Drug interactions

Outline of the lecture

- Problem
- Mechanisms of drug interactions:
  - Pharmaceutical incompatibility
  - PD interaction
  - PK interaction
- Interaction with herbal products
- Conclusions

"MY DRUGS ARE INTERACTING!"

- Female, 25 years; depression, insomnia; irritability, palpitation, tremor
- Treatment: sertraline, zolpidem
- Neurologist referred to cardiologist
- Cardiologist suspected drug effect, referred to CP
- Patient's treatment:
  - Morning: sertraline, tee of St. John's wort, vitamins, alprazolam
  - Midday: tee of St John's wort, clonazepam
  - Evening: tee of St John's wort, zolpidem

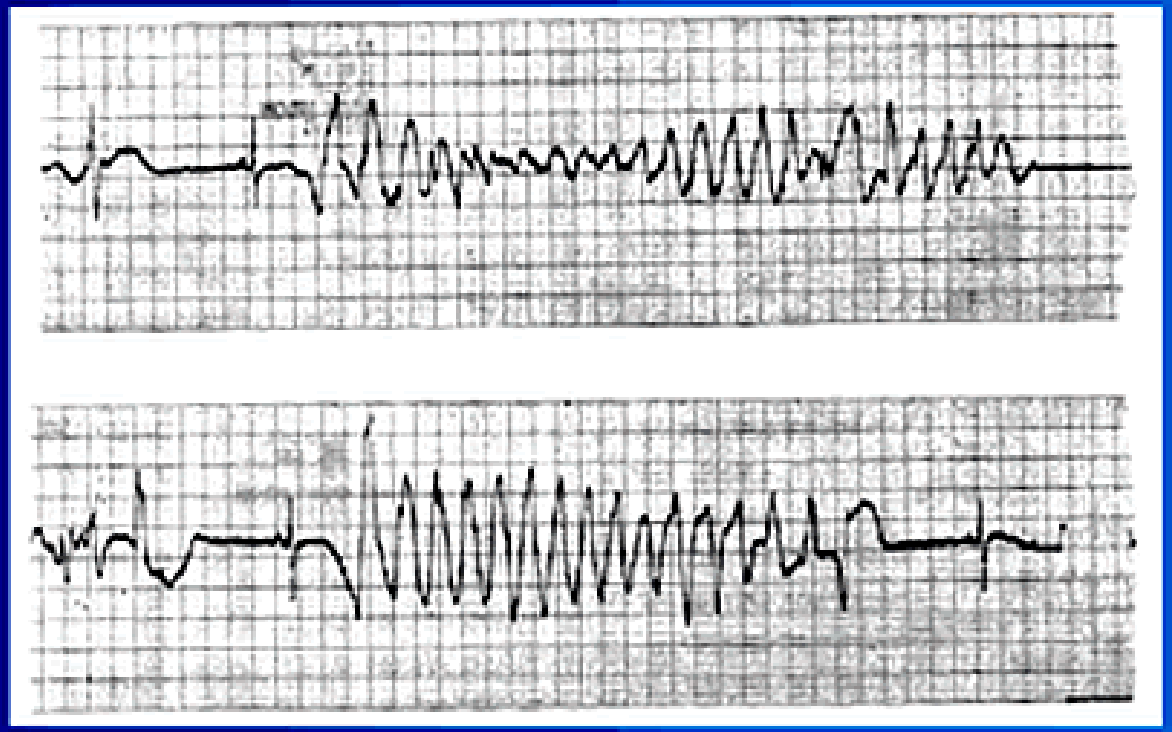
What is your diagnosis? Your action?

- Female, 39 years, hospitalised due to syncope and dizziness, which started 2 days ago
- Ten days ago she was prescribed terfenadine (60 mg x 2) and cefaclor (250 mg x 3). On eight day of treatment, the patient started ketoconazole due to vaginal candidiasis (200 mg x 2). In addition, she was using medroxyprogesterone (2,5 mg)
- At hospital: QTc - 665 ms; syncope, EKG – torsades de pointes
- Medicines were withdrawn, QTc return to normal

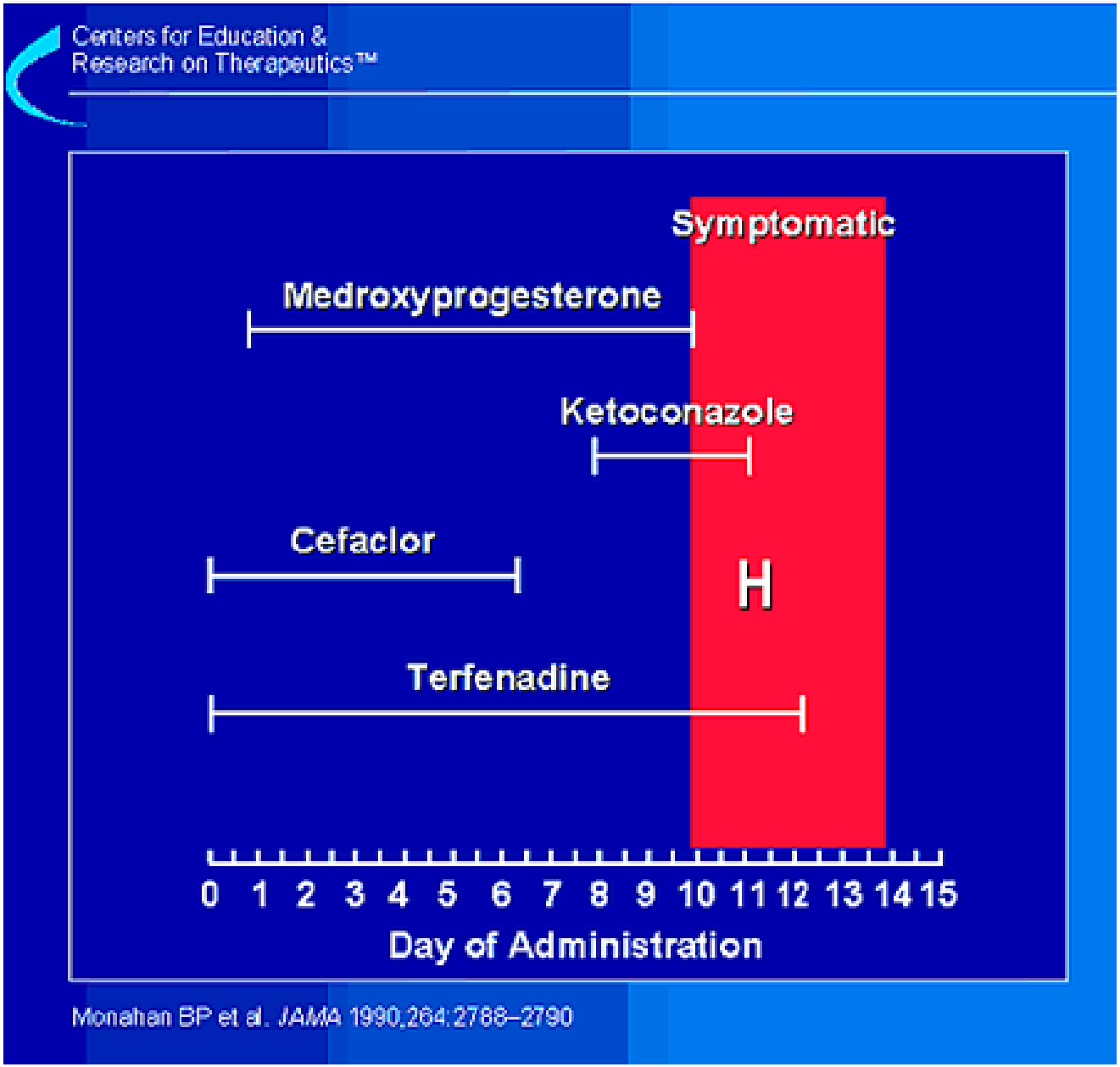
JAMA 1990; 264: 2788-2790

Research on Therapeutics™

Torsades de Pointes



Monahan BP et al. JAMA 1990;264:2788–2790


Centers for Education &
Research on Therapeutics™
Symptomatic
Medroxyprogesterone
Ketoconazole
Cefaclor
H
Terfenadine
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Day of Administration
Monahan BP et al. JAMA 1990;264:2788–2790

What has caused QTc prolongation?

- Medroxyprogesterone
- Ketoconazole
- Cefaclor
- Terfenadine

Ketoconazole is very potent CYP3A4 inhibitor

CYP3A4

Fexofenadine

Allegra, Altiva

Drug interactions

- Effect of one medicine may be changed when co-administered with other medicines, herbal medicines, food, drinks, or influenced by chemical substances of environment
- Effect:
  - Additive, synergistic
  - Antagonistic, decreased
  - Altered or idiosyncratic
- Result may be:
  - beneficial (positive)
  - Negative (adverse drug reaction)

A little bit of history

- First cases of drug interactions reported about possibly increased or decreased effect of medicine
- Reporting on clinically important drug interactions started in 1960s
- First cases reported hypertensive crisis in patients using MAOI with certain kind of cheese
- Since 1970s drug interaction tables have been published in medicinal journals, and the problem addressed systematically
- Since 1980s medicine control agencies require that pharmaceutical companies submit information on drug interaction

Frequency of drug interactions

- In primary health care, 4-70% patients experience drug interactions
- 1-26% of these interactions are clinically important
- Its is expected that the real numbers are higher due to use of OTC medicines and food supplements

Strandell, 2011

Drug interactions – the cause of ADRs

- Drug interactions are responsible for 3-5% of avoidable adverse drug reactions in hospital
- Drug interactions are important cause of acute admissions to hospital

Number of drugs used and frequency of drug interactions

US		JK	
Number of drugs used	ADRs (%)	Number of drugs	ADRs (%)
1-5	4,2	1-5	3,3
6-10	7,4	6+	19,8
11-15	24,2		
16-20	40,0		
21+	45,0		

pagal Smith et al.; Hurwitz

Table 1 | **Examples of drugs withdrawn because of CYP-related DDIs**

Drug name (generic)	Therapeutic use	Safety problem	Year withdrawn
Seldane (terfenadine)	Allergy	QTc prolongation	1998
Posicor (mibefradil)	Hypertension	QTc prolongation	1998
Duract (bromfenac)	Nonsteroidal anti-inflammatory drug	Toxicity	1998
Hismanal (astemizole)	Allergy	QTc prolongation	1999
Propulsid (cisapride)	Heartburn	QTc prolongation	2000
Lotronex (alosetron)	Irritable bowel syndrome	Toxicity	2000
Baycol (cerivastatin)	Hyperlipidaemia	Toxicity	2001
Serzone (nefazodone)	Antidepressant	QTc prolongation	2003

CYP, cytochrome P450; DDIs, drug–drug interactions.

