- **Some newer antidepressants**
 - fluoxetine, paroxetine
- **Antiarrhythmic drugs**
 - propafenone, enkainide
- **Analgesics**
 - tramadol, oksikodone, codeine, dextrometorphane, ethylmorphine
- **Some beta-blockers**
 - metoprolol, timolol, propranolol, carvedilol

Antifungals and QTc-time

- **QTc-time**
 - Electric recovery after heart contraction on electrocardiogram ECG
 - prolonged QTc-time may lead to life threatening arrhythmias
 - familialy long QTc-time often behind sudden deaths

- **Antimicrobials that prolong QTc-time**
 - azole antifungals
 - macrolides
 - fluoroquinolones

QTc-time



Antimicrobials and antifungals have only a minimal own effect on QTc-time

- Not a significant effect on healthy
- **Be cautious in patients with known long QTc-time**
 - a previous history of the same antifungal use?
 - review other medicines
- Effect on QTc-time is studied on new drugs
 - Sparfloxacin ja grepafloxacin drawn from market due to QTc-time prolongation
- Only single cases described with antimicrobials

www.micromedex.com,

Roden DM, NEJM 2004;350(10):1013,

Owens RC Drugs 2004;64(10):1091

QTc-time prolongation in antifungals

- **Interaction with another QTc-time prolongating drug**
 - **Antiarrhythmials**
 - **Malaria drugs: chinin, chloroquin, mefloquin**
 - **Many psychiatric drugs**
 - **Tricyclic antidepressants**
 - **Antipsychotics (particularly klozapin, pimozid)**
 - **Antidepressants: Fluoxetin, venlafaxin**
- **Caution in patients with other diseases**
 - **heart disease**
 - **electrolyte abnormalities**
 - **liver or renal insufficiency**

www.micromedex.com, Roden DM, NEJM 2004;350(10):1013,
Owens RC Drugs 2004;64(10):1091

How to avoid resistance development

PK / PD data on fluconazole

- Resistance development among *Candida* avoided by frequent dosing of fluconazole
 - serum concentration $>$ MIC at least 50 % of dosing interval
 - half life only 30 min \rightarrow frequent dosing needed
 - $t >$ MIC
 - AUC_{24} / MIC *Andes et al, AAC 2006*
- Combination treatment ?
 - systemic + topical?
 - amphotericin B in oral candidiasis