Nature Reviews Drug Discovery **4**, 825-833 (October 2005)

Co-administration of medicines

Condition	Combination
Post-transplant immunosuppression	Corticosteroids, azathioprine, cyclosporine, mycophenolate, monoclonal antibodies
Oncology	Alkylating agents, antimetabolites, anthracyclines, interferon alfa
Infection	β lactams, aminoglycosides
Hypertension	α blockers, β blockers, ACEI, calcium antagonists, diuretics
Asthma	Corticosteroids, β_2 agonists, ipratropium, leukotriene inhibitors

Mechanisms of drug interactions

- Pharmaceutical incompatibilities
- PK interaction
  - Absorption
  - Distribution (binding with plasma proteins)
  - Metabolism
  - Excretion
- PF interaction
  - Target organ/receptor

Interaction before using the medicine (Pharmaceutical incompatibilities)

- Phenytoin and dextrose solution (precipitate)
- Amphotericin B and sodium chloride (precipitate)
- Gentamycin and beta lactam (loose of activity)

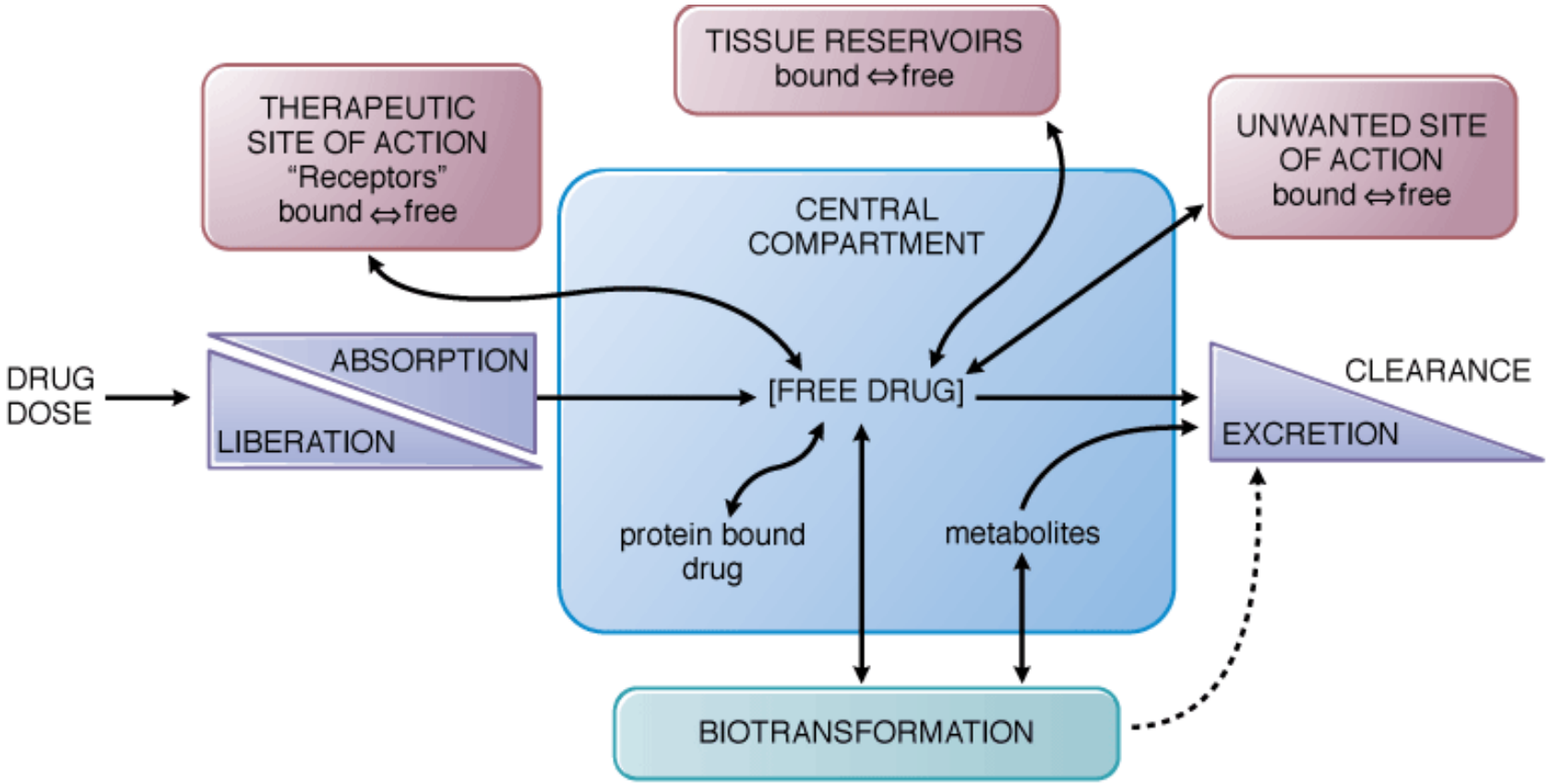
Pharmacodynamic interaction

- Interaction on the level of receptors
- Result:
  - Additive effect/ synergism
  - Antagonism (antidote)
  - Altered electrolyte balance

Common PD interactions

Result	Examples	Pharmacological action
Additive / synergism	• NSAID + warfarin • Verapamil + beta blockers	Increased risk of bleeding Bradycardia, asystole
Antagonism	• Beta agonists + beta blockers • Benzodiazepines + flumazenil • Opioids + naloxone	Inhibits pharmacological action
Altered electrolyte balance	• ACEI + spironolactone • Digoxin + loop diuretics • ACEI + NSAIDs	hyperkalemia Toxicity of therapeutic dose of digoxin Fluid retention, hyperkalemia, renal impairment

Pharmacokinetic interaction (1)



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

The interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its sites of action. Possible distribution and binding of metabolites in relation to their potential actions at receptors are not depicted.

Pharmacokinetic interaction(2)

- Interaction during absorption (1)
  - Changed gastric pH
    - Antacids (magnesium hydroxide increases absorption of weak acids: ↑ibuprofen, glibenclamide, glipizide absorption; due to chelate formation ↓ciprofloxacin absorption);
    - H_2 receptor antagonists and PPI (↓ketoconazole and itraconazole [weak bases], ↓cyanocobalamin, ↑glibenclamide, glipizide)
  - Changes in gastrointestinal motility
    - Affects absorption rate, rarely amount
    - decreased (levodopa + anticholinergics = BA ↓50%)
    - increased (prokinetics + cyclosporine)

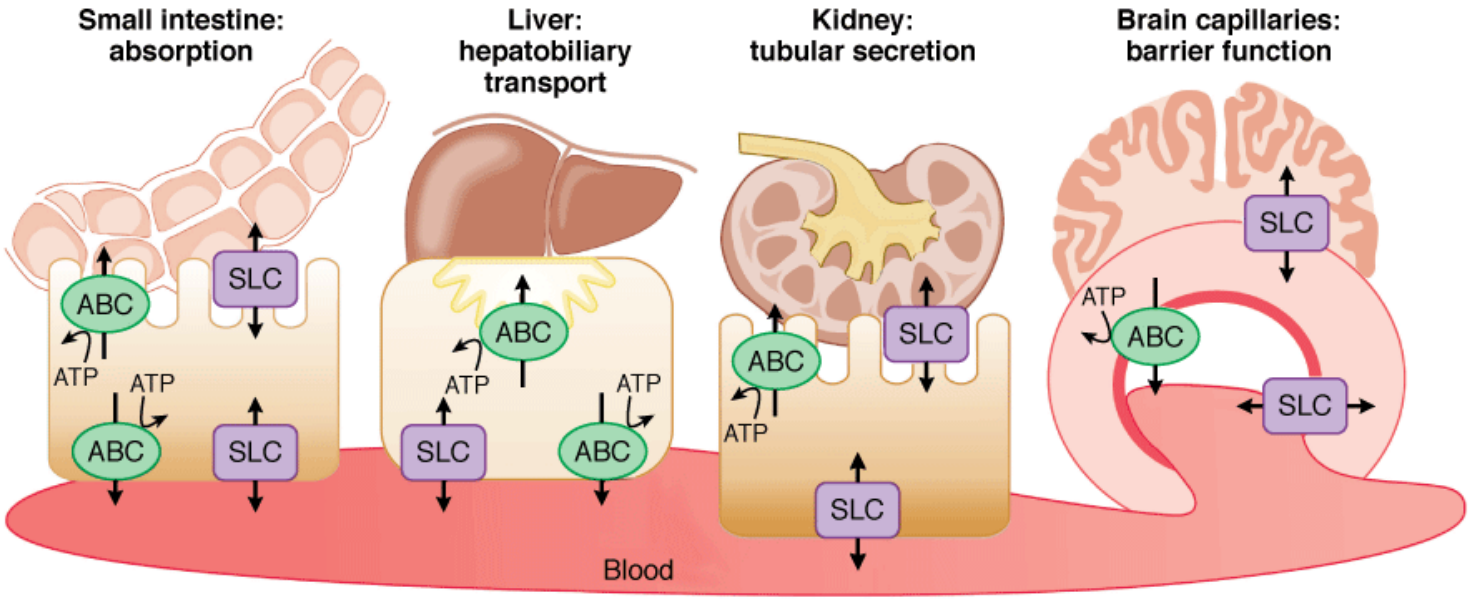
Pharmacokinetic interaction (3)

- Interaction during absorption (2)
  - Formation of insoluble chelates
    - iron + fluoroquinolones, antacids + tetracyclines; activated charcoal, cholestyramine; bisphosphonates + calcium
    - Avoidable using with 2 hours interval
  - Competition for transporters
    - amoxicillin transport (↑nifedipine, ↓amiloride)
  - Gastrointestinal toxicity
    - Cytotoxic agents (↓digoxin, verapamil, phenytoin)
  - Changes in gut microbiome
    - sulfasalazine, levodopa, digoxin

Role of transporters

- SLC transporters
  - 43 families, 300 gens
  - Transport variety of ionic and non-ionic endogenous compounds and xenobiotic
  - Act as facilitating transporters, secondary activated symporters and antiporters
- ABC superfamily
  - 49 gens, 7 groups
  - Majority exports compounds from cytoplasm outside of cell or to intracellular structures (endoplasmic reticulum)
  - Responsible for multidrug resistance (MDR)
  - One of the main transporters – P glycoproteine (P-gp)

Transporters



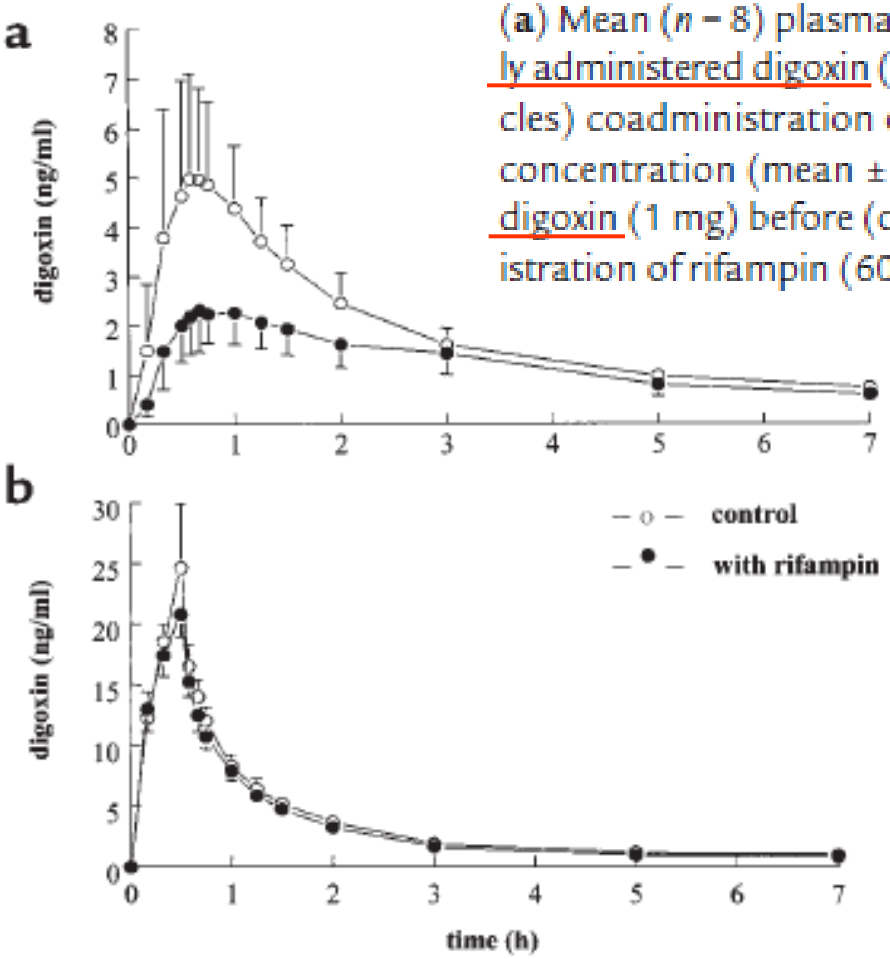
Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

Transepithelial or transendothelial flux. Transepithelial or transendothelial flux of drugs requires distinct transporters at the two surfaces of the epithelial or endothelial barriers. These are depicted diagrammatically for transport across the small intestine (absorption), the kidney and liver (elimination), and the brain capillaries that comprise the blood-brain barrier.

P-pg substrates, inductors and inhibitors

Substrates	Inhibitors	Inductors
Digoxin	Cyclosporine	Rifampicin
Fexofenadine	Ketoconazole, itraconazole	St John's wort
Loperamide	Carvedilol	
Quinidine	Reserpine	
Talinolol	Ritonavir, lopinavir, saquinavir, telaprevir	
Vinblastine, docetaxel, etoposide	Tacrolimus	
Dabigatran	Verapamil	
Amlodipine	Amiodarone, dronedarone, propafenone, quinidine	
Cyclosporine, tacrolimus	clarithromycin	

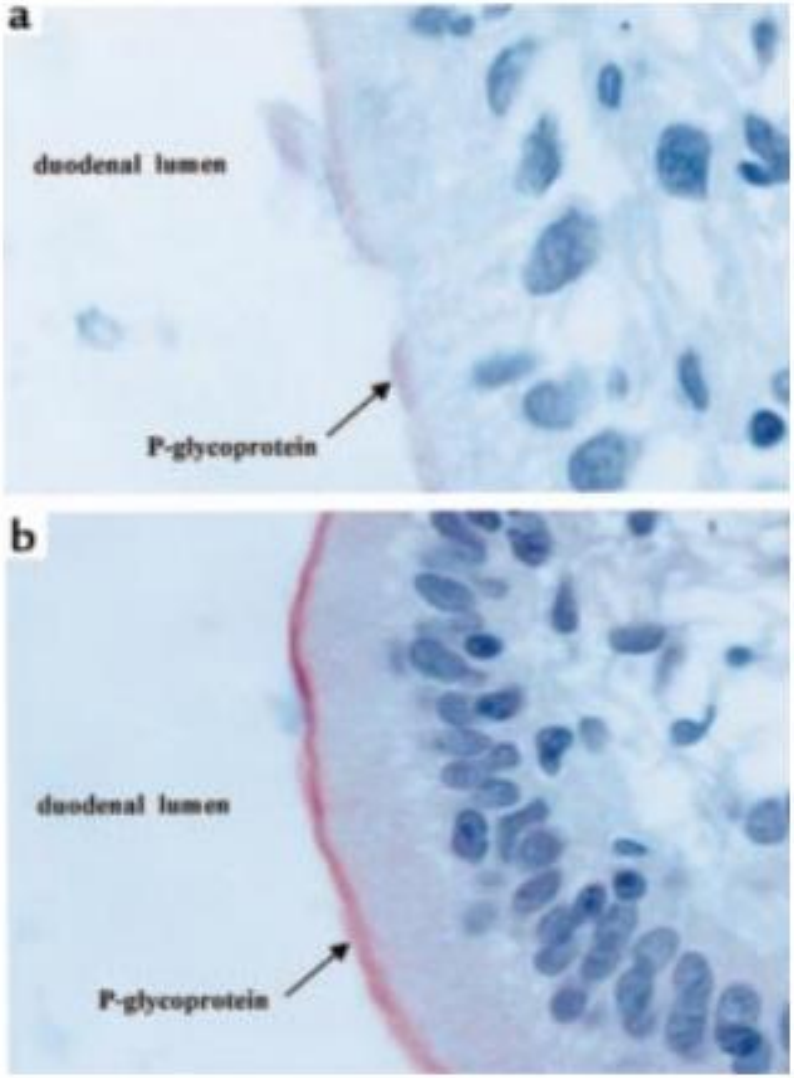
Induction of P-gp by rifampin



(**a**) Mean (n = 8) plasma concentration (mean ± SD) time curves of orally administered digoxin (1 mg) before (open circles) and during (filled circles) coadministration of rifampin (600 mg). (**b**) Mean (n = 8) plasma concentration (mean ± SD) time curves of intravenously administered digoxin (1 mg) before (open circles) and during (filled circles) coadministration of rifampin (600 mg).

The Journal of Clinical Investigation | July 1999 | Volume 104 | Number 2

Induction of P-gp expression by rifampin



- Duodenal biopsy (villus tip, ×40) immunostained for P-gp before administration of rifampin.

- Duodenal biopsy (villus tip, ×40) immunostained for P-gp after 9 days administration of rifampin (600 mg), obtained from the same volunteer as in a.

The Journal of Clinical Investigation | July 1999 | Volume 104 | Number 2

Drug interaction due to P-gp

Cardiovascular	Oncological	Other
Antiarrhythmics Amiodarone Dronaderone Quinidine Propafenone Calcium antagonists Verapamil Diltiazem Digoxin Dipyridamole Reserpine Spironolactone	Vinblastine Vincristine Doxorubicin Daunorubicin Paclitaxel Docetaxel Etoposide Teniposide Mitoxantrone Topotecan Tamoxifen	Phenothiazines Ketoconazole Itraconazole Erythromycin Clarithromycin Levofloxacin HIV protease inhibitors Immunosuppressants Domperidone Ondansetron Loperamide

Circulation 2000;101:1749-53

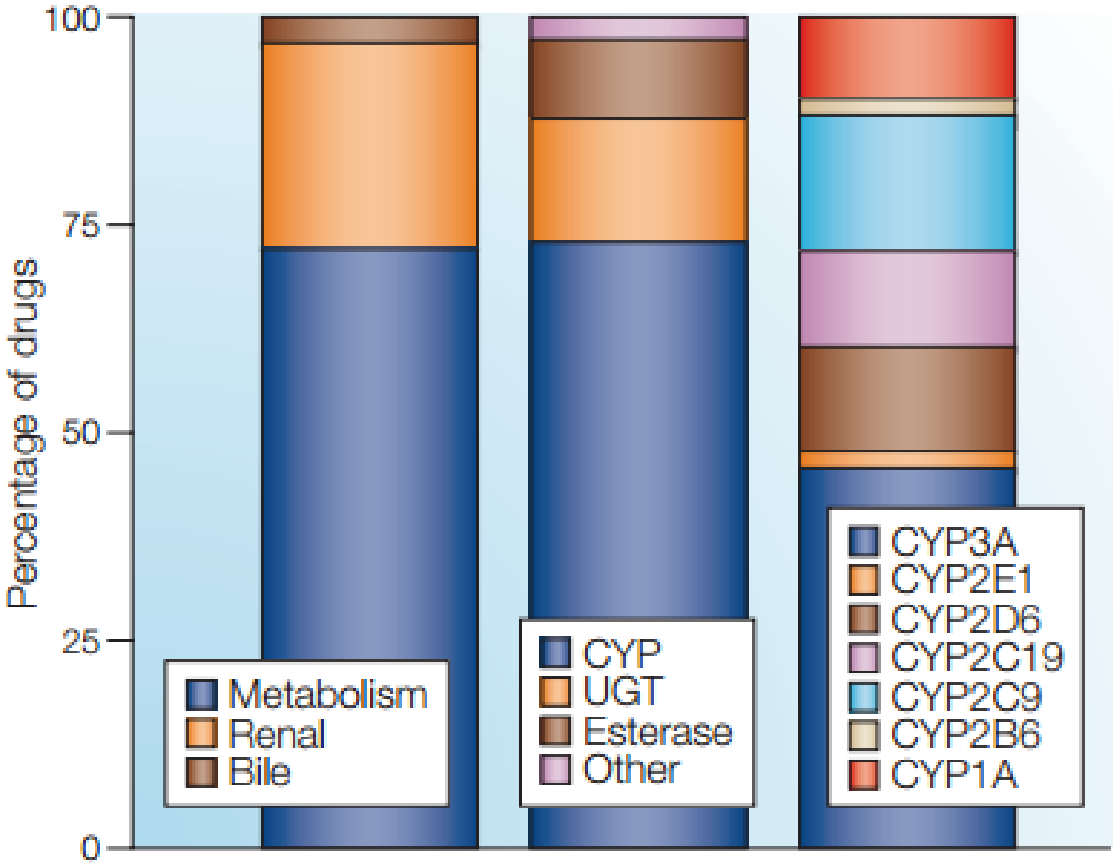
Pharmacokinetic interactions (4)

- Distribution related interaction
  - Concomitantly used medicines may change distribution of each other, however change in free drug concentration is transient and clinically insignificant
    - Altered binding to plasma proteins
    - Altered binding to target proteins

Metabolism related drug interactions

- I phase „oxygenases“
  - Cytochrome P450 (CYP)
  - Flavin monooxygenases (FMO)
  - Epoxide hydroxylases
- II phase „transferases“
  - Sulphotransferase
  - Gluthatione-S-transferase
  - N-acetyltransferase
  - Methyltransferase
- Other enzymes
  - Alcohol dehydrogenase
  - Aldehyde dehydrogenase
  - NADPH-quinone oxidoreductase

Elimination of 200 most frequently prescribed medicines in 2002



Metabolism represents the listed clearance mechanism for ~73% of the top 200 drugs. Of the drugs cleared via metabolism, about three-quarters are metabolized by members of the cytochrome P450 (CYP) superfamily. For the CYP-mediated clearance mechanisms, the majority of drug oxidations (46%) were carried out by members of the CYP3A family; followed by 16% by CYP2C9; 12% for both CYP2C19 and CYP2D6; 9% for members of the CYP1A family; and 2% for both CYP2B6 and CYP2E1. UGT, uridine diphosphate glucuronyl transferase.

Nature Reviews Drug Discovery **4**, 825-833 (October 2005)

I phase reactions
Cytochrome P450

- CYtochrome P450 – CYP450
- CYP1, CYP2, CYP3... – families (at least 40% homology in AA sequence)
- CYP1A, CYP2A, CYP2B, CYP2C... – subfamilies (at least 55% homology in AA sequence)
- CYP2A2, CYP2D6, CYP3A4... – enzymes
- 74 CYP genes families are described

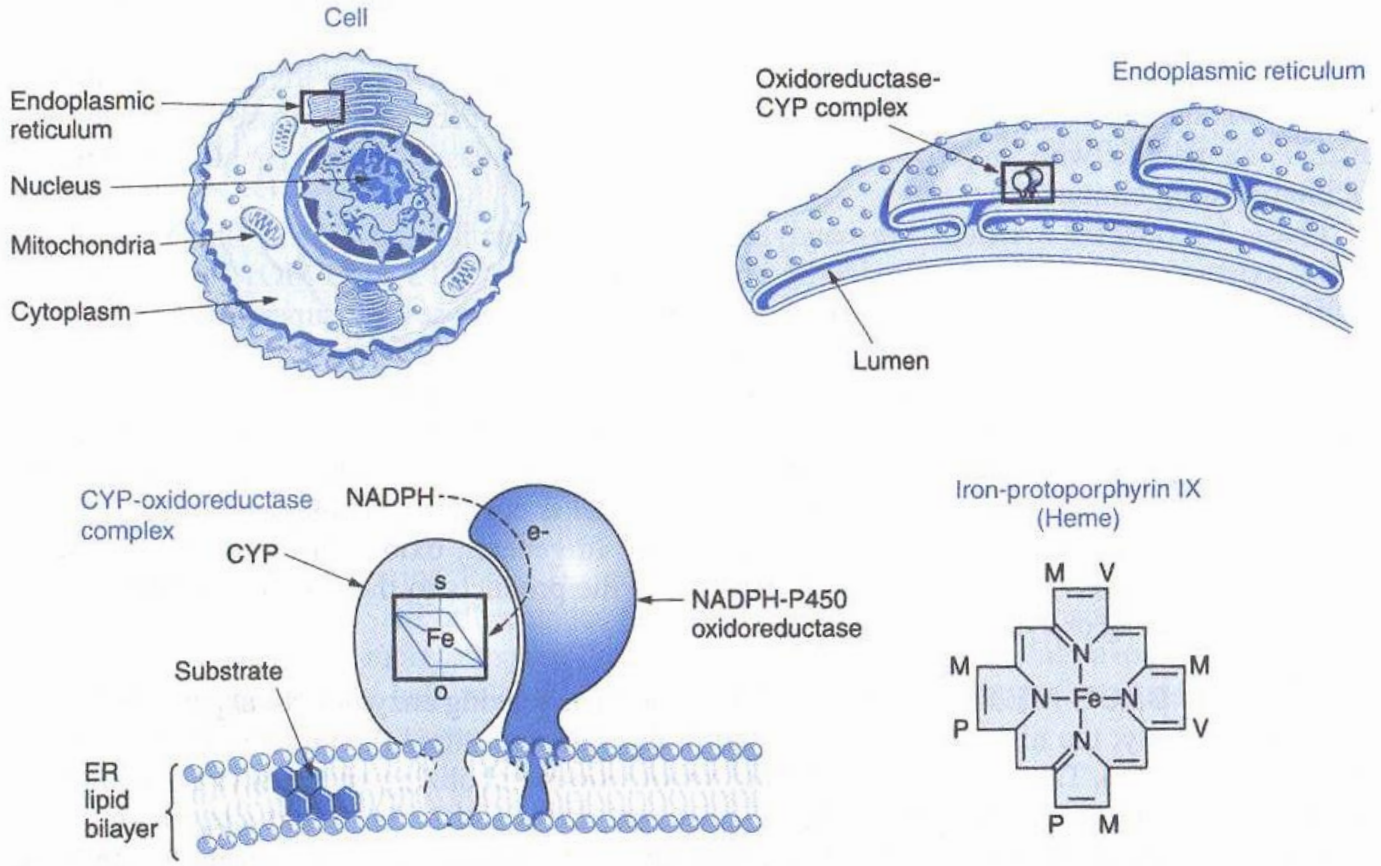
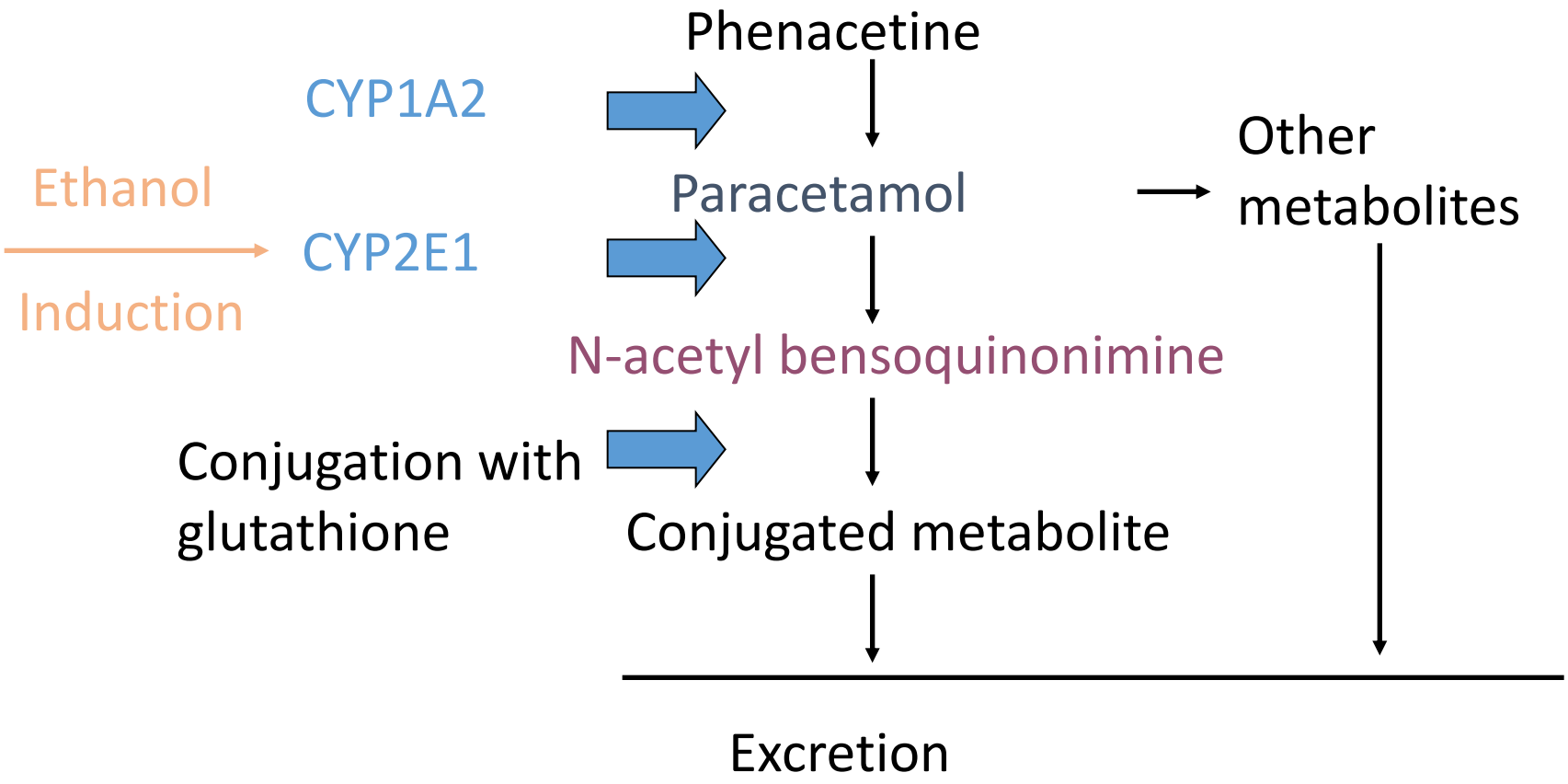


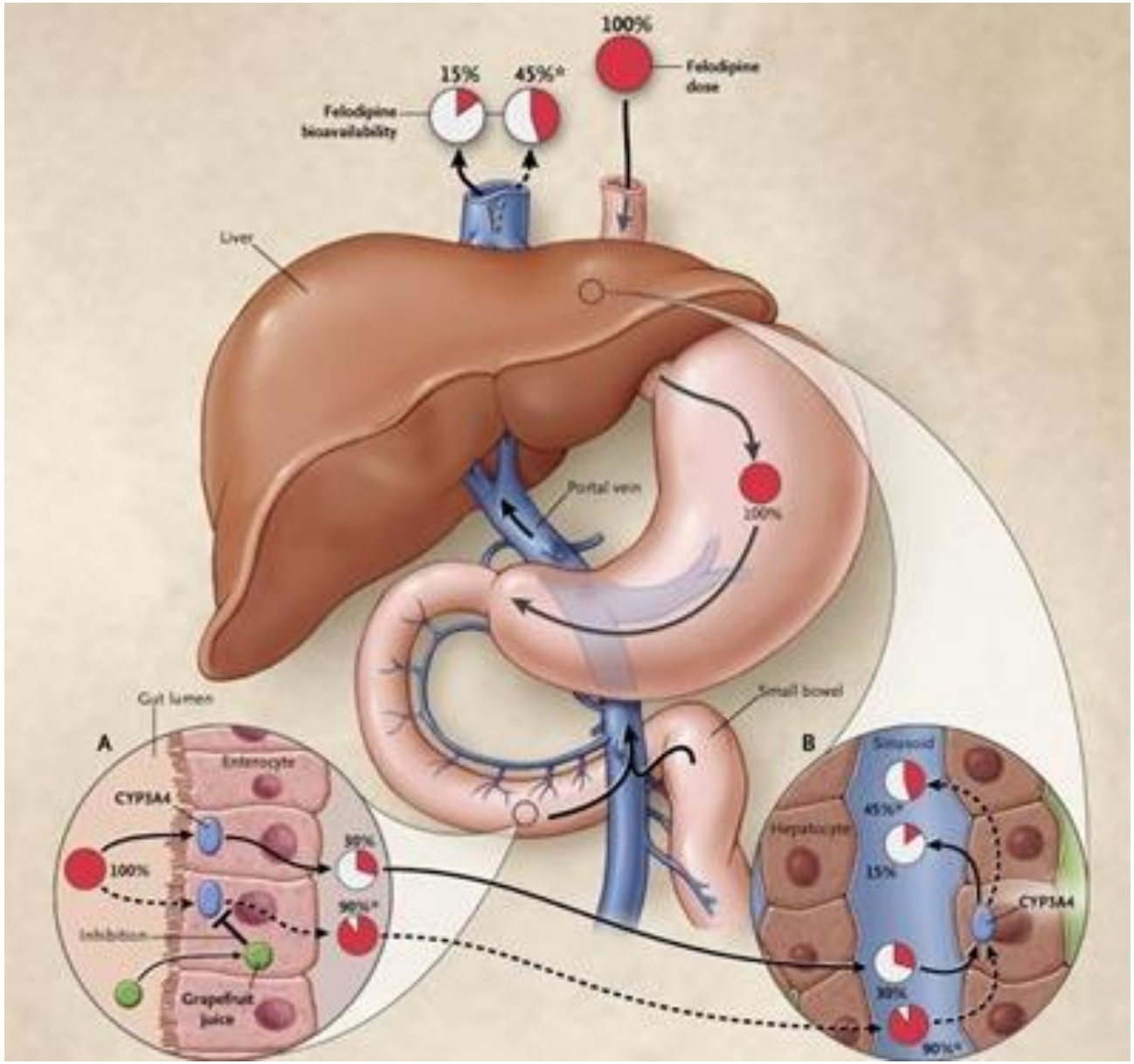
FIGURE 3–1 ***Location of CYPs in the cell.*** The figure shows increasingly microscopic levels of detail, sequentially expanding the areas within the black boxes. CYPs are embedded in the phospholipid bilayer of the endoplasmic reticulum (ER). Most of the enzyme is located on the cytoplasmic surface of the ER. A second enzyme, NADPH-cytochrome P450 oxidoreductase, transfers electrons to the CYP where it can, in the presence of O_2, oxidize xenobiotic substrates, many of which are hydrophobic and dissolved in the ER. A single NADPH-CYP oxidoreductase species transfers electrons to all CYP isoforms in the ER. Each CYP contains a molecule of iron-protoporphyrin IX that functions to bind and activate O2. Substituents on the porphyrin ring are methyl (M), propionyl (P), and vinyl (V) groups.

- http://medicine.iupui.edu/clinpharm/ddis/main-table

Metabolism of paracetamol



Felodipine grapefruit juice interaction



Bailey DG et al. Br J Clin Pharmacol, 1998

Felodipine grapefruit juice interaction

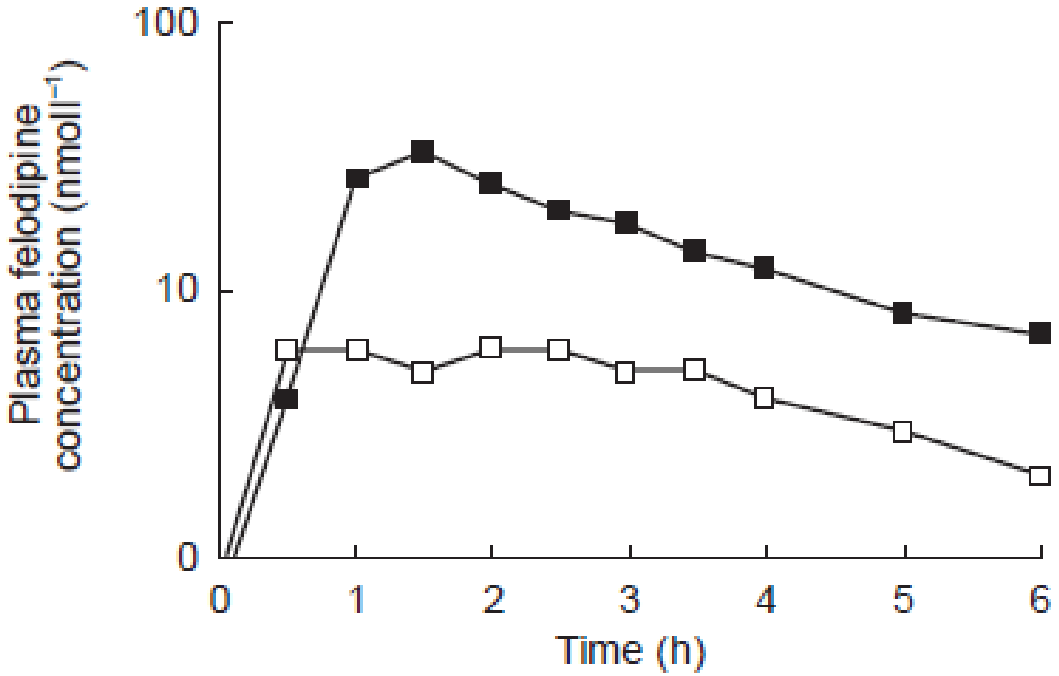


Figure 1 Plasma felodipine concentration-time profile from the pilot study in which the effect of grapefruit juice was evaluated in one of the authors (DGB). Felodipine 5 mg regular tablet was administered with 350 ml double-strength grapefruit juice (■) or water (□).

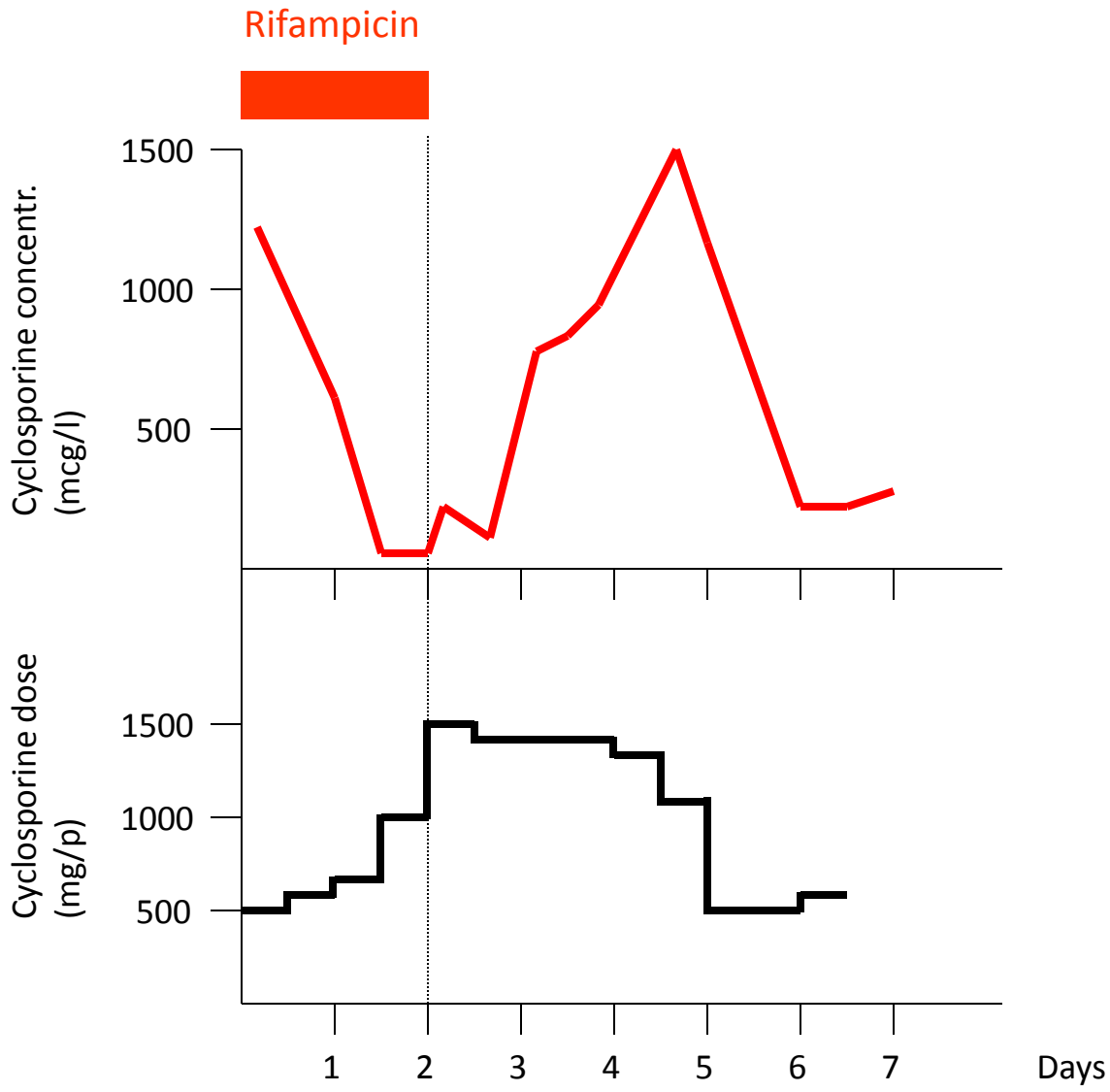
Bailey DG et al. Br J Clin Pharmacol, 1998

Grapefruit juice and calcium antagonists interaction

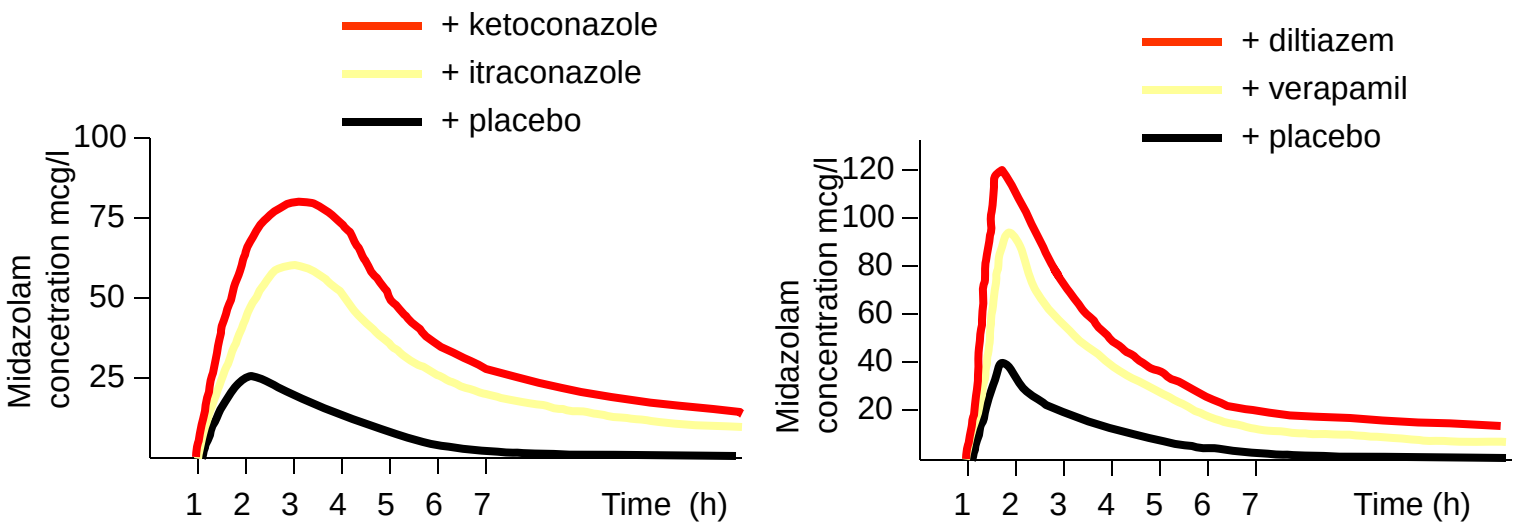
Bioavailability	Medicine	Relative *AUC* (%) compared to control	Relative C_{max} (%) compared to control
<5%	Nisoldipine	198	406
	Nimodipine	151	124
15-20%	Felodipine	145-345	170-538
	Nicardipine	134-196	125-153
	Nitrendipine	140-206	140-199
30-40%	Verapamil	143	161
60%	Nifedipine	134-203	104-194
>80%	Amlodipine	108-116	115

Bailey DG et al. Br J Clin Pharmacol, 1998

Induction of cyclosporine metabolism



Inhibition of midazolam metabolism



Pharmacokinetic interaction(6)

- Excretion related interaction
  - Changes in hepatic blood flow
  - Excretion to bile and enterohepatic circulation cirkuliacija
  - Enterohepatic circulation
    - Prolongs half-life of medicines (may be inhibited by broad spectrum antibiotics)

Pharmacokinetic interactions (7)

- Excretion related interaction
  - Drug induced renal impairment
    - Altered glomerular filtration (NSAIDs, ACEI, aminoglykosides)
  - Renal tubular secretion
    - Competition for transporters (e.g. sulfonamides, acetazolamide, thiazide diuretics, indomethacin, salicylates, probenecid, penicillins, cefalosporins, methotrexate)
  - Alteration in urine pH
    - Alkaline urine increases excretion of weak acids phenobarbital, salicylic acid

Clinically significant interactions

- Warfarin
  - Effect increased: macrolides, fluoroquinolones, metronidazole, penicillins, NSAIDs, platelets aggregation inhibitors, anticoagulants, amiodarone, etc.
- QT prolonging medicines
  - Imidazoles, TCA, macrolides, chlorpromazine, haloperdol, amiodarone, ivabradine, hypokalemia inducing drugs
- Statins
  - CYP3A4 inhibitors (macrolides, verapamil, diltiazem, amiodarone, cyclosporine, greipfruit juice) increase risk of rabdomiolysis
- SSRI/SNRI and triptans
  - Serotonergic syndrome

Most common combinations

TOP ten

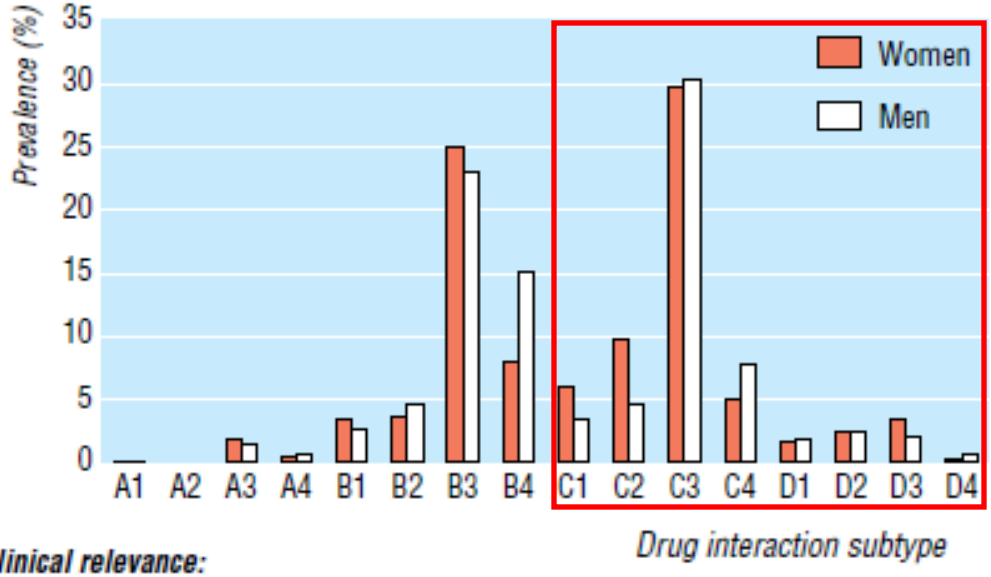
varfarinas	NSAIDs	D	3479
propafenonas	metoprololio sukcinatas	D3	1058
amlodipinas	karbamazepinas	D0	389
kalio chloridas	spironolaktonas	D3	372
azitromicinas	flukonazolas	D0	305
silimarinas	varfarinas	D1	297
karbamazepinas	kvetiapinas	D4	269
metoprololio sukcinatas	verapamilis	D3	265
nebivololis	verapamilis	D0	247
ciprofloksacinas	flukonazolas	D0	219

varfarinas	acetilsalicilo rūgštis	D4	1158

Prescriptions with potential drug interactions dispensed at Swedish pharmacies in January 1999: cross sectional study

Juan Merlo, Hans Liedholm, Ulf Lindblad, Agneta Björck-Linné, Jürgen Fält, Gunnar Lindberg, Arne Melander

BMJ 2001;323:427–8



Prevalence of potential drug-drug interaction subtypes[34] among 962 013 prescriptions containing two or more drugs dispensed to patients aged 15-95 from Swedish pharmacies in January 1999.

Clinical relevance:

A = Probably no clinical relevance.

B = Clinical relevance not completely assessed.

C = Clinical relevance. Interaction may modify the effect of the drug, but this is susceptible to control by dose adjustment (includes both beneficial and adverse drug interactions).

D = Clinically relevant. Interaction may have serious clinical consequences, may suppress a drug effect, or the effect modification is difficult to control by dose adjustment. This type of drug interaction ought to be avoided.

Documented evidence:

1 = Incomplete case reports, in vitro studies, or a drug interaction is presumed on the basis of evidence coming from similar drugs.

2 = Well documented case reports.

3 = Based on studies in volunteers or on pilot studies in patients.

4 = Based on controlled studies in relevant patient groups.

The most clinically relevant herb-drug interaction

HMP	Synthetic drug	Clinical outcome
Ginkgo	Anticoagulants, anti-inflammatory agents, antihypertensives, anaesthetics	Haemorrhage, apraxia, haematoma, hyphaema, permanent neurological deficit, death
Ginseng	Antidepressants, antidiabetics, anticoagulants, calcium channel blockers, cholesterol lowering agents, diuretics, hormonal agents	Inhibition of platelet aggregation, reduced platelet adhesiveness, hypoglycaemia, changes in blood pressure and heart rate, mania, headache, tremor, insomnia
Kava	Antidepressants, antiplatelets, CYP-450 metabolized agents, sedatives	Coma, sedation, lethargy, drowsiness
St John's wort	Antineoplastics, antimicrobials, antiretrovirals, hormonal agents, immunnosupressants	Transplant rejection, unwanted pregnancy, delayed emergence from anaesthesia, CVD collapse

Br J Clin Pharmacol DOI:10.1111/j.1365-2125.2012.04350.x

Review

Herb-drug interactions

Adriane Fugh-Berman

Concurrent use of herbs may mimic, magnify, or oppose the effect of drugs. Plausible cases of herb-drug interactions include: bleeding when warfarin is combined with ginkgo (*Ginkgo biloba*), garlic (*Allium sativum*), dong quai (*Angelica sinensis*), or danshen (*Salvia miltiorrhiza*); mild serotonin syndrome in patients who mix St John's wort (*Hypericum perforatum*) with serotonin-reuptake inhibitors; decreased bioavailability of digoxin, theophylline, cyclosporin, and phenprocoumon when these drugs are combined with St John's wort; induction of mania in depressed patients who mix antidepressants and *Panax ginseng*; exacerbation of extrapyramidal effects with neuroleptic drugs and betel nut (*Areca catechu*); increased risk of hypertension when tricyclic antidepressants are combined with yohimbine (*Pausinystalia yohimbe*); potentiation of oral and topical corticosteroids by liquorice (*Glycyrrhiza glabra*); decreased blood concentrations of prednisolone when taken with the Chinese herbal product xaio chai hu tang (sho-saiko-to); and decreased concentrations of phenytoin when combined with the Ayurvedic syrup shankhapushpi. Anthranoid-containing plants (including senna [*Cassia senna*] and cascara [*Rhamnus purshiana*]) and soluble fibres (including guar gum and psyllium) can decrease the absorption of drugs. Many reports of herb-drug interactions are sketchy and lack laboratory analysis of suspect preparations. Health-care practitioners should caution patients against mixing herbs and pharmaceutical drugs.

"Poisons and medicines are oftentimes the same substances given with different intents."

Peter Mere Latham (1789–1875)

Lancet 2000; **355:** 134–38

Herb and drug(s)	Results of interaction	Comments
Betel nut (*Areca catechu*)		
Flupenthixol and procyclidine	Rigidity, bradykinesia, jaw tremor[5]	Betal contains arecoline, a cholinergic alkaloid.
Fluphenazine	Tremor, stiffness, akithesia[5]	
Prednisone and salbutamol	Inadequate control of asthma	Arecoline challenge caused dose-related bronchoconstriction in six asthma patients.[6]
Chilli pepper (*Capsicum* spp)		
ACE inhibitor	Cough[7]	Capsaicin depletes substance P.
Theophylline	Increased absorption and bioavailability[8]	
Danshen (*Salvia miltiorrhiza*)		
Warfarin	Increased INR, prolonged PT/PTT[9-11]	In rats, danshen decreases elimination of warfarin.[12] Danshen is in at least one brand of cigarettes.[13]
Devil's claw (*Harpagophytum procumbens*)		
Warfarin	Purpura[14]	
Dong quai (*Angelica sinensis*)		
Warfarin	Increased INR[15,16] and widespread bruising[16]	Dong quai contains coumarins.
Eleuthero or Siberian ginseng (*Eleutherococcus senticocus*)		
Digoxin	Raised digoxin concentrations[17]	Herb probably interfered with digoxin assay (patient had unchanged ECG despite digoxin concentration of 5·2 nmol/L).
Garlic (*Allium sativum*)		
Warfarin	Increased INR[18]	Postoperative bleeding,[19,20] and spontaneous spinal epidural haematoma[21] have been reported with garlic alone. Whether garlic prolongs PT is unclear, but it does cause platelet dysfunction.
Ginkgo (*Ginkgo biloba*)		
Aspirin	Spontaneous hyphema[22]	Ginkgolides are potent inhibitors of PAF.[23,24]
Paracetamol and ergotamine/caffeine	Bilateral subdural haematoma[25]	May not be interaction but due to ginkgo alone. Subarachnoid haemorrhage[26] and subdural haematoma[27] have been reported with the use of ginkgo alone.
Warfarin	Intracerebral haemorrhage[28]	
Thiazide diuretic	Hypertension[18]	This effect may be an unusual adverse reaction to the drug or herb; ginkgo alone has not been associated with hypertension.
Ginseng (*Panax* spp)		
Warfarin	Decreased INR[29]	In rats, concomitantly administered ginseng had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin.[30]
Phenelzine	Headache and tremor,[31] mania[32]	Patient with mania also ingested bee pollen, and had previously had unipolar depression.
Alcohol	Increased alcohol clearance[33]	In mice, ginseng increases the activity of alcohol dehydrogenase and aldehyde dehydrogenase.
Guar gum (*Cyamopsis tetragonolobus*)		
Metformin, phenoxymethylpenicillin, glibenclamide	Slows absorption of digoxin, paracetamol, and bumetanide; decreases absorption of metformin, phenoxymethylpenicillin, and some formulations of glibenclamide[18]	Guar gum prolongs gastric retention.

Herb and drug(s)	Results of interaction	Comments
Karela or bitter melon (*Momordica charantia*)		
Chlorpropamide	Less glycosuria[34]	Karela decreases glucose concentrations in blood.[35]
Liquorice (*Glycyrrhiza glabra*)		
Prednisolone	Glycyrrhizin decreases plasma clearance, increases AUC,[36] increases plasma concentrations prednisolone[37]	11β-dehydrogenase converts endogenous cortisol to cortisone; orally administered glycyrrhizin is metabolised mainly to glycyrrhetinic acid.[36]
Hydrocortisone	Glycyrrhetinic acid potentiates of cutaneous vasoconstrictor response[38]	Glycyrrhetinic acid is a more potent inhibitor of 5α-, 5β-reductase and 11β-dehydrogenase than is glycyrrhizin.[36]
Oral contraceptives	Hypertension, oedema, hypokalaemia[39]	Oral contraceptive use may increase sensitivity to glycyrrhizin acid.[39] Women are reportedly more sensitive than men to adverse effects of liquorice.[40]
Papaya (*Carica papaya*)		
Warfarin	Increased INR[14]	
Psyllium (*Plantago ovata*)		
Lithium	Decreased lithium concentrations[41]	Hydrophilic psyllium may prevent lithium from ionising.
St John's wort (*Hypericum perforatum*)		
Paroxetine	Lethargy/incoherence[42]	
Trazodone	Mild serotonin syndrome[43]	A similar case is described with the use of St John's wort alone.
Sertraline	Mild serotonin syndrome[44]	
Nefazodone	Mild serotonin syndrome[44]	
Theophylline	Decreased theophylline concentrations[45]	
Digoxin	Decreased AUC, decreased peak and trough concentrations[46]	Most, but not all, studies indicate that St John's wort is a potent inhibitor of cytochrome P450 isoenzymes[47]
Phenprocoumon	Decreased AUC[48]	
Cyclosporin	Decreased concentrations in serum[49]	
Combined oral contraceptive (ethinyloestradiol and desogestrel)	Breakthrough bleeding[49]	
Saiboku-to (Asian herbal mixture)		
Prednisolone	Increased prednisolone AUC[50]	Contains all the same herbs as sho-saiko-to, and *Poria cocos*, *Magnolia officinalis*, and *Perillae frutescens*.
Shankhapushpi (Ayurvedic mixed-herb syrup)		
Phenytoin	Decreased phenytoin concentrations, loss of seizure control[51]	In rats, multiple coadministered doses (but not single doses) decreased plasma phenytoin concentrations; single doses decreased the antiepileptic effect of phenytoin.[51] Shankhapushpi is used to treat seizures.
Sho-saiko-to or xiao chai hu tang (Asian herb mixture)		
Prednisolone	Decreased AUC for prednisolone[50]	Contains liquorice (*Glycyrrhiza glabra*), *Bupleurum falcatum*, *Pinellia ternata*, *Scutellaria baicalensis*, *Zizyphus vulgaris*, *Panax ginseng*, and *Zingiber officinale*.
Tamarind (*Tamarindus indica*)		
Aspirin	Increased bioavailability of aspirin[52]	Tamarind is used as a food and a medicine.
Valerian (*Valeriana officinalis*)		
Alcohol	A mixture of valepotriates reduces adverse effect of alcohol on concentration[53]	
Yohimbine (*Pausinystalia yohimbe*)		
Tricyclic antidepressants	Hypertension[54]	Yohimbine alone can cause hypertension, but lower doses cause hypertension when combined with tricyclic antidepressants. Effect is stronger in hypertensive than normotensive individuals.[55]

ACE=angiotensin-converting enzyme; INR=international normalised ratio; PT=prothrombin time; PTT=partial thromboplastin time; ECG=electrocardiogram; PAF=platelet-activating factor; AUC=area under the concentration/time curve.

St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes

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Aims The aim of this work is to identify the medicines which interact with the herbal remedy St John's wort (SJW), and the mechanisms responsible.

Methods A systematic review of all the available evidence, including worldwide published literature and spontaneous case reports provided by healthcare professionals and regulatory authorities within Europe has been undertaken.

Results A number of clinically significant interactions have been identified with prescribed medicines including warfarin, phenprocoumon, cyclosporin, HIV protease inhibitors, theophylline, digoxin and oral contraceptives resulting in a decrease in concentration or effect of the medicines. These interactions are probably due to the induction of cytochrome P450 isoenzymes CYP3A4, CYP2C9, CYP1A2 and the transport protein P-glycoprotein by constituent(s) in SJW. The degree of induction is unpredictable due to factors such as the variable quality and quantity of constituent(s) in SJW preparations. In addition, possible pharmacodynamic interactions with selective serotonin re-uptake inhibitors and serotonin ($5\text{-}HT_{1d}$) receptor-agonists such as triptans used to treat migraine were identified. These interactions are associated with an increased risk of adverse reactions.

Conclusions In Sweden and the UK the potential risks to patients were judged to be significant and therefore information about the interactions was provided to health care professionals and patients. The product information of the licensed medicines involved has been amended to reflect these newly identified interactions and SJW preparations have been voluntarily labelled with appropriate warnings.

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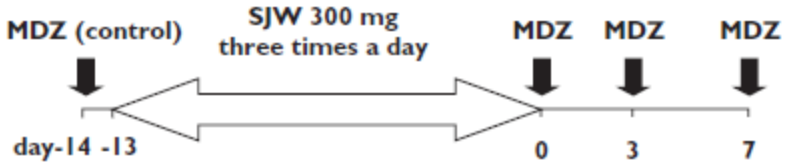
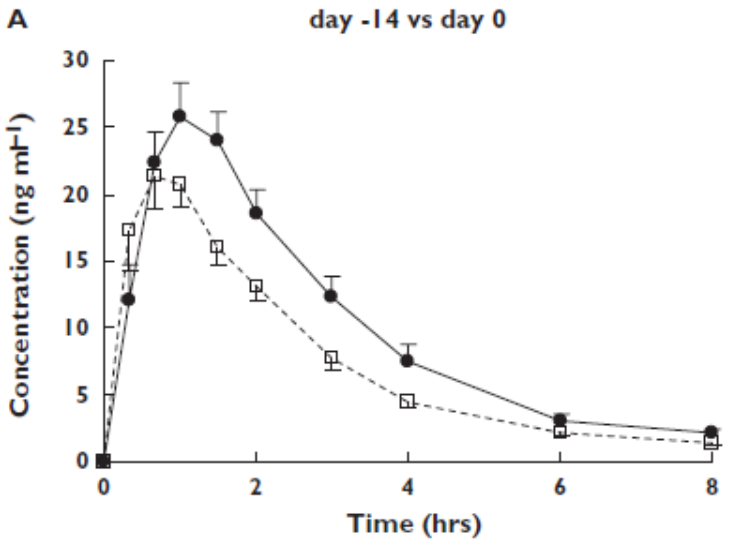
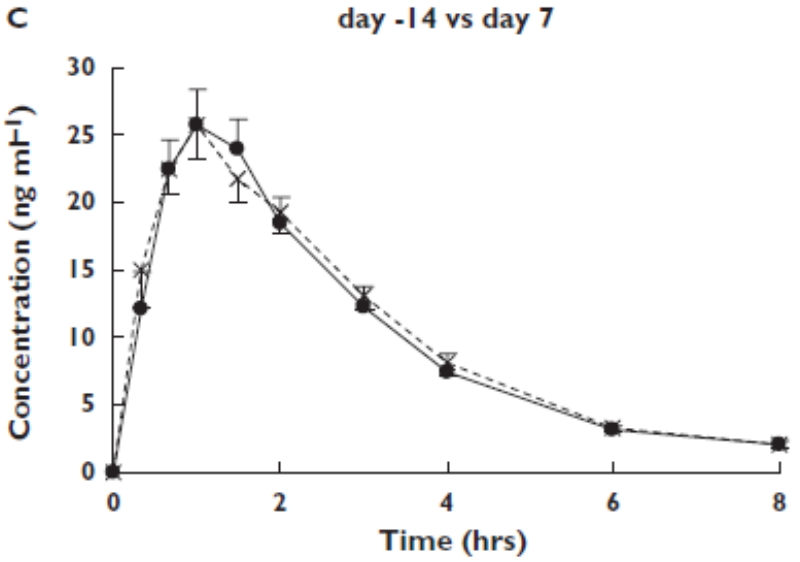
St John's wort midazolam interaction



Mean (±SEM) plasma concentrations of midazolam on day 0 (□) (A), day 3 (△) (B), and day 7 (×) (C) compared with day −14 (●) (control) in 12 subjects





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The main constituents of St John's wort

Constituent	*Percentage of composition*	*Possible contribution to mode of action*
Phenylpropanes	Not reported	–
Flavonol glycosides (including hyperoside)	2–4%	Inhibition of MAO-A
Biflavones	Not reported	Weak affinity for the benzodiazepine receptor
Tannins and proanthocyanidins	15%	–
Xanthones	Very low concentrations	Inhibition of MAO-A
Phloroglucinols (hyperforin)	4% of the buds and flowers	Affinity for GABA receptors
Essential oils	Not reported	–
Amino acids	Not reported	–
Naphthodianthrones (including hypericin)	Not reported	–

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Possible pharmacokinetic and pharmacodynamic interactions with SJW

Drug	*Possible mechanism of action*
Pharmacokinetic interactions	
Warfarin and phenprocoumon	Induction of CYP2C9
Cyclosporin	Induction of CYP3A4 and the transport protein P-glycoprotein
Oral contraceptives	Induction of CYP1A2 and CYP3A4
Theophylline	Induction of CYP1A2
Digoxin	Induction of transport protein P-glycoprotein
HIV protease inhibitors	Induction of CYP3A4
HIV non-nucleoside reverse transcriptase inhibitors	Induction of CYP3A4
Anticonvulsants (carbamazepine, phenobarbitone and phenytoin)	Induction of CYP3A4
Pharmacodynamic interactions	
SSRIs	Potentiation of serotonin concentrations
Triptans	Potentiation of serotonin concentrations

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Drug	*Effect of interaction on drug*	*Suggested management of patients already taking SJW preparations*
HIV protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir)	Reduced blood concentrations with possible loss of HIV suppression.	Measure HIV RNA viral load and stop SJW.
HIV non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine)	Reduced blood concentrations with possible loss of HIV suppression.	Measure HIV RNA viral load and stop SJW.
Warfarin	Reduced anticoagulant effect and need for increased warfarin dose.	Check INR and stop SJW. Monitor INR closely as this may rise on stopping SJW. The dose of warfarin may need adjusting.
Cyclosporin	Reduced blood concentrations with risk of transplant rejection.	Check cyclosporin blood concentrations and stop SJW. Cyclosporin concentrations may increase on stopping SJW. The dose of cyclosporin may need adjusting.
Oral contraceptives	Reduced blood concentrations with risk of unintended pregnancy and breakthrough bleeding.	Stop SJW.
Anticonvulsants (carbamazepine, phenobarbitone, phenytoin)	Reduced blood concentrations with risk of seizures.	Check anticonvulsant concentrations and stop SJW. Anticonvulsant concentrations may increase on stopping SJW. The dose of anticonvulsant may need adjusting.
Digoxin	Reduced blood concentrations and possible loss of control of heart rhythm or heart failure	Check digoxin concentrations and stop SJW. Digoxin concentrations may increase on stopping SJW. The dose of digoxin may need adjusting.
Theophylline	Reduced blood concentrations and possible loss of control of asthma or chronic airway limitation.	Check theophylline concentrations and stop SJW. Theophylline concentrations may increase on stopping SJW. The dose of theophylline may need adjusting.
Triptans (sumatriptan, naratriptan, rizatriptan, zolmitriptan)	Increased serotonergic effects with risk of increased incidence of adverse reactions.	Stop SJW.
SSRIs (citalopram, fluoxetine, fluvoxamine,paroxetine, sertraline)	Increased serotonergic effects with risk of increased incidence of adverse reactions.	Stop SJW.

Conclusions (1)

- The effect of one drug may be strengthened, weakened or altered by another medicine which was used concomitantly or later.
- Many of drug interactions can be predicted from their mechanism of action, PD and PK. Majority of them are avoidable.

Conclusions (2)

- *In vitro* seen PK or PD interaction not necessarily will present in patient
- Interaction may not occur in all patients using the same combination of medicines
- Many clinically relevant interactions (e.g. PK) depend also on other factors

Conclusions (3)

- PK drug interaction seen with a combination od certain medicines cannot be extrapolated to other similar medicines. However, it is advisable to take precaution measures.
- Growing number of medicines and polypharmacy increases the risk of drug interactions. Fortunately the majority of interactions are clinically insignificant or rarely significant.

Conclusions (4)

- The most common drug interactions – PD interactions of CNS depressants – benzodiazepines, barbiturates, antidepressants, ethanol, opioid analgesics, sedative antihistamine agents, antiepileptic drugs and other centrally acting medicines

Conclusions (5)

- The most pronounced drug interactions occur due to altered PK using oral anticoagulants, antidiabetic medicines, digoxin, 2nd generation antihistamines, benzodiazepines, immunosuppressant drugs, cytotoxic medicines. Due to narrow therapeutic window, the consequences may be fatal.

- *One of the first duty of the physician is to educate the masses not to take medicine*

  Sir William Osler